Academia, Clinical Pharmacy Careers in

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INTRODUCTION

If you are contemplating a pharmacy practice career in academia, this may stem from the intellectual and cultural stimulation and the variety of interesting and eager people that you encountered while in college. However, there are many aspects of this career path that are not readily apparent. The goal of this article is to expand your perspectives about clinical pharmacy academia so that you are more informed about it as a career opportunity. Specifically, this article provides an overview of the clinical pharmacy careers in academia, insight into important issues in academia, and recommendations for making informed decisions about career options.

OPTIONS AND ISSUES

Academic positions are often cited as being either a *tenure-track* or a *nontenure-track* and are often available to clinical pharmacy faculty at either a pharmacy or a medical school. A tenure-track position is one that requires an individual to successfully demonstrate scholarly accomplishments within the initial six years of employment, and in return, the university guarantees lifetime employment unless the institution falls into financial exigency or the faculty member exhibits misconduct. With a nontenure-track position, the faculty member must also demonstrate some level of scholarly accomplishment, but there is more flexibility in the window of time during which this occurs. Although the university does not commit itself to lifetime employment of individuals in nontenure positions, it does provide a contract that conveys a commitment of employment for a given period of time and the contract is usually renewable at the end of each period. Individuals who enjoy teaching but who do not desire scholarship/research responsibilities are encouraged to seek an adjunct or affiliate clinical faculty appointment with a nearby pharmacy and/or medical school.

Activities and Overview of Career Options

Most full-time clinical pharmacy faculty positions require the individual to balance and accomplish responsibilities related to four missions: 1) teaching, 2) scholarship/research, 3) service, and 4) patient care/practice. Although all faculty must make some level of contributions to each of these responsibilities, many institutions expect faculty to excel in only one or two of these four missions. There are several important career options that must be considered in order to successfully balance and achieve these responsibilities. First, an individual pursuing an academic career must decide upon either a tenure- or nontenure-track option. Second, because it is difficult to be accomplished in all four of these areas, there are primarily two types of tenure-track clinical faculty position models now offered by pharmacy schools.[1,2] Individuals who assume the practitioner-educator model have equal responsibility for patient care/teaching and research/scholarship. Those who fulfill the researcher/educator model spend the majority of their time in research and teaching with much less time devoted to patient care. A nontenure-track position is similar to the practitioner-educator model but, at some institutions they have less time devoted to research. The following sections provide insight into issues and factors to consider when contemplating either a full-time, college-based tenure- or nontenure-track position.

Academia in Transition

Higher education is currently undergoing rigorous financial restriction, external demands for accountability, and self-scrutiny. Therefore, any future academic career will likely be different than that of the faculty you had in college. For example, those entering academic clinical

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006174

pharmacy today are encountering changes in the tenure system, a different reward system, and continued evolution of academic clinical pharmacy.

Changes in the tenure system

In the early 1900s the tenure system was established so that faculty would have the academic freedom to express their thoughts without fear of dismissal.[3] Due to statutory repeal of the mandatory retirement age and financial restrictions in higher education, many institutions are finding tenure limits their flexibility in responding to fluctuations in admissions to different degree programs.[4] Advocates believe tenure is necessary since it provides a healthy environment that encourages new ideas; individuals can say what they want and be protected from dismissal.[5] Opponents believe it protects the incompetent and reduces the flexibility institutions need to be responsive to new demands such as limited financial resources and accountability.

At most institutions, the tenure system provides new assistant professors a time span of approximately six years in which to demonstrate achievement in teaching, service, practice, and scholarship/research.[5] After this window of time, the faculty decides whether to grant tenure. The granting of tenure implies a guaranteed position within the university unless there is financial exigency or the faculty member is found guilty of misconduct.

When contemplating the tenure- versus nontenure-track alternatives, the individual should weigh the benefit of academic freedom with the difficulty, stress, and anxiety that many academicians encounter when trying to accomplish promotion and tenure criteria within a six-year window. Because clinical pharmacy faculty members have to establish a practice in addition to teaching, scholarship/research, and service, these time constraints can be particularly stressful and inflexible.[6] To facilitate long-term success, some institutions are offering clinical faculty members the opportunity to begin on a nontenure-track and move to the tenure track once their practice and research abilities are established.

Changes in the reward system

In the early 1600s when the first colleges were established in the United States, the primary college mission of the faculty was teaching.[7] However, since then our universities have added service as a second mission in order to meet a need of society for practical assistance in everyday living, and research as a third mission due to the influence of higher education from Germany. This research mission requires faculty to generate new knowledge rather than just convey knowledge.[7] Institutions with medical and health-related profession educational programs also have practice/patient care as an extension of their service or outreach mission.

Unfortunately, by the mid-1900s the faculty reward system, even in institutions with no graduate programs, had evolved to one in which decisions about faculty promotions were largely based only on the individuals research and publication record.[7] The effectiveness of one's teaching was given little, if any consideration at the time of promotions.

In 1990, Boyer called for academia to move beyond this problem.[7] He stated that each institution should clearly establish its unique missions and measure itself by these values rather than the traditional research reputation. To accomplish this, Boyer asserted that higher education must establish and adopt a new way of defining and rewarding *scholarship*. Boyer proposed that the term scholarship must take on a broader meaning than just original research in order to characterize the full scope of duties an academician is expected to accomplish in today's higher-education institutions. He further characterized the scholarship expected among a faculty as encompassing four distinct functions: 1) the scholarship of discovery (i.e., original research), 2) the scholarship of application, 3) the scholarship of integration, and 4) the scholarship of teaching. Glassick and colleagues[8] have since facilitated acceptance of this concept by establishing criteria by which scholarship can be measured. These criteria have helped distinguish the difference between achievement of excellence and scholarship, and they are enabling institutions to place equal value on all four types of scholarship.[9] Although all four types of scholarship are recognized by most institutions, most institutions require faculty to excel in only one or two of these four options.

During the last 11 years, these pivotal reports have led most institutions to reevaluate how faculty members prioritize their time and the faculty reward system. Therefore, when contemplating an academic position, an individual should clearly understand the institution's mission and faculty reward system. The faculty candidate should also ascertain whether the assigned duties can be accomplished according to the projected allocation of time and effort and that they are consistent with the faculty reward system. Individuals who select either a college-based tenure- or nontenure-track position should clearly understand that success in academia requires achievement of not only excellence in completion of assigned duties, but also scholarship.[1,9]

Evolution of clinical pharmacy academicians

Similar to the evolution of other clinical disciplines, clinical pharmacy practice grew from the commitment of a cadre of clinicians who contributed significant time in practice and teaching.[10] Because they had little time for research and scholarship and often had limited skills in these areas, early clinical pharmacy academicians were sometimes viewed as quasi-faculty members. In the last 30 years, the discipline has overcome this stigma by establishing peer-reviewed discipline-specific journals, becoming accepted authors to journals of other academic disciplines, and developing specialty residency and fellowship programs that prepare future clinical pharmacy faculty members for academic careers.

The discipline now also has a cadre of clinical scientists who are fulfilling the typical academic scientist role; but in order to accomplish this, these individuals have had to focus primarily on teaching and research with minimal activities in practice. Since the fundamental role of the discipline is to prepare students for actual practice, a cadre of clinical faculty whose primary duties are practice and teaching are therefore also essential.

Because a broader definition of scholarship is now accepted in higher education and it is realized that faculty members cannot effectively accomplish all four missions, two faculty models are most frequently used today. Individuals who assume the practitioner-educator model are enabled to accomplish either the scholarship of integration, application, and/or teaching because of their focus on teaching and practice. Individuals who fulfill the researcher-educator model are able to pursue the scholarship of discovery because they have minimal practice expectations.

Although clinical pharmacy has established itself in academia, it is still in its infancy and there are unresolved needs. Individuals who are planning for an academic clinical pharmacy career or who are pursuing an academic position should talk with their mentors and do further reading about these needs. For example, fellowship-training programs are providing fellows with too little time devoted to development of research abilities and too much time devoted to teaching and practice.[11] It has been proposed that clinical pharmacy training programs at the Ph.D. level may better prepare clinical faculty to compete for NIH funds and to study the pharmacotherapeutic and practice issues that need to be addressed in today's healthcare environment.[12] Other needs that pharmacy schools are addressing include development of promotion and tenure guidelines that are equitable and consistent with the assigned duties or faculty model, strategies to ensure that both faculty models are equally respected and valued, and the relative proportions of each faculty model that are needed at a pharmacy school in order to achieve the institutional mission.[1,2,6,10]

Faculty Roles and Responsibilities

As noted above, a faculty member's roles and specific responsibilities are largely determined by the institution's mission and the assigned duties. Although there are differences in the percentage of time that is assigned to the areas of teaching, practice, scholarship/research, and service, all college-based faculty members are expected to demonstrate some level of scholarship.[1,9]

Because faculty members have significant autonomy in accomplishing university assignments, their responsibilities are not always clearly defined. Kennedy[13] has concluded that in accepting academic freedom, academicians must also realize their academic duty to the institution. Kennedy further vows that academic duty is accomplished by meeting a set of responsibilities. He notes that the primary responsibility of academia is to meet the needs of society since it nurtures our existence. Faculty members can help accomplish this by meeting specific responsibilities such as: 1) accomplishing all four missions/responsibilities with excellence, 2) demonstrating commitment to students by mentoring and being well-prepared for classes, 3) maintaining high standards of individual scholarship, 4) working "collegially" with other faculty members so that all academic missions are accomplished, and 5) completing all assignments ethically. It should be emphasized that collegiality requires the faculty member to be a team member by actively contributing to the departmental and school/college work and actively participating in decision-making; collegiality does not infer that the faculty member is just friendly to everyone. Kennedy also notes that academicians have a responsibility of commitment such that outside activities (e.g., consulting) do not interfere with one's responsibilities to the university.

DESCRIPTION OF ACADEMIC SITES AND SETTINGS

At the present time, there are 84 pharmacy schools in the United States and each has clinical pharmacy faculty members. Because the number of new pharmacy schools continues to increase and a number of senior faculty members are likely to retire in upcoming years, it has been predicted that we may encounter a shortage of

academic faculty members.[14,15] Since the current shortage of pharmacy practitioners is expected to continue in the foreseeable future, the need for new clinical pharmacy faculty members will likely persist.

Both public and private institutions serve as the settings for these pharmacy schools. Therefore, an individual pursuing a faculty position should learn about the characteristics of working in each of these settings. Other considerations when selecting the institutional setting for your faculty position include whether the institution has its own medical center and whether your practice will be located at a distant site away from the pharmacy school. These factors will greatly impact opportunities for research/scholarship, access to mentors, and ability to develop collegial relationships.

USUAL DEGREE, TRAINING, AND EXPERIENCE REQUIRED

Today, most academic clinical pharmacy faculty positions require a Pharm.D. degree although individuals with another advanced degree may be considered at some institutions. Completion of post-doctoral training programs such as specialized residencies and fellowships are also required. Because specialized residencies focus on development of practice skills and teaching, they can appropriately prepare an individual for a tenure-track practitioner-educator or a nontenure-track faculty position. Individuals who desire a researcher-educator faculty position should complete a fellowship that emphasizes development of research skills. Postgraduate coursework such as biostatistics and research design would also facilitate success in a researcher-educator position and a fellowship should provide opportunity to complete such coursework. Many specialized residency and fellowship training programs require completion of a general practice pharmacy residency as a prerequisite. The requirement for specialty faculty to become board certified is increasing and individuals planning to enter academic clinical pharmacy are encouraged to obtain this credential.[16]

Some individuals may elect to gain several years of experience as a practitioner before pursuing either post-doctoral training or a faculty position. Although this is not required, the experience can certainly be beneficial.

CAREER LADDER AND GROWTH

Most entry-level faculty positions involve appointments at the level of assistant professor. The successful junior faculty member usually achieves the criteria established for promotion to the level of associate professor after a period of 5–7 years.[5] At most institutions, this requires demonstration of scholarship/research and excellence in accomplishing assigned duties. Most faculty members are able to achieve the rank of full professor approximately 5–10 years after promotion to the associate professor level. Promotion to this rank usually requires development of an established scholarship/research theme and recognition by peers at a national level.[5] The American Association of Colleges of Pharmacy (AACP) surveys pharmacy schools on an annual basis about the salaries of each academic rank and publishes the results. Individuals interested in an academic career should review these data to gain insight into the financial aspects of the academic pharmacy career ladder and growth. These data are published annually and may be obtained by contacting either an AACP faculty member or the senior vice president at AACP.

Once either the associate professor or full professor rank is achieved, the academician may also opt for an academic administration career.[5] An administrative position requires an additional set of knowledge and skills that emphasize leadership and management. These attributes may be gained by pursuing postgraduate degrees and, attending workshops and/or fellowships in higher education. Most individuals begin this track by serving as a department chair or assistant/associate dean. Success in one of these positions can enable the individual to become a dean. After several years of experience in any of these positions, an individual may also pursue administrative positions in higher education that are outside of pharmacy schools.

CONCLUSIONS

Although the need for clinical pharmacy faculty members will likely continue, the transformation that is occurring in higher education will make the expectations of faculty in the future different than what they have been in the past. Individuals contemplating an academic pharmacy career must have a clear understanding about the current issues and needs in order to make informed career decisions.

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PROFESSIONAL ORGANIZATIONS

Academy of Managed Care Pharmacy

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INTRODUCTION

The Academy of Managed Care Pharmacy (AMCP)[a] was founded in 1989 as a professional society for pharmacists practicing in managed care settings and for their associates who subscribe to the principles underlying managed care pharmacy. It has grown steadily and substantially since its founding and is today's voice for managed care pharmacy.

ORGANIZATIONAL STRUCTURE AND GOVERNANCE

An nine-member Board of Directors, eight of whom are elected by the active membership, governs the Academy of Managed Care Pharmacy; the ninth member is the employed Executive Director. Thirteen committees aid the Board in its governance, with jurisdiction over various segments of the organization's activities.

Committees are comprised of member volunteers who develop policy recommendations for the Board. All policy-making authority is vested in the Board of Directors. Professional staff handles the implementation of those policies.

The Academy is comprised of over 4800 individual members nationally who are part of more than 600 healthcare organizations that provide comprehensive coverage and services to the 170 million Americans served by managed care organizations. Its active members are those pharmacists who have responsibility and accountability for the design and implementation of managed care pharmacy benefits, and those individuals who aspire to that status.

MISSION STATEMENT

The AMCP is a professional association of pharmacists and associates who serve patients and the public through the promotion of wellness and rational drug therapy by the application of managed care principles.

The mission of AMCP is to serve as an organization through which the membership pursues its common goals: to provide leadership and support for its members; to represent its members before private and public agencies and healthcare professional organizations; and to advance pharmacy practice in managed healthcare systems.

VISION STATEMENT

By 2005, the AMCP will be:

- Recognized as the primary national professional association for pharmacists and associates who practice in managed healthcare systems.
- The principal source of knowledge regarding pharmaceutical care in managed healthcare systems.
- An association whose members value and promote application and advancement of pharmaceutical care principles in managed care pharmacy.
- An effective voice for the principles and practices of managed care pharmacy.
- An effective and credible public policy advocate.

[a] The AMCP is located at 100 N. Pitt Street, Alexandria, Virginia 22314; phone: (703) 683-8416; fax: (703) 683-8417; www.AMCP.org.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006282

- Effective at maintaining a dynamic organizational structure that allows the association to meet its goals through the responsible management of human, financial, technological, and other resources.

CURRENT MAJOR INITIATIVES

- Serve AMCP's core constituency.
- Establish a model defining the role of pharmacy within managed care.
- Define the value of managed care pharmacy.
- Be public policy advocates.
- Develop a professional policy digest.
- Encourage the professional development of members; develop and improve the governance and leadership of the organization.
- Define AMCP's relationship with the pharmaceutical industry.
- Define AMCP's customers and audiences.
- Identify AMCP's leadership on quality issues.

MAJOR MEETINGS

In the spring of each year, the AMCP holds its Annual Meeting. In the fall of each year, an Educational Conference is held.

ACPE Standards 2000

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INTRODUCTION

The American Council on Pharmaceutical Education (ACPE) is the national agency for accreditation of professional degree programs in pharmacy and for approval of providers of continuing pharmaceutical education. The ACPE was established in 1932 for accreditation of preservice education. In 1975, its scope of activity was broadened to include continuing pharmaceutical education. The ACPE is an autonomous and independent agency whose Board of Directors (the decision and policy-making body) includes pharmacy educators, pharmacy practitioners, state board of pharmacy members/executives, and public representation. A public interest panel having at least two members also provides public perspectives in the policy and decision-making processes of accreditation.

ACCREDITATION

Accreditation is the public recognition accorded a professional program in pharmacy that is judged by ACPE to meet established standards through initial and subsequent periodic evaluations. The values of accreditation are several and the ACPE accreditation process serves several constituencies concurrently including the general public, students and prospective students, licensing bodies, colleges and schools of pharmacy and their parent institutions, and the profession. Graduates of accredited professional programs in pharmacy should be educationally prepared for practice and should satisfy educational requirements for licensure. However, decisions concerning eligibility for licensure reside with the respective licensing bodies in accordance with their state statutes and administrative rules and regulations.

ACCREDITATION STANDARDS

Accreditation standards reflect professional and educational qualities identified by ACPE as essential to quality professional programs of Colleges and Schools of Pharmacy and serve as the basis for program evaluation. Standards are set by the ACPE in accordance with a procedure that provides adequate time and opportunity for all parties significantly affected by the accreditation process to comment on such standards prior to their adoption. Advance notice is given whenever revision of standards is proposed by ACPE. The initial standards were published in 1937 and revisions have been effected, on the average, every seven years in keeping with changes in pharmaceutical education and practice. (The standards and guidelines in use prior to those presented herein were adopted in July 1984 and became effective in January 1985.) These standards and guidelines are presented in the *ACPE Accreditation Manual*, 9th Edition, September, 2000.

"STANDARDS 2000"

New accreditation standards and guidelines were adopted June 14, 1997. This occurred following a nearly 50-year consensus building process, often fraught with controversy. The revision process leading to *Accreditation Standards and Guidelines for the Professional Program in Pharmacy Leading to the Doctor of Pharmacy Degree* was initiated in September 1989 and conducted in accord with the *Procedure and Schedule for the Revision of Accreditation Standards and Guidelines*, issued January 7, 1990. This *Procedure and Schedule* involved a stepwise, decade-long process. The early years were devoted to study and formulation of proposed revisions and the later years provided for two comment periods, each affording open hearings and opportunities to submit written comments. Final consideration of the last iteration of proposed revisions, *Proposed Revision, January 15, 1996*, was given during the June 1997 meeting of the ACPE. The *Accreditation Standards and Guidelines for the Professional Program in Pharmacy Leading to the Doctor of Pharmacy Degree*, as adopted June 14, 1997, will be contained in the next edition of the *ACPE Accreditation Manual*. Copies of the new standards and guidelines may be obtained by writing the ACPE office (311 West Superior Street, Chicago, Illinois 60610, U.S.A.), and may be found on the ACPE web site (www.acpe-accredit.org).

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006267

"Standards 2000" reflects broad input from the profession, and sets forth expectations for quality in Doctor of Pharmacy programs offered by colleges and schools of pharmacy. It is expected that colleges and schools of pharmacy maintain a fundamental commitment to the preparation of students for the general practice of pharmacy with provision of the professional competencies necessary to the delivery of pharmaceutical care. For these purposes, pharmaceutical care is defined as the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. These outcomes are: 1) cure of a disease; 2) elimination or reduction of a patient's symptomatology; 3) arresting or slowing of a disease process; or 4) preventing a disease or symptomatology.

Pharmaceutical care involves the process through which a pharmacist cooperates with a patient and other professionals in designing, implementing, and monitoring a therapeutic plan that will produce specific therapeutic outcomes for the patient. This in turn involves three major functions: 1) identifying potential and actual drug-related problems; 2) resolving actual drug-related problems; and 3) preventing drug-related problems.

Pharmaceutical care is a necessary element of healthcare, and should be integrated with other elements. Pharmaceutical care is, however, provided for the direct benefit of the patient, and the pharmacist is responsible directly to the patient for the quality of that care. The fundamental relationship in pharmaceutical care is a mutually beneficial exchange in which the patient grants authority to the provider, and the provider gives competence and commitment (accepts responsibility) to the patient. The fundamental goals, processes, and relationships of pharmaceutical care exist regardless of practice setting.

"Standards 2000" sets forth 18 professional competencies that should be achieved through the college or school of pharmacy's curriculum. additionally, "Standards 2000":

1. Emphasizes pharmaceutical care, as considered in the professional literature and as presented in the Position Paper of the AACP Commission to Implement Change in Pharmaceutical Education, as a part of the mission statement of a college or school of pharmacy, and as an organizing principle for curricular development.
2. Reflects new competencies and outcome expectations for the preparation of a generalist practitioner, which are requisite to the rendering of pharmaceutical care in a variety of practice settings.
3. Encourages the development of non-traditional curricular pathways and innovative program delivery modes (e.g., external degrees) to address the needs of baccalaureate-degreed practitioners already in practice.
4. Encourages increased practitioner involvement in pharmaceutical education as volunteer faculty and in the affairs of colleges and schools of pharmacy.
5. Places emphasis upon the importance of developing good problem-solving, decision-making, critical-thinking, and communication skills.
6. Does not distinguish between externships and clerkships; rather, it is expected that experiential education will be incorporated as a curricular continuum throughout the professional program, as both introductory and advanced practice experiences, and that experiences will begin earlier in the educational process.
7. Increases expectations regarding quality control in the pharmacy practice experience component of the curriculum (introductory and advanced practice experiences).
8. Encourages innovation in the development and innovation of new tactics for teaching and learning, with particular emphasis upon increasing student involvement as active learners.
9. Encourages the development and implementation of new and innovative methods for student evaluation and assessment which measure learning at a variety of levels beyond the memorization and reiteration of facts.
10. Incorporates expectations that the leadership of colleges and schools of pharmacy will undergo formal evaluations in a regular and systematic manner.
11. Expects that curricular management and editing processes will strive to assure that the addition of material will be counterpoised with the elimination of outdated and/or unnecessary material, so as to avoid unnecessary and undesirable overlap.
12. Incorporates Total Quality Management (TQM) principles throughout the standards and guidelines.
13. Expects particular emphasis to be placed upon the professionalization (professional development) of students.
14. Recognizes the broad range of responsibilities of pharmacy faculty, including teaching, research and scholarly activities, professional practice, service, and administration.
15. Expects that colleges and schools will develop and utilize admission criteria, policies, and procedures that consider not only academic qualifications but also other factors which may impact upon success in the professional program (e.g., communication skills, etc.).

Adherence to Pharmaceutical Care

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INTRODUCTION

Nonadherence to medication regimens remains a major problem in health care. The National Council on Patient Information and Education (NCPIE) has termed noncompliance "America's other drug problem."[a] Pharmacists are in an ideal position to assess and treat adherence-related problems that can adversely affect patients' health outcomes. Strategies to monitor and improve adherence are key components of pharmaceutical care plans, especially for patients with chronic diseases, such as hypertension, diabetes, and atherosclerotic heart disease. Nonadherence is a behavioral disorder that can be assessed and managed through a carefully devised pharmaceutical care plan.

NONADHERENCE: DEFINITION AND SCOPE OF THE PROBLEM

Medication nonadherence is most simply defined as the number of doses not taken or taken incorrectly that jeopardizes the patient's therapeutic outcome.[2] NCPIE[1] has noted that nonadherence can take a variety of forms, including not having a prescription filled, taking an incorrect dose, taking a medication at the wrong time, forgetting to take doses, or stopping therapy too soon. In this article, we use the term "adherence" instead of compliance, because the former connotes an interactive, collaborative relationship between pharmacist and patient. Compliance originates from a practitioner-centered paradigm and is more control oriented. It relies on patient obedience and sometimes stigmatizes the patient as engaging in deviant behavior if another course of action is chosen.[3,4] A patient-centered approach is one in which the pharmacist engages patients to become more active in the continuum of decision making about their treatment and the consequent health outcomes.

Although medication nonadherence is the primary focus of this article, it is only one form of nonadherence. Poorer health outcomes may also result when a patient does not adhere to recommended lifestyle changes, such as exercise or smoking cessation, or to prescribed nonpharmacologic interventions, such as physical therapy or dietary plans. Pharmacists who counsel patients with chronic diseases, such as asthma, hypertension, or diabetes, need to assess and promote adherence to these nonpharmacologic treatments as well.

Medication nonadherence is a major public health problem that has been called an "invisible epidemic."[5,6] Nonadherence to pharmacotherapy has been reported to range from 13% to 93%, with an average rate of 40%.[7] The problem encompasses all ages and ethnic groups. It has been estimated that 43% of the general population, 55% of the elderly, and 54% of children and teenagers are nonadherent.[8] A host of individual characteristics also influence adherence, such as the patient's religion, health beliefs, social support system, and ethnicity.

Rates of nonadherence vary with different disease states. For example, the nonadherence rate for hypertension is reported to be 40%, while that for arthritis has been found to range between 55% and 70%.[9] Nonadherence rates are especially high among patients with chronic diseases.[10] These patients, who typically require long-term, if not lifelong, medications to control symptoms and prevent complications, often must make significant behavioral changes to adhere with pharmacotherapy. Such changes can be difficult to integrate into everyday life.

Nonadherence to pharmacotherapy has been shown to decrease productivity and increase disease morbidity, physician office visits, admissions to nursing homes, and

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006252

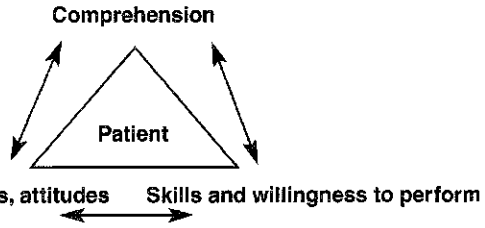

Fig. 1 Patient-centered adherence paradigm. In the patient-centered adherence paradigm, the pharmacist integrates information about a patient's medication use from three perspectives: the patient's knowledge of the medication (comprehension); the patient's beliefs and attitudes toward his or her illness and its treatment (beliefs, values, and attitudes); and the patient's ability and motivation to follow the regimen (skills and willingness to perform).

death.[1,9,11] For example, an estimated 125,000 deaths per year have been attributed to nonadherence to treatment for cardiovascular disease.[11] Many studies have documented poorer health outcomes due to nonadherence, especially in patients with chronic diseases such as hypertension, diabetes, and epilepsy.[5,6,12,13]

Finally, nonadherence places a huge burden on the United States' economy. Its direct and indirect costs have been estimated to be $100 billion per year in this country alone.[12] Pharmacies also lose revenue because patients often fail to refill prescription medications, especially for chronic diseases.[14] According to The Task Force for Compliance,[9] only 25% of prescriptions for chronic conditions are refilled after 1 year.

For pharmacists, the message is clear: To improve adherence to pharmacotherapy, and hence to improve health outcomes, we must assess each patient individually, then provide targeted interventions that are responsive to his or her unique risk factors and needs (see Fig. 1). Research, such as the American Pharmaceutical Association Foundation's Project ImPACT: Hyperlipidemia,[15] has clearly documented the value of pharmacist-led patient care in fostering better adherence and outcomes.

NONADHERENCE AS A BEHAVIORAL DISORDER

Nonadherence has been studied widely by behavioral scientists whose models, such as the Health Belief Model and the Theory of Reasoned Action, attempt to explain and predict nonadherence.[16] However, despite the numerous articles that have been published on this topic, nonadherence remains a problem of epidemic proportions. An alternative model that can be useful for understanding and treating nonadherence is to view the problem as a disorder—a behavioral disorder.[3] Although not a true physiological disease, nonadherence shares many of the same characteristics as a medical disorder. For example:

- *Numerous risk factors for nonadherence have been identified.* Clearly, nonadherence is a multifactorial problem, and a host of contributing social, economic, medical, and behavioral factors have been identified.[5,6,9,17–19] As shown in Table 1, some risk factors for nonadherence relate to the disease (e.g., a chronic or asymptomatic illness), others relate to the patient (forgetfulness, sensory impairment, and economic problems), and still others relate to the drug regimen (concerns about cost, real or perceived adverse effects, or dosing schedule).
- *Nonadherence can be assessed and monitored.* A variety of direct and indirect methods are available to assess the presence and severity of nonadherence. As pharmacotherapy specialists, pharmacists may be the best suited of health providers to evaluate adherence problems on an ongoing basis.
- *Effective interventions are available to treat nonadherence.* Many cases of nonadherence can be treated with carefully selected interventions. However, other cases may not be resolvable, despite the best efforts of health care providers.[5]
- *Nonadherence frequently leads to increased morbidity and mortality.* Just as untreated medical disorders often progress to serious complications, nonadherence has a well-documented adverse impact on health outcomes.[17,20,21]
- *Nonadherence tends to have a variable course.* Nonadherence is not a stable condition, but tends to progress or change over time in a given patient.[7] Just as most chronic medical conditions require periodic reevaluation and therapeutic adjustments, patients with adherence problems should also be reassessed on a regular basis.

Table 1 Major risk factors for nonadherence

Asymptomatic conditions
Chronic conditions
Cognitive impairments, especially forgetfulness
Complex regimens
Multiple daily doses
Patient fears and concerns related to medication effects
Poor communication between patients and practitioners
Psychiatric illness

ASSESSING ADHERENCE

Before effective strategies can be devised to improve adherence, pharmacists need to evaluate how well a patient is adhering to pharmacotherapy and identify risk factors that may predispose the individual to nonadherence. Both direct and indirect methods are available to assess adherence.

Direct Methods

Direct and objective methods of assessing adherence include blood-level monitoring and urine assay for the measurement of drug metabolites or marker compounds. Collecting blood or urine samples can be expensive and inconvenient for patients and, moreover, only a limited number of drugs can be monitored in this way. The bioavailability and completeness of absorption of various drugs, as well as the rate of metabolism and excretion, are factors that make it difficult to correlate drug levels in blood or urine with adherence. The ability of direct methods to identify nonadherence also depends on the accuracy of the test and the degree to which the patient was nonadherent before the urine or blood sample was taken.

Indirect Methods

Indirect methods of assessing adherence include patient interviews, pill counts, refill records, and measurement of health outcomes. In one study, the use of patient interviews identified 80% of nonadherent patients, as verified by pill counts.[22] The interview method is inexpensive and allows the pharmacist to show concern for the patient and provide immediate feedback. A drawback of this method is that it can overestimate adherence, and its accuracy depends on the patient's cognitive abilities and the honesty of their replies, as well as the interviewer's correct interpretation of responses. Pill counts provide an objective measure of the quantity of drug taken over a given time period. However, this method is time consuming and assumes that medication not in the container was consumed. The refill record provides an objective measure of quantities obtained at given intervals, but assumes that the patient obtained the medication only from the recorded source.

Pharmacists can generally obtain reliable information on medication-taking behaviors from the patient or a family member or caregiver. The interview should be systematic and include specific questions on forgetfulness, the patient's understanding of medication instructions, and the conditions for which therapy has been prescribed. The patient's health beliefs and the degree of support available from friends and family should also be assessed.[4]

Interviewing patients to detect nonadherence is most effective when indirect probes are used. For instance, the probe "Most people have trouble remembering to take their medications. Do you have any trouble remembering to take yours?" will solicit more reliable information than asking: "Are you taking your medications as prescribed?" Table 2 gives examples of specific probes that the pharmacist can use to assess whether a patient has been or is likely to be adherent.

Table 2 Probes pharmacists can use to assess adherence

Assessing the patient's medication knowledge or medication-taking behavior
What is the reason you are taking this drug?
How do you take this medication?
Are you taking the medication with food or fluid?
Where did you receive information about this medication?
Are you taking nonprescription drugs while on this medication?
Do you use any memory aids to help you remember to take your medication?
Do you depend on anyone to help you remember to take your medication or to assist you in taking it?
Assessing attitudes, values, and beliefs regarding medication-taking behaviors
What results do you expect to receive from this medication?
What are the chief problems that you feel your illness has caused you?
Do you have any concerns about your illness and its treatment?
Are you satisfied with your current treatment plan?
How well do you usually follow a treatment plan?
What is the main concern you have about your medication?
Do you feel comfortable asking your physician or pharmacist questions about your medications?
Assessing whether the patient has the proper skills and is motivated or willing to follow through on the therapy plan
Have you encountered any problems with your medication- or pill-taking procedure?
Are you confident that you can follow your treatment plan?
What might prevent you from following the recommended treatment plan?
How likely is it that you will ask your physician or pharmacist about your medications?
Can you explain how you remind yourself to take your medication on schedule?
Do you normally write down questions to ask your physician or pharmacist before an appointment?

Pharmacy computerized prescription records provide perhaps the most practical and least intrusive method for assessing adherence. This method allows the pharmacist to review and monitor prescription records to determine whether the patient is refilling medications in a timely manner. Computer algorithms can be incorporated into the pharmacy computer software system as a tool for monitoring adherence and measuring the timeliness of prescription refills.[23] This method also has the potential to flag potential adherence problems that may develop over the course of several refills. One disadvantage of this method is that it does not assess actual medication-taking behaviors (e.g., this method would not detect a patient who was swallowing a sublingual tablet or improperly inhaling an asthma medication from a metered-dose inhaler).

Factors that have a negative or positive influence on medication adherence are shown in Table 3. This table may be used both to identify factors that contribute to nonadherence and to develop interventions to address adherence problems.

Table 3 Factors that affect medication adherence

Factors that promote adherence
Disease-related factors
Perceived or actual severity of illness
Perceived susceptibility to the disease or developing complications
Treatment-related factors
Perceived benefits of therapy
Written and verbal instructions
Convenience of treatment
Medication provides symptomatic relief
Patient-related factors
Good communication and satisfactory relationship with physician
Participation in devising the treatment plan
Confidence in the physician, the diagnosis, and the treatment
Support of family members and friends
Knowledge about the illness
Factors that reduce adherence
Disease-related factors
Chronic disease
Lack of symptoms
Treatment-related factors
Treatment requires significant behavioral changes
Actual or perceived unpleasant side effects
Regimen complexity and duration
Medication takes time to take effect
Patient-related factors
Sensory or cognitive impairments
Physical disability or lack of mobility
Lack of social support
Educational deficiencies (literacy problem or poor English fluency)
Failure to recognize the need for medication
Health is a low priority
Conflicting health beliefs
Economic problems
Negative expectations or attitudes toward treatment

From Refs. [3,56–58].

DESIGNING PATIENT-FOCUSED INTERVENTIONS FOR NONADHERENCE

Strategies to improve adherence should target the specific risk factors and causes identified during the patient assessment. Adherence aids may be used alone or in combination, but should be tailored to the individual patient. For example, a forgetful patient may benefit from a special package or container that provides a visual reminder that a medication was taken (e.g., blister packaging or a computer-aided compliance package). Forgetful patients also can be advised to take dosages in conjunction with other routine daily activities, such as at mealtimes or before tooth brushing. Refill reminders or automatic delivery to the home can also be valuable for the forgetful patient, as can simplification of the dosage schedule, such as changing to a once-daily prescription.

Once the initial adherence plan is implemented, follow-up is important to gauge how well the plan is working and whether changes are needed. Most studies have reported that almost all adherence strategies, regardless of their initial acceptability, will decline in responsiveness over time.[7] Therefore, the pharmaceutical care plan must include periodic reinforcement strategies for long-term success. The plan should also be reevaluated from time to time to assess its effectiveness and determine how well it meets patient expectations.

Identifying and measuring the outcomes of a pharmaceutical care adherence plan is also important. Objective measures of improved health status and/or reduced health care expenditures document success in a well-designed pharmaceutical care plan. Examples of measurable outcomes include a reduction in inappropriate use of the health care system (e.g., fewer emergency department visits for asthma exacerbations) or improved control of the patient's disease (e.g., HbA_{1c} levels below 7% in a patient with type 2 diabetes).

The results of Project ImPACT: Hyperlipidemia demonstrate that a pharmacist-oriented program to improve adherence can dramatically improve health out-

comes.[15] Project ImPACT, which stands for *Im*prove *P*ersistence *A*nd *C*ompliance with *T*herapy, was conducted in 26 community-based ambulatory care pharmacies in 12 states. The program's objective was to demonstrate that pharmacists, working collaboratively with patients and physicians, could improve patients' adherence to prescribed therapy for dyslipidemia and help them achieve their National Cholesterol Education Program (NCEP) goals.

Remarkably, over an average of 24.6 months, 93.6% of Project ImPACT patients adhered to their prescribed therapy and 90.1% persisted with therapy through the study's end.[15] Among patients with existing coronary artery disease, 48% attained their NCEP goal, far better than in any previously published national study of patients with hyperlipidemia. The authors stated that collaboration between pharmacists, patients, and physicians, using pharmacy-based testing for blood lipids and pharmacist-led counseling, could reduce the risk of heart disease and stroke by one-third.

STRATEGIES FOR ENHANCING ADHERENCE TO PHARMACOTHERAPY

Although pharmaceutical care plans should be individualized, some adherence-promoting strategies tend to be helpful in the majority of patients. Whenever possible, the pharmacist should strive to

- *Promote self-efficacy.* Encourage patients to assume an active role in their own treatment plans. In general, the more confident people feel about their ability to manage a problem, the more likely they will be to take positive action to solve that problem. Involving patients in decisions about their care is important for promoting self-efficacy. For example, a study by Nessman and colleagues[24] showed that patients with hypertension who were highly involved in decisions about their therapy and trained to take their own blood pressure had significantly better health outcomes than patients who did not have these characteristics. The authors attributed the improved outcomes to the patients' ability to make choices about health care decisions and follow through on a monitoring plan.
- *Empower patients to become informed medication consumers.* A pharmaceutical care plan to enhance adherence should first focus on educating the patient and family members or caregivers about the patient's disease and medications. Pharmacists should provide both written and oral information to address such basic questions as: What is the disease? Which treatments have been prescribed or recommended and why? What is the patient's role in managing the disease? Which adverse effects may occur? Perhaps surprisingly, the amount of factual information that a patient has about his or her medication is *not* highly correlated with adherent behavior.[7] Instead, the patient's functional knowledge—that is, information that is directly useful and meaningful to the patient—and clear instructions for medication use are more significant.[25] Opportunities to impart functional knowledge begin with the physician and/or nurse at the time of the initial prescription, and should be reinforced by the pharmacist when the prescription is filled or refilled.
- *Avoid fear tactics.* Scaring patients or giving them dire warnings about the consequences of less-than-perfect adherence can backfire and may actually worsen adherence.[26] A more constructive approach is to help the patient focus on ways to integrate medication taking into their daily routine.[27]
- *Help the patient to develop a list of short- and long-term goals.* These goals should be realistic, achievable, and individualized. The pharmacist can also make "contractual" agreements with the patient to encourage development of constructive behaviors, such as getting more exercise or beginning a smoking cessation program.
- *Plan for regular follow-up.* The pharmacist should plan to interact with the patient at regular, usually brief intervals to reinforce the adherence plan. For example, brief appointments can be scheduled when patients visit the pharmacy for prescription refills. The plan should be adapted to the patient's lifestyle and be reevaluated from time to time to adjust for life changes, such as aging or a change in work or school schedules. If possible, the time for counseling on adherence should be separated from the dispensing and pick-up functions.
- *Implement a reward system.* Giving prescription coupons or specific product discounts for successfully reaching a goal in the treatment plan can help to increase adherence, particularly in patients with low motivation.

Considerations for Special Populations

Although the problem of nonadherence affects all ethnic and age groups, some populations are more vulnerable than others. Pharmacists should be especially alert for adherence problems in high-risk populations, such as the

Table 4 Resources for improving patient adherence

Organizations

National Council on Patient Information and Education (NCPIE)
4915 Saint Elmo Ave., Suite 505
Bethesda, MD 20814-6053
301-656-8653
www.talkaboutrx.org
Among other resources, NCPIE publishes "Prescription Medicines and You: A Consumer Guide," a large print brochure available in English, Spanish, and Asian languages.

United States Pharmacopeia (USP)
12601 Twinbrook Parkway
Rockville, MD 20852
800-822-8772
www.usp.org
USP's many resources include "MedCoach" patient information leaflets, which are available at two reading levels and may contain pictograms.

Resources for Special Populations

For low literacy patients

Responding to the Challenge of Health Literacy. The Pfizer Journal. Spring 1998;2(1):1-37.
Available from: Impact Communications, Inc.
330 Madison Avenue, 21st Floor
New York, NY 10017
212-490-2300

For older adults

The ElderCare Patient Education Series
The Peter Lamy Center for Drug Therapy and Aging
University of Maryland School of Pharmacy
506 West Fayette Street, Suite 101
Baltimore, MD 21201
http://gerontology.umaryland.edu/docs/lamy.html
e-mail: lamycenter@rx.umaryland.edu

For children

The Pediatric Medication Text
(Patient information for 200 commonly prescribed pediatric medications; available in English and Spanish)
American College of Clinical Pharmacy
3101 Broadway, Suite 380
Kansas City, MO 64111
816-531-2177, ext. 20
www.accp.com/ped_medtxt.html

For ethnic minorities

Closing-the-Gap.com
This online magazine provides resources for health care providers and consumers to promote minority health through culturally relevant care.

elderly, children, low-literacy individuals, and some ethnic minorities. Table 4 provides resources that can aid pharmacists in improving adherence in these high-risk groups.

The elderly

Although older Americans (ages 65 and older) account for less than 15% of the population, they consume about 33% of all prescription medications and 40% of nonprescription drugs.[28] Poor adherence in the elderly often leads to additional physician or emergency department visits, hospitalization, and uncontrolled chronic diseases. One study estimated that about 17% of elderly hospitalizations are due to adverse medication reactions—nearly six times the rate in the nonelderly population.[29]

A variety of often-interacting risk factors increase the risk of nonadherence among the elderly. Risk factors in this population include

- *Polypharmacy.* Elderly patients are more likely to take multiple medications, including both prescription and nonprescription products. Whenever possible, the medication regimen should be simplified. The pharmacist also should consider the extent to which the mode of drug delivery (e.g., pill, patch, or inhaler) may influence adherence.
- *Physical impairments.* Age-related physical disabilities, such as difficulty getting out of bed or a chair, may limit an elderly person's ability to take medication consistently. Traditional packaging of medication also may be an impediment to some elderly patients; for example, individuals with arthritis in their hands may have trouble opening containers. For these patients, consider options such as use of unit-of-use packaging, unit-dose packing, or blister packaging. The pharmacy environment should also be friendly to senior citizens. For example, elderly patients with hearing problems may need a quiet place to receive patient counseling so as not to be distracted by ambient noise. Written materials should be available in large type (14-point font size) for people with vision problems.[30]
- *Cognitive limitations.* Memory loss and other cognitive problems may interfere with adherence by causing patients to fail to understand or remember medication instructions.[30] For these patients, pharmacists may need to provide medication instructions several times and in different formats, such as both verbal and written information.
- *Limited access to or affordability of health care services.* Many elderly patients are on fixed incomes. A study conducted by the consumer advocacy group Families USA reported that over the past 5 years, the prices for the 50 prescription drugs most commonly used by the elderly have increased faster than inflation.[31] Elderly patients who are unable to afford

certain medications may be eligible for various forms of state or federal aid, or special discounts from pharmaceutical manufacturers.

Pharmacists should also consider how an elderly patient's relationship with other health care providers might influence adherence. For example, research shows that the elderly tend to favor partnership-type relationships with their physicians and that satisfying patient–provider relationships contribute to better adherence.[32] However, with the growing number of managed care and group practices, these relationships are often more difficult to develop. A good pharmaceutical care plan can help elderly patients relate more effectively with primary care providers by helping these patients understand the nature of their diseases and how to better communicate their needs to physicians.

The role of a patient's caregivers in helping or hindering medication adherence also should be considered. A motivated and well-informed caregiver can be essential for optimizing adherence in an elderly patient. However, caregivers can sometimes hinder adherence efforts. For example, a caregiver who is having trouble coping with an elderly patient's behavioral or cognitive problems may demand medications to sedate the patient. Pharmacists who serve communities with a large elderly population may want to hold special classes to teach caregivers about medication management, addressing topics such as medication administration and how to monitor and report adverse effects.

Low-literacy patients

Patients who read poorly or not at all are at high risk for poor adherence. According to the U.S. Department of Education National Adult Literacy Survey,[33] 40 million people in the United States are functionally illiterate and another 55 million are only marginally literate. Patients with low literacy skills are less likely to be adherent to their medication regimens and appointments, or to present for care early in the course of their disease.[34]

Inadequate health literacy skills have been shown to adversely affect the management of a number of chronic diseases, including diabetes and hypertension. For example, in a study of hospitalized patients, 49% of patients with hypertension and 44% of those with diabetes were found to have inadequate health literacy.[35] In that study, as many as 50% of patients did not understand how many times a prescription should be refilled. After examining a standard appointment slip, up to 33% could not describe when a follow-up appointment was scheduled, and as many as 50% could not determine whether they were eligible for financial assistance based on their income and number of children.[35]

People with low health literacy may not understand the health risks associated with errors in medication management. Shame or embarrassment about their low literacy may deter them from seeking help with medication instructions. Pharmacists can assess health literacy using nonobtrusive screening tests such as the Test of Functional Health Literacy in Adults (TOFHLA), which is available in English and Spanish versions.[36] This test includes items that assess the patient's ability to understand labeled prescription vials, blood glucose test results, clinic appointment slips, and financial information forms.

On a more practical level, pharmacists also should strive to provide patient educational materials that are written at a low literacy level. The National Work Group on Literacy and Health[37] recommends that materials should be at the fifth-grade level or lower, yet most patient education materials are written at the eleventh-grade level. Patient education materials should be short, simple, and contain culturally sensitive graphics. Easy-to-read written materials should be combined with verbal instructions, which ideally should be repeated on several different occasions to reinforce patient understanding. Involving family members in the patient education process also can promote adherence.

Many literacy organizations recommend that pictograms and warning stickers be affixed to prescription bottles and nonprescription product packages. A detailed list of pictograms and a summary of research on their usefulness for low-literacy populations are available from the United States Pharmacopeia (USP) at www.usp.org. In addition, multimedia computer-based educational programs are available that permit patients to choose to see or hear information about their particular medical condition.

Ethnic minorities

An extensive literature documents persistent differences in health outcomes between ethnic minorities and white Americans. These disparities include differences in health care access and utilization as well as health status and outcomes. Wolinsky[38] showed that differences in access and use of health services by various ethnic groups stems in part from their varying cultural traditions. Pharmacists can assist in closing this gap in health outcomes by providing culturally sensitive patient care. Information about patients' cultural health care beliefs and practices is essential for devising interven-

tions to improve adherence. To provide care that is responsive to cultural differences, pharmacists should strive to develop the following three skills:[37]

- *Communicate information that is both accurate and understandable to the patient.* This skill involves the use of interviewing techniques to assess the patient's literacy level, possible language barriers, and cultural health beliefs. Insufficient English language skills are a major barrier for some minority patients. Depending on the pharmacy's location and clientele, Spanish or other foreign language versions of patient education materials may be necessary.
- *Openly discuss racial or ethnic differences.* A patient's cultural health beliefs can contribute greatly to adherence problems. For example, a patient may believe that the body needs periodic rests from medications during long-term therapy or that daily medication use is dangerous because it can lead to addiction. Getting to know the patient and their beliefs requires time, but it fosters the development of a trusting relationship. The pharmacist should try to ascertain the answers to the following questions: Does the patient understand their diagnosis and the purpose of the medication? How do the patient's cultural health beliefs influence their understanding of the illness? Is the patient using any other therapies, such as complementary or alternative medicine, in addition to prescription medications? Does the patient have any religious beliefs that might affect the decision to adhere to the treatment plan?
- *Use community and other resources on behalf of the patient.*[37] A disproportionate number of patients in some minority groups have limited incomes, which can be a major barrier to obtaining medications. Patients with low or fixed incomes who do not qualify for medicare and medicaid often have difficulty in securing the appropriate supply of their medications. A number of programs are in place to provide free medication and counseling for low-income patients. For example, the volunteer-managed Crisis Control Pharmacy in North Carolina provides free medications that range from one-time-only prescriptions to long-term maintenance therapy. Each patient is evaluated on the basis of their financial need. Another example is the Medical Access Program (MAP), offered by the University of Georgia College of Pharmacy through the Carlos and Marguerite Mason Trust. The mission of MAP, which serves an ethnically diverse low-income population, is to increase medication access for organ transplant patients who live in Georgia.[39]

Children

With a growing number of prescription drugs being developed and marketed specifically for children and adolescents, nonadherence is becoming a significant problem in the pediatric population. According to NCPIE,[40] only one-third of children take medications as prescribed or recommended by physicians. In a study by Bush et al.[43] one-third of the children in grades 3 to 7 reported they had used one or more prescription or nonprescription medications in a 48-hour period. Another study of children 9 to 16 years old, who were attending summer camp, revealed that almost one-half had brought and used a supply of medications, many without the knowledge of camp personnel.[42] Adherence plans for children often require innovative approaches to teach them how to use their medications appropriately and to encourage active participation in caring for their own health.

The literature offers a number of recommendations that can help pharmacists to improve adherence in children. Some suggestions are as follows:

- *Teach children early in life to assume some responsibility for taking their medications.* According to the Children's Health Belief model developed by Bush and Ianotti,[43] children formulate health beliefs and expectations about medication use early in their development. The authors recommend that children, especially those with chronic illnesses, assume some responsibility at an early age for taking their medications. Young children who are taught to use medications wisely may be less likely in later life to engage in high-risk behaviors such as illicit drug use or medication abuse.[44] Such children may also be more discerning about the quality of information they receive about medications from their peers, and from television and other media.
- *Educate the parents, too—particularly the mother.* In young children, most risk factors for nonadherence reside in the parent. In most cultures, the mother plays an extremely important role in supervising the care of a sick child. For example, even though young children may have an aversion to the "bad taste" of the drug, they usually take their medications because their mothers tell them it is necessary to feel better. Research shows that children internalize parental beliefs, which greatly influence their attitudes and behaviors toward health problems as they mature into adults.[41]
- *Adapt the educational program to the child's cognitive level and stage of development.* Education should be based on the child's maturity and ability to grasp

essential concepts about the disease and medication. According to one study, physicians and pharmacists rarely talked with children about medications, yet most children wanted to know about their medicines and would ask their physicians or pharmacist if they could.[41] Children as young as 5 years of age knew there was a difference between medications for children versus those for adults.[41] They could grasp the concept that medications for adults would be "too powerful for a little body." Older children perceived the risk for adverse reactions better than the younger children did. Older children also could understand the "cost–benefit" of getting well despite the need to take a bad-tasting medicine. These children wanted to have more personal control and independence in making decisions about their medication use. Finally, although most children did not know how medications worked, they were very much interested in this topic.

Bush and her colleagues[45] developed a cognitive developmental model for educating children about medications that is based on Piaget's cognitive development theory. This model recommends teaching children about the therapeutic purpose of their medications and that medications can be both helpful and harmful (i.e., good drugs versus bad drugs, or poisons). For younger children, learning activities should be interactive and fun. For older children, education should correct earlier misconceptions and naive theories about medications that may have been learned earlier in their development. Older children may enjoy learning about medications through the use of computer games, videos, and reading materials.

- *Relate the need for medications to a child's past experiences with the illness.* For example, if child is being recalcitrant about receiving immunization against influenza, the pharmacist might use a probe such as, "Do you remember the yucky flu you had last year? Would you like to avoid that this year?" This approach can help the child remember previous bouts of the flu as an awful-feeling illness. The child then can understand the need to prevent the illness by receiving the flu vaccination.

Specific guidelines for developing interventions to address adherence problems in children can be found in the USP's *Ten Guiding Principles for Teaching Children and Adolescents about Medicines*. These principles were developed on recommendations from more than 100 health care professionals, educators, and consumer representatives who attended the USP's fall 1996 open conference, *Children and Medicines: Information Isn't Just for Grownups*. The proceedings of this conference and the recommendations can be accessed at www.usp.org/information/programs/children/principles.htm.

PATIENT-CENTERED ADHERENCE MANAGEMENT FOR CHRONIC DISEASES

Each chronic disease presents its own constellation of adherence problems. A brief overview of adherence strategies for two major public health problems—hypertension and type 2 diabetes—illustrates disease-specific risk factors for nonadherence and shows how pharmaceutical care services can enhance adherence.

Hypertension

Because hypertension is usually a silent disease, most patients do not experience symptoms that remind them of the need for taking medications. Without symptoms, it is more difficult to establish a link in the patient's mind between taking the medication and controlling hypertension and its complications. Because patients often do not feel or perceive the benefits of their treatment, the first step in enhancing adherence is to educate them about hypertension and its serious complications, such as coronary heart disease, stroke, and renal failure.

Pharmacists who want to maximize adherence to pharmaceutical care programs for hypertension should first read the *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*.[46] This report encourages a greater interdisciplinary role for pharmacists in monitoring medication use and providing patient information. Adherence to therapy is a key consideration for reaching the 2010 national goals for blood pressure control.[46] Only one-half of patients with hypertension still take their medications after the first year of treatment, and one-third of them do not take enough medications to keep their blood pressure under control.[7]

The primary goals of a pharmaceutical care plan for hypertension are to improve patient adherence, decrease the risk of developing complications, and reduce the cost of unnecessary emergency department visits and hospital stays. Simplified dosage regimens, such as once- or twice-daily dosing, have been shown to enhance adherence in hypertensive patients. In one study, adherence rates were 73% and 70% for once-or twice-daily regimens, respectively, versus 52% and 42% for three- and four-times-a-day regimens.[47] Improving adherence is particularly important with the newer regimens, because drug concentrations may be subtherapeutic when dosing delays or omissions occur.[48] Common adverse effects of antihy-

pertensive therapy, such as fatigue, impotence, and lightheadedness, also can adversely affect adherence.

Patients may need advice on how to incorporate medications and other antihypertensive treatments, such as exercise recommendations, into their daily activities and lifestyles. One useful strategy is to help patients establish cues that will serve as reminders to take medication, such as after breakfast, after brushing teeth, or just before bed.

As with other chronic diseases, education of caregivers and family members is crucial. In one study, 70% of patients wanted their family members to know more about hypertension. The patients reported that negative attitudes, insufficient family support, and lack of confidence in the management of their blood pressure were contributing factors to their long-term adherence problems.[49] Whenever possible, a family member or caregiver should be included in educational sessions to help the patient follow instructions and stay on track over time.

Social or group support can also help to boost the patient's confidence and sense of self-efficacy. Group social support may be available from a patient advocacy organization, such as a local chapter of the American Heart Association.

To promote adherence to long-term therapeutic interventions, the pharmacist and patient may agree on a "contract" that includes a series of mutually agreed-upon and realistic health goals. Once a target goal has been achieved, the pharmacist can provide the patient with a reward, such as a discount on a prescription, a coupon for store merchandise, or a colorful certificate announcing successful goal attainment. Rewards should be carefully staged so they serve as motivators and are not so ostentatious as to overpower the effect of personal satisfaction from a job well done. The pharmacist and patient also can collaboratively develop periodic reports about the patient's progress for the primary care physician.

The pharmaceutical care plan should include outcome measures to gauge the success of adherence strategies for hypertensive patients. Outcomes might include refill patterns for patients taking long-term medications and periodic measurement of blood pressure control over time. Quality-of-life measurements and patient satisfaction surveys are also appropriate outcome measures. The former are useful to monitor the progress or potential complications in patients receiving lifelong therapy for asymptomatic diseases such as hypertension.[50]

Type 2 Diabetes

Type 2 diabetes is reaching epidemic proportions in the United States, largely because of rising rates of obesity, physical inactivity, and an aging population. Studies have conclusively demonstrated that the complications of type 2 diabetes can be greatly reduced or delayed by intensive medical management.[51] However, it is estimated that only 7% of patients with diabetes adhere fully to all aspects of their regimen.[52] Adherence rates for insulin-injection regimens range from 20% to 80%, adherence to dietary recommendations is about 65%, and adherence to exercise regimens varies from 19% to 30%. Glucose-monitoring adherence rates range from 57% to 70%.[52]

Hsiao and Salmon[53] reported that patients' beliefs about the benefits of diabetes therapy are important in determining whether they obtain and use medication. In general, the more severe the patient's disease and the greater the perceived susceptibility to complications, the more likely the patient is to be adherent. Patients must be convinced of the seriousness of their disease and empowered to monitor themselves for diabetic complications. Patients with diabetes who were at high risk for nonadherence included older people, men, and those with low socioeconomic status.[53]

Pharmacist-led programs can be extremely effective in improving adherence to diabetes care, as two independent pharmacies in Richmond, VA, recently demonstrated in a year-long program. During the first 6 months of the program, enrolled patients experienced an average decrease in their morning glucose values from 178.6 mg/dL to 159.3 mg/dL.[54] Remarkably, over the 12-month study period, participants had an average adherence rate of 90% for their use of diabetes medications.

To help the pharmacists identify medication problems, a prescription record review was performed 6 months after the start of the study. In addition, a computerized "diabetes checklist" was generated and given to each patient to complete at every prescription refill. Along with other information, the checklist asked about any medication-related problems the patient had experienced since the last refill and assessed the patient's pattern of blood glucose self-monitoring. The program also included a systematic review of appropriate medication dosages, potential drug or disease interactions, and potential adverse drug reactions.

At each refill visit, the pharmacist reviewed the plan with the patient and provided reminders about the need for other preventive care, such as yearly eye exams and proper foot care. When appropriate, the physician was contacted, with the patient's consent, regarding specific treatment recommendations. In summary, this diabetes monitoring program showed the value of combining multiple interventions to improve adherence and outcomes.

TIME AND MONEY: PRACTICAL ASPECTS OF ADHERENCE SERVICES

Payment for Adherence Services

Considering that pharmacies lose nearly $8 billion yearly from unrefilled prescriptions, improving adherence is well worth the effort.[14] Huffman and Jackson[55] estimated that by increasing the number of refills by only 10%, a pharmacy could increase its annual sales by $55,000 and net profit by more than $8000. Adherence screening, monitoring, and implementation of interventions also take time, and pharmacists may seek compensation for the hours they spend in those activities. Third-party payers have begun to realize the value of adherence management, and some payers may be willing to pay for adherence-related services. Patients also may be willing to pay out of pocket for these services. To increase the likelihood of reimbursement, pharmacists should be sure to document their adherence-related activities, such as patient assessment, education, and counseling.

Pharmacists also can benefit from building professional relationships with a core network of physicians who can refer patients to the pharmacy for adherence-related services. Reimbursement for cognitive services or disease state management programs is often tied to provider referrals. Providers usually make referrals to other specialists based on trust and their expertise and professional competence. A physician is more likely to refer a patient to a pharmacy when they have confidence in the content of the services and the competence of the pharmacist administering the therapeutic plan. Accountability (i.e., having the name of an individual, rather than an organization, responsible for the services rendered) is also important.

Space Considerations

Assessment of and counseling on adherence is best done face to face. The use of a special counseling area is recommended, especially when counseling requires more time or privacy. Although extensive renovation of the pharmacy is usually not needed, the environment should be conductive to open communication, with enough privacy for patients to feel free to discuss personal matters.

Environmental barriers, such as a desk or prescription counter, may pose a physical barrier to communication and should be avoided, if possible. Adequate privacy is also important, especially when patients are discussing sensitive medical matters and others could overhear. Ideally, the counseling area should be free of distractions, such as ringing telephones or other conversations. The counseling area should have enough space for the pharmacist to demonstrate the use of medications or devices, to write instructions, and to store written materials for distribution. A chair should also be available for patients to sit during counseling sessions.

Making Time for Adherence Services

It can be challenging for pharmacists to find ways to incorporate adherence screening and monitoring into their current organizational structures. Use of pharmacy technicians to perform routine dispensing duties can free time for the pharmacist to provide cognitive services, such as assessment and counseling. Innovative scheduling methods may also free up time for patient education and counseling. For example, there may be a brief overlap of pharmacist coverage during the times immediately before and after work shifts. Another strategy is to schedule patient appointments during times when the pharmacy workload is lighter.

SUMMARY

Adherence to pharmacotherapy is essential to optimal therapeutic outcomes. The pivotal role of the pharmacist in optimizing adherence encompasses many actions: assessing the adherence problem, identifying predisposing factors, providing comprehensive counseling, and recommending specific adherence strategies targeted to the patient's needs. Patients who have chronic conditions, physical or cognitive impairments, or cultural backgrounds outside the mainstream may have special needs that should be addressed in the adherence plan. Pharmaceutical care plans also should take into account the patient's age, stage of life, and literacy level. Although a wide range of adherence aids and strategies are available, the key to success is to tailor the intervention to the individual patient and, when necessary, to combine interventions to optimize adherence.

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Adverse Drug Reactions

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INTRODUCTION

Adverse drug reactions (ADRs) are types of adverse drug events (ADEs) (1). ADEs include ADRs, medication errors, and other drug-related problems. ADEs are the negative consequences of drug misadventures. Henri Manasse defined drug misadventure as the iatrogenic hazard that is an inherent risk when drug therapy is indicated. This chapter will focus on ADRs.

DEFINITIONS

The World Health Organization's (WHO) and Karch and Lasagna's definitions of an ADR are quite similar. An ADR is any response to a drug that is noxious and unintended, and occurs at doses used for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose (2). The Food and Drug Administration (FDA) focuses on ADRs that have unexpected reactions and/or those of more significant morbidity. These ADRs would include those where the patient outcome is death, life-threatening, hospitalization, disability, congenital anomaly, or required intervention to prevent permanent impairment or damage (3). The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) is concerned with the reporting of significant ADRs. Those that result in morbidity, require additional treatment, require an increased length of stay, temporarily or permanently cause disability, or cause death must be reported to the FDA (4). The American Society of Health-System Pharmacists (ASHP) defines significant ADRs as any unexpected, unintended, undesired, or excessive response to a drug that includes the following:

- Requires discontinuing the drug
- Requires changing the drug therapy
- Requires modifying the dose
- Necessitates admission to the hospital
- Prolongs stay in a health care facility
- Necessitates supportive treatment
- Significantly complicates diagnosis
- Negatively affects prognosis or results in temporary or permanent harm, disability, or death (5)

The ASHP definition does not include reactions due to drug withdrawal, drug abuse, poisoning, or drug complications.

Other terms that may be included as ADRs are side effects, drug intolerance, idiosyncratic reactions, toxic reactions, allergic reactions, or hypersensitivity reactions (6). *Side effects* are reactions that are unintended and unwanted but are known pharmacologic effects of the drug and occur with predictable frequency. *Drug intolerance* is a mild reaction to a drug that results in little or no change in patient management. *Idiosyncratic reaction* is an unexpected response that occurs with usual dose of a drug. *Toxic reaction* is a predictable response that results from greater than recommended drug dosages or drug concentration in the body. *Allergic or hypersensitivity reaction* is an unusual sensitivity to a drug of an immunologic nature.

CLASSIFICATION SYSTEMS

Four classification systems are used to describe ADRs (1, 7). ADRs can be classified according to thepharmacologic effect of the drug—Type A, B, C, and D reactions. Type A reactions are exaggerated but normal pharmacologic actions of a drug. They are predictable and dose dependent. Type B reactions are not predictable given the known pharmacologic action of a drug and are not dose related. Many of these Type B reactions are hypersensitivity or immune-based. These reactions can be further subdivided into type I (IgE-mediated reaction), II(IgG or IgM-mediated cytotoxic reaction), III (IgG-mediated immune complex reactions), and IV (cell-mediated immune reaction). Type C reactions are those due to long-term use of a drug. Type D reactions are delayed drug effects, such as due to carcinogenicity or teratogenicity.

ADRs can also be classified according to the dose relationship, i.e., dose-related and non-dose-related reactions. Another classification system is based on the causal relationship between the reaction and the drug. One of the

DOI: 10.1081/E-ECP 120006420

most widely used causality classifications is based on Naranjo's descriptions. These categories include definite (drug is likely the true cause), probable (drug is the apparent cause), possible (drug appears to be associated), and remote (drug is not likely to be the cause). The fourth classification system is based on degree of injury or severity of reaction. There are mild reactions (temporary discomfort and tolerable), moderate (significant discomfort), and severe (potentially life threatening or causing permanent disability or death).

INCIDENCE

The frequency of ADRs in the general population is unknown. However, the reported rates of new occurrences for ADRs are noted for selected patient populations. A meta-analysis of 39 prospective studies reported an overall incidence of serious ADRs in hospitalized patients of 6.7% and of fatal ADRs of 0.32% (8). The fatality rate makes ADRs the fourth to sixth leading cause of death in the United States. Another meta-analysis of 36 studies indicated that approximately 5% of hospital admissions are due to ADRs (9). The costs of ADRs are estimated to be $1.56–$4 billion in direct hospital costs per year in the United States (10).

FACTORS PREDISPOSING TO ADRS

Two major factors predispose to adverse drug reactions: the drug itself and patient factors. Factors related to the drug include its dose, dosage form and delivery system, and interactions between drugs. Patient-related factors include age, disease states, genetics, gender, nutrition, multidrug therapy use, and use of herbal therapies.

Drug-Related Factors

Dose

ADRs may be the result of ingestion of increased amounts of a drug. Dosing issues are especially likely with narrow therapeutic index drugs. Examples of these types of drugs include digoxin, anticoagulants, anticonvulsants, antiarrhythmics, antineoplastic agents, bronchodilators, sedatives, and hypnotics (11).

Dosage form and delivery system

Many of the ADRs related to the dosage form and delivery system are the result of local irritation or hypersensitivity reactions (12). Local irritation to the gastrointestinal (GI) tract can occur with oral dosages. For example, toxicity resulting in mouth ulcerations is associated with antineoplastic drugs. In addition, the use of certain formulations, such as sustained release preparations, can increase esophageal injury if esophageal transit is delayed. For example, a controlled release wax matrix of potassium chloride has been associated with significant esophageal erosions. Factors identified to predispose to esophageal injury include large film-coated tablets, capsules, large sustained-release preparations, rapidly dissolving formulations, and ingestion of solid oral dosage forms before bed rest with very little water intake (12).

Localized tissue irritation can be seen from the intramuscular (IM) route. This is especially an issue when the formulation pH differs from the pH of the surrounding tissue or when precipitation of poorly soluble drugs occurs (12). Incorrect administration of IM injections is probably the most important factor that causes local adverse effects. Local skin irritation can also be seen with transdermal delivery systems due to the alcohols, nonionic surfactants, and adhesives.

Hypersensitivity reactions can occur due to the presence of contaminants or excipients in pharmaceutical dosage forms (e.g., outbreaks of eosinophilia-myalgia syndrome associated with oral tryptophan contaminants in various drugs) (12). Another example is the anaphylactoid reactions to the surfactant Cremaophor EL, which is used in paclitaxel (Taxol).

Direct toxicity effects related to use of preservatives also has been documented. For example, severe metabolic acidosis and death in infants was attributed to the presence of benzyl alcohol, a preservative used in bacterostatic normal saline that was used to flush catheters (12).

The use of specific intravenous (IV) delivery devices also can cause ADRs. For instance, use of plastic infusion sets for IV administration of nitroglycerin has resulted in subtherapeutic effects due to diffusion of the drug into the plastic tubes (12).

Formulation effects, such as bioavailability differences, can cause ADRs when patients are switched to generic products. For example, significant adverse effects have occurred with anticonvulsants and thyroid preparations (12).

Interactions between drugs

It has been estimated that 6.9% of ADRs are due to drug–drug interactions (6). The most likely reason for an adverse drug interaction is the pharmacokinetic changes that result in altered metabolism or excretion of drugs, or the

pharmacodynamic changes that result in synergistic or additive effects of drugs.

Patient-Related Factors

Age, disease states, genetics, gender, nutrition, multidrug therapy use, and herbal therapies use are patient-related factors that influence the likelihood of adverse drug reactions.

Age—geriatrics

Age-related alterations in pharmacokinetics and pharmacodynamics may affect the response of elderly patients to certain medications, and may increase the susceptibility for ADRs among elderly patients (13–15) (Table 1). The risk of ADRs among elderly patients is probably not due to age alone. ADRs may be related more to the degree of frailty and medical conditions of the patient (15). On average, older persons have five or more coexisting diseases that may increase the risk of adverse events. Polypharmacy seems to be more of a common problem among the elderly. The average elderly patient takes 4.5 chronic medications and fills 13 prescriptions yearly (15). Elderly patients appear to have a decline in homeostatic mechanisms. The imbalance of homeostatic mechanisms and the decline in function reserves may put a patient at greater risk for ADEs due to decreased tolerance of medications and the ability to handle stressful situations (16).

Age—pediatrics

The two factors responsible for increasing risks of ADRs in children are pharmacokinetic changes and dose delivery issues. Age-related differences in pharmacokinetics in children are documented (17). However, the data on both efficacy and safety are often limited or not studied at all in this population. Thus, it is unclear whether an increased risk for ADRs exists in this group. However, there is a potential risk for increased ADRs if appropriate considerations are not taken into account in view of pharmacokinetic changes (18).

It is important to note that only one-fourth of the drugs approved by the FDA have indications specific for use in a pediatric population (17). Medications used in adults are often given to children without FDA safety and efficacy data. Compatibility and stability issues with dosage forms intended for adults that have been altered (e.g., dilution or reformulation) can increase risks for ADRs.

Information on pediatric age-related difference in neonates, children, and adolescents may aid in prevention of pediatric ADRs (18) (Table 2). Further studies of drug use in pediatrics are needed in order to prevent ADRs.

Concurrent diseases

Diseases such as hepatic or renal diseases can influence the incidence of ADRs by altering the pharmacokinetics of drugs, such as absorption, distribution, metabolism, or excretion (6).

Hepatic disease

Patients with liver disease have an increased susceptibility to certain drugs due to decreased hepatic clearance for drugs metabolized by the liver or due to enhanced sensitivity (6). For example, impaired hepatic metabolism can precipitate central nervous system (CNS) toxicity in patients on theophylline, phenytoin, or lidocaine; or ergot poisoning on ergotamine (19).

Increased sensitivity to drugs is also encountered in liver disease(19). The use of anticoagulants increases the risk of bleeding due to the reduced absorption of vitamin K or decreased production of vitamin K-dependent clotting factors. There is an enhanced risk for respiratory depression and hepatic encephalopathy due to morphine

Table 1 Geriatric age-related changes in pharmacokinetics

Pharmacokinetic phase	Pharmacokinetic parameters
Gastrointestinal absorption	Unchanged passive diffusion and no change in bioavailability for most drugs
	↓ Active transport and ↑ bioavailability for some drugs
	↓ First-pass effect and ↑ bioavailability
Distribution	↓ Volume of distribution and ↑ concentration of water soluble drugs
	↑ Volume of distribution and ↑ half-life for fat soluble drugs
	↑ or ↓ free fraction of highly plasma protein-bound drugs
	↓ Clearance and ↑ half-life for some Phase I
Oxidation drugs	↓ Clearance and ↑ half-life of drugs with high extraction ratio
Renal excretion	↓ Clearance and ↑ half-life of renally eliminated drugs

↓ = Decreased; ↑ = Increased.

Table 2 Pediatric age-related risk factors and causes of ADRs

Neonates:
Placental transfer of drug before birth
Differing drug action
Altered pharmacokinetics
Increased percutaneous absorption
Decreased renal/hepatic function
Decreased plasma protein binding
Use of multiple drugs
Limited information on drug action in critically ill and premature neonates
Children:
Paradoxical effect of medications (excitability rather than sedation from antihistamines)
Excipients of liquid dosage forms
Sugar as sweeteners
Propylene glycol as solvent
Large volume intravenous solutions
Treatment of viral infections with antibiotics
Disruption of neurologic and somatic development
Adolescents:
Autonomy seeking
Use and misuse of devices (e.g., tampons)
Use and misuse of prescription and nonprescription medications
Poor compliance with instructions
Use of multiple medications
Recreational use of alcohol and illicit drugs
Effects of changing hormone levels on drugs

(From Ref. 7.)

or barbiturates in patients with severe liver disease. Vigorous use of diuretics can precipitate hepatic coma due to potassium loss in liver disease. There is an increased risk of hypoglycemia with sulphonylurea antidiabetic drugs due to decreased glycogenesis in liver disease.

Liver disease can also cause hypoalbuminemia due to decreased liver synthesis of albumin. For drugs that are extensively bound to albumin, such as phenytoin, an enhanced risk of drug toxicity could occur because of the increase in free drug concentration.

There are no useful methods to quantify the degree of liver disease that can assist in dosage adjustment. A practical approach involves checking patients for elevated prothrombin time, rising bilirubin levels, and/or falling albumin levels. In such instances, drugs that have an altered response in liver disease or cause hepatotoxicity need to be avoided.

Renal disease

Impaired renal function increases the incidence of ADRs for drugs that depend on the kidney for their elimination. Unlike liver disease, use of pharmacokinetic dosing principles can minimize the risk for adverse effects.

Mechanisms responsible for enhanced ADRs in renal disease include delayed drug excretion, decreased protein binding due to hypoalbuminemia, and increased drug sensitivity (6). Delayed renal excretion is responsible for enhanced toxicity with drugs such as aminoglycosides, digoxin, vancomycin, chlorpropamide, H2-antagonists, allopurinol, lithium, insulin, and methotrexate (20). For some drugs, the accumulation of a toxic metabolite during renal failure is responsible for ADRs. This is the case with meperidine, where a toxic metabolite, normeperidine, accumulates in renal failure (20).

Patients with accumulation of uremic toxins have increased sensitivity to certain drugs. There may be an enhanced response to CNS depressants (such as barbiturates and benzodiazepines), hemorrhagic effects from aspirin or warfarin, and other bleeding effects from antibiotics that inhibit platelet aggregation, such as carbenicillin, ticarcillin, and piperacillin.

Other diseases

On theoretical grounds, other diseases associated with hypoalbuminemia could predispose patients to adverse reactions and to altered responses to drugs that are highly protein bound (21) (Table 3).

The presence of other diseases can influence the risk for ADRs. Many of these adverse effects are related to an extension of the pharmacologic effects of the drug in the presence of certain pathophysiology. Numerous examples are given in Table 4 (6).

Patients who have had a previous reaction to drugs are also more likely to experience an ADR (22). Patients with history of allergic diseases also have an increased risk due to a genetically related ability to form immunoglobulin E.

Genetic factors

Genetic factors account for some ADRs due to either altered pharmacokinetics or by altering tissue responsiveness. Altered metabolism of drugs occurs due to

Table 3 Conditions associated with hypoalbuminemia

Aging	Liver disease
Burns	Nephrotic syndrome
Cancer	Nutritional deficiency
Cardiac failure	Pregnancy
Protein-losing enteropathy	Renal failure
Inflammatory diseases	Sepsis
Injury	Stress
Immobilization	Surgery

Table 4 Influence of diseases on adverse drug reactions

Disease	Drug	Adverse reactions
Gastrointestinal		
Peptic ulcer	Aspirin, corticosteroids, nonsteroidal antiinflammatory drugs	Risk of bleeding or perforation of ulcer
Cardiovascular		
Heart failure	β-Blockers	Aggravate or precipitate heart failure
	Lidocaine, theophylline	Enhanced toxicity—seizures
Myocardial ischemia	Tricyclic antidepressants	Disturbances of cardiac rate, rhythm, and conduction
	Digoxin	Arrhythmias
Bradycardia	β-Blockers	Cardiac standstill
	Quinidine	
Hypertension	Oral contraceptives, vasoconstrictors	Increased blood pressure
	Phenothiazines, nitrates	Decreased blood pressure
	Tricyclic antidepressants	
Hematologic		
Bleeding disorders—hemophilia	Aspirin	Increased risk of hemorrhage
Neurological disorders		
Myasthenia gravis	Aminoglycosides	Aggravate muscle weakness
	Quinidine, quinine	Paralysis
Epilepsy	Phenothiazines	Lower seizure threshold
	Tricyclic antidepressants	
Cerebrovascular	Ergotamine	Ischemic episodes
Rheumatic		
Systemic lupus	Drugs	Increased incidence of drug reactions in general
Hyperuricemia	Thiazide diuretics, furosemide	Gouty attack
Respiratory		
Asthma	β-Blockers	Acute bronchospasms
Respiratory insufficiency	Narcotic analgesics	Hypoventilation, respiratory arrest
Endocrine disorders		
Diabetes mellitus	Thiazide diuretics, furosemide, corticosteroids, oral contraceptives	Hyperglycemia; aggravates diabetic control
Hypothyroidism	Digoxin	Enhanced response
Hyperthyroidism	Oral anticoagulants	Enhanced response
	Digoxin	Decreased response
Ocular		
Narrow-angle glaucoma	Anticholinergics	Glaucoma attack

differences in hydrolysis, acetylation, and hepatic oxidation of drugs. Altered pharmacodynamic reactions could be either an exaggerated response or a qualitative response. These types of reactions are unpredictable. Examples of altered drug response due to genetic factors are found in Table 5 (6).

Gender

A higher incidence of ADRs has been reported for women in comparison to men (6). One reason for this observation is that women take more drugs than men. Yet, no sex-linked differences in drug pharmacokinetics have been documented. Other reports have not supported a higher incidence of ADRs in women as compared to men. Thus, sex alone is unlikely to be a major determinant of ADRs.

Nutrition

Nutritional factors are also responsible for ADRs. These factors include the interaction of drugs and nutrients, and altered pharmacokinetics related to nutritional status.

One study reported a very low incidence (0.4%) of clinically significant drug–nutrient interactions in a teaching hospital (23). Three mechanisms postulated for drug–nutrient interactions are interference with drug absorption, alteration of drug excretion, and affecting drug activity. For example, the absorption of tetracycline is reduced by chelation with iron, calcium, and magnesium. Foods that acidify or alkalinize the urine can affect drug excretion. Foods that contain a large amount of vitamin K can inhibit the activity of warfarin. A listing of important drug–nutrient interactions is found in Table 6 (23). A review article on drug–food interactions in clinical practice is found in Ref. 24.

Drug–nutrient interactions may be more highly significant in renal failure patients. A review article of drug–nutrient interactions in renal failure has been published (25).

Nutritional status can affect drug pharmacokinetics. Malnutrition states can cause the following: 1) the liver and kidneys changes affect drug elimination; 2) GI system changes affect drug absorption; 3) changes in the heart affect blood flow; 4) hormone changes affect metabolic enzymes and drug binding proteins; 5) plasma, tissue proteins, and body composition changes affect protein binding and elimination; 6) mineral and electrolyte changes affect drug metabolism and protein binding; and 7) tissue changes affect uptake of drugs and drug–receptor interactions (26).

Multidrug use

According to several epidemiological studies, multiple drug use has a strong association in the causality of ADRs. It has been suggested that the more medications used, the higher the risk for ADRs (27). Consistent drug regimen reviews by healthcare providers in order to reduce polypharmacy may decrease the risk of ADRs.

Herbal therapies use

The use of herbal therapies increased dramatically during the 1990s. Herbal therapy sales are estimated to be $4 billion a year, with sales increasing at 20% per year since the early 1990s (28). Patients often mistakenly believe that since these products are natural, they do not possess the potential harm as in prescription medications. Since herbal medications are sold and marketed without stringent FDA approval and guidelines, limited evidence-based data on efficacy, adverse effects, and drug interactions exist. Recently, two review articles examined available data on ADRs for the most common herbal medications (28, 29). Many of these available reports fall short on documentation of temporal relationship with the specific ADR and the herbal drug.

For most conditions, herbal products are not a replacement for proven prescription or nonprescription drugs. Patients should be aware that health care practitioners cannot guarantee the safety and consistency of herbal products. Patients should start with the recommended effective doses and report any unusual side effects to their health care practitioner. Patients should always consult with their pharmacist for possible drug–herbal interactions. Side effects and possible drug interactions for the ten most commonly used herbals are listed in Table 7.

ADVERSE DRUG REACTION REPORTING SYSTEMS

The WHO, the FDA, the JCAHO, and the Health Care Financing Administration (HCFA) have all addressed and mandated the need for health care institutions to implement an ADE detection and reporting system. Detection systems are instrumental in postmarketing surveillance of ADRs. The JCAHO requires all accredited health care institutions to have an ongoing drug surveillance program (4). The goals of ADR detecting and reporting systems are to aid in postmarketing surveillance of FDA approved medications and to identify ways to decrease ADR risks. The main focus of all of these reporting systems is to aid in promoting improvements in the medication use process.

Table 5 Genetic factors and altered drug responses

Genetic mechanism	Drug(s)	Adverse drug response
Pharmacokinetic		
Low plasma pseudocholinesterase	Succinylcholine	Prolonged neuromuscular blockade leading to apnea
Slow acetylator	Isoniazid	Increased incidence of peripheral neuropathy; SLE-like syndrome; and more prone to phenytoin toxicity
	Hydralazine, procainamide	Increased incidence of SLE-like syndrome
	Phenelzine, sulfasalazine	More prone to side effects
Rapid acetylator	Isoniazid	More prone to hepatitis
Deficiency of epoxide hydrolase	Phenytoin, carbamazepine, phenobarbital	Life threatening hypersensitivity syndrome due to accumulation of toxic intermediates
Pharmacodynamic		
Glucose 6-phosphate dehydrogenase deficiency (G-6-PD)	Aspirin, BAL (dimercaprol), chloroquine, chloramphenicol, dapsone hydroxychloroquine, nalidixic acid, nitrofurantoin, primaquine, probenecid, quinine, quinidine, sulfonamides	Hemolytic anemia
Methemoglobin reductase deficiency	Acetaminophen, anesthetics, topical, benzocaine, chloroquine, dapsone, nitrites, primaquine, sulfonamides	Methemoglobinemia
Abnormality of calcium regulation	Anesthetics, general, (halothane), muscle relaxants (succinylcholine)	Malignant hyperpyrexia

Table 6 Important drug-nutrient interactions

Drug	Nutrient	Interaction
Phenytoin	Alcohol	Enhanced metabolism of phenytoin
	Enteral feedings	Decreased phenytoin absorption
Tetracycline	Dairy products	Impaired drug absorption
Theophylline	Caffeine	Potential for toxic effects
Warfarin	Foods high in vitamin K	Decreases anticoagulant response
Chlorpropamide, tolbutamide, tolazamide, acetohexamide, metronidazole	Alcohol	Disulfiram-like reaction
Trancylcypromide	Foods high in tyramine	Hypertensive crisis
Disulfiram	Alcohol	Nausea, blurred vision, chest pain, dizziness, fainting
Spironolactone	Foods high in potassium	Hyperkalemia

(Adapted from Ref. 23.)

ADR Screening Methods

The best methodology for screening for ADRs has not been determined. However, several screening methods have been proposed. In particular, the literature has highlighted five screening methods using clinical data (30–34). The five include screening for: 1) "tracer drugs," e.g., antidotes such as vitamin K and diphenhydramine; 2) "narrow therapeutic range drugs," e.g., follow-up of computer lab values for warfarin and digoxin; 3) change in medications, e.g., documentation of discontinued medications or decreased dose; 4) diagnosed ADRs documented in the medical record, e.g., chart review or reviewing ICD-9 CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes; and 5) ADR computer report tracking systems. Although each of these ADR screening methods has been described in detail, limited data are available on the productivity of these screens.

Systems for Pharmaco-epidemiologic Studies

Pharmacoepidemiology is used to detect ADRs (35, 36). Several types of systems use pharmacoepidemiologic methods. These include spontaneous reporting, studies of therapeutic classes, and studies of specific medical syndromes.

Spontaneous reporting

Spontaneous reporting is currently the major backbone for the detection of ADRs (37). It occurs in one of three ways:

1. Reporting to the FDA as part of clinical trials;
2. Reporting by practitioners to medical journals; or
3. Patients' self-reporting to either manufacturers or the FDA (38).

Clinical trials in new drug development cannot detect all the possibilities for drug safety. Limitations in Phase III clinical trials include a relatively small sample size, short duration of the trial, restricted populations (e.g., geriatrics and pediatrics), uncomplicated patients, (e.g., limited disease states), and limited power for adverse drug reaction detection (30). Thus, the FDA relies heavily on spontaneous reporting of suspected ADRs (39). Spontaneous reporting is important in early market history of the drug to determine previously unidentified drug reactions. This has been particularly true in the last few years because of numerous new medications that have entered the market and now carry a black box warning. For example, Rezulin® and Trovan® are associated with hepatotoxicity and carry black box warnings.

Additional advantages of spontaneous reporting systems include the detection of extremely rare ADRs and ability to identify at-risk subgroups. In order to enhance the spontaneous reporting system approach, the FDA developed the MedWatch form. This form can be faxed to the agency (1-800-FDA-1078) or called in (1-800-FDA-1088) (40). The forms also can be obtained by the "MedWatch Online" internet-based website (http://www.fda.gov/medwatch/).

Limitations of FDA spontaneous reporting include both under-reporting and over-reporting.

An example of over-reporting occurs with recently approved drugs. This is partly due to enhanced publicity about these drugs.

Table 7 ADRs for the top ten herbal medicines

Herbal	Common use	Side effects and interactions
Echinacea	Treatment and prevention of upper respiratory infections, common cold	Rash, pruritis, dizziness, unclear long-term effects on the immune system.
St. John's wort	Mild to moderate depression	Gastrointestinal upset, photo-sensitivity. Mild serotonin syndrome with the following medications: paroxetine, trazodone, sertraline, and nefazodone. May decrease digoxin levels. May decrease cyclosporine serum concentrations. Combined oral contraceptives—breakthrough bleeding.
Gingko biloba	Dementia	Mild gastrointestinal distress, headache, may affect warfarin (increase INR). Interaction with aspirin (spontaneous hyphema)
Garlic	Hypertension, hypercholesterolemia	Gastrointestinal upset, gas, reflux, nausea, allergic reactions, and antiplatelet effects. May effect warfarin (increase INR)
Saw palmetto	Benign prostatic hyperplasia	Uncommon
Ginseng	General health promotion, sexual function, athletic ability, energy, fertility	High doses may cause diarrhea, hypertension, insomnia, nervousness, may affect warfarin (decreased INR)
Goldenseal	Upper respiratory infections, common cold	Diarrhea, hypertension, vasoconstriction
Aloe	Topical application for dermatitis, herpes, wound healing, and psoriasis, orally for constipation	May delay wound healing after topical application. Diarrhea, and hypokalemia with oral use
Siberian ginseng	Similar to ginseng	May raise digoxin levels. May affect warfarin (increased INR)
Valerian	Insomnia, anxiety	Fatigue, tremor, headache, paradoxical insomnia (not advised with other sedative-hypnotics)

Studies of therapeutic classes

Observational cohort or case control designs have been used to determine ADR relationships with specific therapeutic classes (36, 41). Medical claims data are often used in these studies and caution should be warranted due to lack of definite confirmation of drug exposure and the potential for confounding variables (38). However, these studies have been beneficial in determining risk of ADRs with specific classes (e.g., NSAIDs and the risk of peptic ulcer disease) (42).

Studies of specific medical syndromes

Observational cohort or case control designs can also be useful to study possible causality relationships of specific medical conditions or syndromes due to drug exposure (36, 41). These types of studies have been particularly useful in examining ADRs in a specific population, such as geriatric or pediatric patients. These groups of patients are often excluded in Phase III trials. However, a disadvantage of these studies is that they also often use administrative data. These data can warrant risk of problems in determining causality due to potential confounding variables (38).

Assessing Adverse Drug Reactions

After detection of a possible ADE, causality assessment needs to be performed. It is important to be able to rank the likelihood of an ADR as unlikely, possible, probable, or definite. A major problem with determining causality is that confounding variables can contribute to the complexity of causality assessment (43). In order to determine causality, several important points of data are required. These include the nature of the adverse event, name of the putative drug, other potential causes, and the temporal relationship

Table 8 ADR Naranjo causality algorithm

	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	
5. Are there alternative causes (other than drug) that could on their own caused this reaction?	−1	+2	0	
6. Did the reaction reappear when a placebo was given?	−1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score	

Probability category scores: Definite ≥ 9; Probable 5–8; Possible 1–4; Doubtful ≤ 0.

between the drug and adverse event. Potential causes are obtained by examining the medical history, physical examination findings, and directed diagnostic tests.

Identification of causality can be performed simply by using a health care provider's clinical reasoning and judgment. The main disadvantage to this approach is a low inter-rater and intra-rater agreement for ADR causality (44, 45).

An ADR causality algorithm addresses the issue of inter-rater and intra-rater reliability with a series of clinical questions. For example, the Naranjo algorithm consists of a series of clinical questions that focus on temporal and dose–response relationships, consistency of the ADR with previous clinical reports or patient experiences, placebo response, drug dechallenge and rechallenge, toxic blood drug concentrations, alternative causes of the reaction, and whether the event was confirmed by objective evidence (44) (Table 8). Numerous health care institutions and the FDA use some type of causality algorithm to minimize disagreement among different evaluators and improve inter-rater and intra-rate agreement.

PREVENTING ADVERSE DRUG REACTIONS

ADRs are problematic in that they cause significant morbidity and mortality. Almost 95% of ADRs are Type A (predictable) reactions, and thus with quality improvement measures, ADRs can be avoided and prevented (46). Knowledge of causative factors and an increase in patient education may help prevent ADRs. Improvements in the documentation of allergic reactions (e.g., via computer tracking), development of tools to enhance compliance, and application of tools to improve prescribing and administration of drugs are other preventative approaches to ADRs.

In 1994, the ASHP, the American Medical Association (AMA), and the American Nurses Association (ANA) generated the following system of recommendations to prevent ADRs in health care systems:

1. Health care systems should establish processes in which prescribers enter medication orders directly into computer systems.
2. Health care systems should evaluate the use of machine-readable coding (e.g., bar coding) in their medication use processes.
3. Health care systems should develop better systems for monitoring and reporting adverse drug events.
4. Health care systems should use unit dose medication distribution and pharmacy-based intravenous medication admixture systems.
5. Health care systems should assign pharmacists to work in patient care areas in direct collaboration with prescribers and those administering medications.

6. Health care systems should approach medication errors as system failures and seek system solutions in preventing them.
7. Health care systems should ensure that medication orders are routinely reviewed by the pharmacist before first doses and should ensure that prescribers, pharmacists, nurses, and other workers seek resolution whenever there is any question of safety with respect to medication use (47).

SUMMARY

Adverse drug reactions are of significant concern in the pharmaceutical technology arena. Various drug and patient factors that predispose to ADRs have been identified. Reporting systems used to screen and assess ADRs facilitate the understanding of risk factors and contribute to the development of systematic improvement in the prevention of ADRs.

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Agency for Healthcare Research and Quality

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INTRODUCTION

As early as 1965, when Medicare and Medicaid became law, it was recognized that research and evaluation would be necessary to guide the progress of these programs. Because Medicare and Medicaid were born as amendments to the Social Security Act, the Office of Research in the Social Security Administration provided modest support for research to address important issues. Under the rubric "health services research" the effort was expanded, first as the National Center for Health Services Research (NCHSR), and later as the Agency for Healthcare Policy and Research (AHCPR). The legislature that established AHCPR described its mission as:

> The purpose of the Agency is to enhance the quality, appropriateness, and effectiveness of healthcare services, and access to such services, through the establishment of a broad base of scientific research and through the promotion of improvements in clinical practice and in the organization, financing, and delivery of healthcare services.[1]

In 1999 the name was changed to the Agency for Healthcare Research and Quality, removing the word "policy" from the name. The new name clarified the mission of AHRQ by indicating it is to conduct and disseminate research that may be used by policymakers, but does not itself determine Federal healthcare policies and regulations. It is a scientific research organization; it is not a policy-setting organization. Further, adding the word "quality" to the name established that AHRQ is the lead federal agency on quality of healthcare research. This responsibility includes coordinating all federal quality improvement efforts and health services.

MISSION

The agency supports, conducts, and disseminates research that improves access to care and outcomes of care, as well as the cost, quality, and utilization of healthcare services. Succinctly stated, AHRQ's mandate is to sponsor research that provides better information and enables better decisions about healthcare. In order to accomplish this mission, the agency has three strategic goals:[2]

1. Support improvements in health outcomes.
2. Strengthen quality measurement and improvement.
3. Identify strategies to improve access, foster appropriate use, and reduce unnecessary expenditures.

These goals are pursued and measured using the following definitions:

Health outcomes research examines the end results of the structures and processes employed in delivery of care. An important consideration in this research is the patient's perspective, as well as the public and private-sector policymakers who are concerned with the impact of their investment in healthcare.

Quality measurement and improvement requires developing and testing quality measures and investigating the best ways to collect, compare, and communicate these data so they are useful to decision makers. AHRQ's research emphasizes studies of the most effective ways to implement these measures and strategies in order to improve patient safety and healthcare quality.

Improving access, fostering appropriate use, and reducing unnecessary expenditures continues to be a challenge for the poor, the uninsured, minority groups, rural and inner city residents, and other priority populations. The agency supports studies of access, healthcare utilization, and expenditures to identify whether particular approaches to healthcare delivery and payment alter behaviors in ways that promote access and/or economize on healthcare resource use.

Four specific areas of research were mandated by Congress in 1999 and have been adopted by AHRQ as

DOI: 10.1081/E-ECP 120006178

current research priorities. Research grants or contracts awarded to investigators in the foreseeable future will likely fall within these areas.[3]

Improve the Quality of Healthcare

AHRQ is to coordinate, conduct, and support research, demonstrations, and evaluations related to the measurement and improvement of healthcare quality. AHRQ is also to disseminate scientific findings about what works best and facilitate public access to information on the quality of, and consumer satisfaction with, healthcare.

Promote Safety and Reduce Medical Errors

AHRQ will develop research and build partnerships with heath care practitioners and healthcare systems, and establish a permanent program of Centers for Education and Research in Therapeutics (CERTs). These initiatives will help address concerns raised in a 1999 report by the Institute of Medicine (IOM) that estimates as many as 98,000 patients die as a result of medical errors in hospitals each year.[4]

Advance the Use of Information Technology for Coordinating Patient Care and Conducting Quality and Outcomes Research

AHRQ will promote the use of information systems to develop and disseminate performance measures, create effective linkages between health information sources to enhance healthcare delivery and coordinate evidence-based healthcare services, and promote protection of individually identifiable patient information used in health services research and healthcare quality improvement.

Establish an Office of Priority Populations

The needs of low-income groups, minorities, women, children, the elderly, and individuals with special healthcare needs will be addressed through the agency's intramural and extramural research portfolio.

SPECIAL INITIATIVES

AHRQ has several initiatives that should be of particular interest to the clinical pharmacy community. These include the Centers for Education and Research in Therapeutics (CERTs), the Evidence Based Practice Centers (EPCs), National Guidelines Clearinghouse (NGC), and a coordinated set of activities with the goal of Translating Research Into Practice (TRIP).

Centers for Education and Research in Therapeutics (CERTs)

In 1994 Woosley raised concern about the quality and quantity of prescription drug information available to physicians and other practitioners.[5] He contrasted the billions of dollars available from commercial interests to promote prescribing and use of (primarily new) drugs, with the limited funds available to help practitioners select cost-effective therapeuties. What was missing was a balance between commercially driven information and nonproprietary information, a vacuum that Woosley proposed would be filled by CERTs. The conceptual basis for CERTs was that of an academic entity capable of striking a balance between the relative abundance of pharmaceutical industry-generated information, and the relative paucity of NIH- or FDA-generated information available to practitioners.

Congress recognized the importance of the CERTs concept and directed the formation of the CERTs in Section 409 of the Food and Drug Modernization Act (FDAMA) of 1997 and authorized AHRQ to establish CERTs as a demonstration effort. Congress intended CERTs to have a dual mission of conducting essential research not otherwise performed by the pharmaceutical industry, and to communicate to practitioners information concerning the most effective, safest, and least-expensive therapies. Each Center was to have a focus based upon a therapeutic area of interest and a defined population, leading to a national network with complementary resources and interests.

In October, 1999 AHRQ awarded funds to four CERTs, and soon followed with awards for three additional CERTs. The seven CERTs and their areas of interest are:

Duke University	Improving Prescribing for Cardiovascular Illness
Georgetown University	Preventing Drug–Drug Interactions in Women
Harvard University	Demonstration of Implementation of Improved Prescribing Practices in an Integrated Network of HMOs
University of Alabama at Birmingham	Improving Drug Therapy for Musculo-skeletal Disorders
University of North Carolina at Chapel Hill	Rational Drug Therapy for the Pediatric Population
University of Pennsylvania	Applying Pharmaco-epidemiological Methods to Improved Prescribing
Vanderbilt University	Comparison of Therapeutic Effectiveness of Selected Drugs in the TennCare System

The CERTs legislation has been transferred from FDAMA to AHRQ, and is now a permanently authorized program. The CERTs network is expected to expand, both through addition of new Centers as well as establishment of collaborations with investigators and practitioners throughout the country. Additional information is available at http://www.certs.hhs.gov.

Evidence-Based Practice Centers (EPCs)

The philosophy of evidence-based practice is widely accepted, although operational and implementation issues represent major barriers. One of the significant barriers is a shortage of evidence reports on topics of critical interest, and the lack of a national infrastructure to prepare such reports. In response to this need, AHRQ has funded 12 Evidence-based Practice Centers to conduct systematic, comprehensive analyses and syntheses of the scientific literature to develop evidence reports and technology assessments on clinical topics that are common, expensive, and present challenges to decision makers. Since December 1998, 11 evidence reports have been released on topics that include sleep apnea, traumatic brain injury, alcohol dependence, cervical cytology, urinary tract infection, depression, dysphasia, sinusitis, stable angina, testosterone suppression, and attention deficit hyperactivity disorder.

Pharmacotherapy is a significant interest within the EPCs, and AHRQ welcomes partners such as specialty societies and health systems to submit topics for evidence reports, participate with the EPC's in preparing reports, and most importantly to use the findings of EPC's to develop tools and materials that will improve the quality of care.

National Guidelines Clearinghouse (NGC)

Developed in partnership with the American Medical Association and the American Association of Health Plans, the NGC is a Web-based resource for information on evidence-based clinical practice guidelines. The NGC began providing online access to guidelines at http://www.guideline.gov in 1998. Since becoming fully operational, the site receives over 100,000 visits each month. The site provides information to help healthcare professionals and health system leaders select appropriate treatment recommendations by providing full text or an abstract of the recommendations, by comparing and evaluating different recommendations, and by describing how they were developed. Because almost all guidelines include some consideration of pharmacotherapy, and the NGP should be regarded as an invaluable resource to clinical practitioners, clinical investigators, educators, and others from the pharmacy community.

Translating Research Into Practice (TRIP)

One of the most pressing challenges in healthcare is to apply the knowledge that is currently available; in other words, to close the gap between knowledge and practice. The first round of TRIP initiatives supported development and implementation of evidence-based tools into diverse healthcare settings. Translational efforts included cost-effective approaches to implement smoking cessation, chlamydia screening of adolescents, diabetes care in medically underserved areas, and treatment of respiratory distress syndrome in preterm infants. The second round of TRIP initiatives (funded in 2000) focused on continued development of partnerships between researcher and healthcare systems and organizations (e.g., integrated health service delivery systems, academic health systems, purchaser groups, managed care programs including health maintenance organizations, practice networks, worksite clinics) to help accelerate and magnify the impact of practice-based, patient outcome research in applied settings.

Databases

AHRQ achieves its mission through a combination of efforts, described as a "research pipeline." This pipeline of activities builds the infrastructure, tools, and knowledge for improvements in the American healthcare system. An important part of that pipeline for pharmacy is the maintenance of public use databases that can help identify problems and formulate solutions to improve pharmacotherapy. One database of particular interest is the Medical Expenditure Panel Survey (MEPS) which provides up-to-date, highly detailed information on how Americans as a group, as well as segments of the population, use and pay for healthcare. This ongoing survey of about 10,000 households and 24,000 individuals also studies insurance coverage and other factors related to access to healthcare. AHRQ encourages investigators to write applications that analyze the MEPS data.

CONCLUSION

Today's AHRQ has an annual budget of $270 million for fiscal year 2001, with approximately 80% awarded as grants and contracts to researchers at universities and other institutions across the country. The remaining 20% is allocated to intramural research and administrative support. The agency is administratively located within the

Department of Health and Human Services (HHS), where it reports to the Secretary of HHS through the Undersecretary for Health. Virtually every topic of interest to AHRQ has a pharmacotherapy component, and virtually every topic of interest to the pharmacotherapy community fits within a research priority of AHRQ.

New research investigators might first consider applying for a small grant which funds up to $100,000 total costs. Investigators who have a clinical degree or a research doctoral degree and who are no more than five years out of their latest research training experience might consider applying for an Independent Scientist Award (K02). Individuals with a clinical doctoral degree, who have identified a mentor with extensive research experience, and are willing to spend a minimum of 75% of full-time professional effort conducting research and developing a research career during the award might consider applying for a Mentored Clinical Scientist Award (K08). The agency also sponsors dissertation grants for students working on their doctoral degrees.

Opportunities are numerous for collaboration between AHRQ and pharmacotherapy investigators, educators, practitioners, and administrators. Potential collaborators are encouraged to contact AHRQ to initiate discussions on topics of interest. Two agency publications are particularly useful in describing researchable questions and methodologies: "The Outcome of Outcomes Research at AHCPR" and "Greatest Hits of Outcomes Research at AHCPR."[6,7] The agency is committed to a research agenda that is "user driven" and welcomes contacts from the pharmacotherapy community on topics of healthcare quality, cost, and effectiveness.

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PROFESSIONAL DEVELOPMENT

Ambulatory Care/Primary Care, Clinical Pharmacy Careers in

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INTRODUCTION

Community pharmacy practitioners have provided ambulatory care services to their customers for years. However, more students who graduated with advanced degrees since the 1980s have moved from the traditional dispensing role to providing direct ambulatory care patient services. Pursuing this patient care role in ambulatory care and primary care settings has increased job opportunities, positioned pharmacists in patient care areas, and changed the expectations and duties of pharmacists. This growth in clinical pharmacy careers has also pushed recent graduates and those seeking employment in this arena to pursue further training and education.

Integration of pharmacists with various disciplines of medicine offers many benefits to the health care system and the patient, including lower costs and improved health outcomes.[1–3] Pharmacists have also ventured away from the team approach to become more independent, which has lead to the same benefits of improved health outcomes and cost savings.[2] Whether integrated into team approach, or operating independently, pharmacists working in ambulatory and primary care have evolved slowly. This chapter discusses these various careers, including typical work settings and job activities. The type of degree, training, salary, and experience, in addition to long-term growth potential, is also discussed. Finally, to give more insight as to what these clinical sites might be like, descriptions of various sites are given.

JOB ACTIVITIES, RANGE OF CAREERS, AND WORK SETTINGS

The job activities, range of careers, and work settings for ambulatory care pharmacists vary as much as disease states. However, most duties required of ambulatory care pharmacists incorporate three to four components. These include clinical, distributive, and administrative duties, and sometimes a teaching or academic role.[4]

To expand on these job activities, a survey of pharmacists who work in ambulatory care positions was conducted, and it was reported that 45% of the pharmacist's time was spent performing distributive functions, while 30% clinical and 21% of the pharmacist's time was spent performing administrative activities. Distributive functions of these pharmacists may be defined as filling and dispensing prescriptions, as well preparing intravenous medications. The clinical portion of ambulatory care pharmacists includes a variety of activities, such as monitoring patient outcomes and compliance, conducting specialized clinics, providing therapeutic drug monitoring services and, in some settings, practicing independently with prescriptive authority. Pharmacists who have been included on multidisciplinary care teams or work at teaching hospitals may have a responsibility to teach students, residents, and fellows about various aspects of drug and disease state management.

Responses of this survey also indicated that approximately one-half of the pharmacists worked in conjunction with a physician or a nurse on an interdisciplinary ambulatory care team and that the medical staff and senior management were very supportive of having pharmacists on these teams.

The aforementioned specialty clinics allow pharmacists to have an enormous impact on patient care and a variety of career opportunities. Pharmacists may be expected to participate on a team in the multidisciplinary approach to patient care, or may need to act independently in disease-specific clinics. The Veterans Affairs Medical Centers (VAMCs) have been leaders in the area of a multidisciplinary approach to health care, and pharmacists have been involved on these teams for a long time. In a study conducted to determine the in-

volvement of clinical pharmacy services in 50 of the VAMCs' specialty ambulatory clinics, it was found that 310 of the 401 (77%) specialty clinics were staffed with a clinical pharmacist and 144 (36%) were managed by pharmacists. These clinics covered a variety of disease states, including congestive heart failure, anticoagulation, lipid management, geriatrics, diabetes, and therapeutic drug monitoring.[2,5]

The work settings for pharmacists in ambulatory and primary care clinics also vary. More recently, for example, pharmacists can be found in private physician offices or large teaching hospitals. Anywhere ambulatory care is being provided by physicians, nurse practitioners, or physician assistants, there is opportunity for pharmacist involvement.

DEGREE, TRAINING, EXPERIENCE, AND SALARY RANGE

Since the push and support for an entry-level Doctor of Pharmacy degree by the American Association of Colleges of Pharmacy in 1992, the majority of colleges of pharmacy in the United States have been converting from the Bachelor of Science degree. One of the goals in switching to the Doctor of Pharmacy degree is for the colleges of pharmacy to produce patient care providers rather than medication dispensers. Because providing patient care is one of the major activities of ambulatory care pharmacists, the majority of graduates have come from an entry-level Doctor of Pharmacy program. Others, however, have returned to school for additional education to gain the knowledge needed to move into the clinical setting and manage the diversity of disease states.

For many ambulatory care pharmacists, training does not end at graduation with acceptance of the degree. Additional training in residency or fellowship for 1 to 2 years is sometimes completed to obtain more clinical experience in patient care as well as to develop a deeper knowledge base. In a 1995 survey of pharmacists practicing in an ambulatory care setting, 67% of the 99 respondents indicated that they had residency training and 21% had fellowship training. Forty-six percent of respondents also specified that they had received board certification.[6]

New graduates who select a career in ambulatory care pharmacy may decide to complete a 1-year general pharmacy practice residency program or to choose a specialized residency in ambulatory care or primary care. The invaluable experience gained in residency programs provides guidance and practical training to pharmacists who are seeking more education and skills to provide patient care. These programs are offered in a variety of work settings from VAMCs and large teaching hospitals to smaller family medicine groups and community pharmacies.

Although the majority of ambulatory care pharmacists have chosen the route of the Doctor of Pharmacy degree and residency, it is not the only course to becoming an ambulatory care pharmacist. Some pharmacists who have been practicing several years have grown and established positions in ambulatory care without residency or fellowship training. However, many institutions require that they have continuing education to practice in an ambulatory care setting with a team or independently, and one means of continuing education is through certificate programs. Many certificate programs that are available will teach specific disease state management such as anticoagulation, diabetes, or asthma care. However, other certificate programs may be more inclusive, covering a broader spectrum of ambulatory care.[7]

Salary range for pharmacists practicing in an ambulatory care setting varies depending on geographic region, years in the work force, and board certification status. However, the median salary in 1995 was $53,500 (average, $55,861; range, $35,000–$90,000), with a higher salary reflective of more years employed.[6]

GROWTH AND LONG-TERM OPPORTUNITIES

Since the 1990s, clinicians in the fields of ambulatory care and primary care have embraced pharmacists as colleagues and as an invaluable source of information. This acceptance has lead to an increase in demand of pharmacists in the ambulatory care arena in several capacities. First, the educational system has experienced the need to increase the education of students in this area, thus producing more students that choose paths in ambulatory care. Second, pharmacists have been dedicating themselves to improving patient outcomes in primary and ambulatory care, which has lead to a tremendous growth and need for pharmacists in this area.

As it is evident that this field is growing, the question arises as to the longevity of these positions. Many pharmacists that are practicing in ambulatory care have created their own positions. Since the mid-1980s and early 1990s, many of these pharmacists have moved from dispensing to the clinical role. Therefore, pharmacists

who have been in ambulatory care several years are some of the first to experience this long-term job stability. However, as the goals for health care continue to move toward more cost-effective ways to administer better health care, pharmacists continue to prove themselves to fit this equation. Thus, pharmacists will most likely continue to be in these positions for quite some time.

SITE DESCRIPTION

One benefit of practicing as an ambulatory care pharmacist is that there are a variety of practice settings. These practice sites vary from physician office buildings to physician residency training programs, as well as large hospitals and retail pharmacies.

One example is that of a private physician's office. Studies have been performed to determine the impact of having a pharmacist providing pharmaceutical care in a physician's office.[8] In this scenario, pharmacists usually have unlimited access to patient information and may have their own office or exam room to evaluate and educate patients. The pharmacist may see these patients independently of the physician or evaluate the patient for pharmaceutical issues before the physician sees them. Other services may be available at these offices such as a laboratory or radiological services, depending on size and specialty of the office.

Another model that may be used to integrate pharmacists into ambulatory care settings is that of a university-based family practice center or residency training program.[9] In this setting, the pharmacist typically works at a larger physician training program and teaching clinic. The pharmacist usually has patient care duties such as specialty clinics, medication refill services, or other consultative services. However, in this environment, the pharmacists also have obligations to teach and evaluate the medical residents in both didactic and clinical situations. This type of position is sometimes affiliated with higher academic institutions, and clinical duties may need to be balanced with administrative, research, or teaching obligations.

Other traditional sites are changing the way that pharmacists see and educate patients. More hospitals are moving to outpatient treatment programs and becoming involved in the multidisciplinary approach to ambulatory care patients, and practice sites for pharmacists are moving from the central pharmacy to walk-in or ambulatory care clinics and even home care teams. These opportunities have allowed pharmacists who traditionally process orders and mix intravenous medications to become involved in the treatment decisions for patients.

Retail pharmacy is also making an effort to get pharmacists out from behind the counter by establishing a variety of clinics in the retail setting. Some pharmacists are providing pharmaceutical care, such as working in conjunction with physician offices to counsel newly diagnosed diabetic patients on the proper use of glucometers and insulin injections, whereas others work more independently, offering services in durable medical equipment, home infusion, and home oxygen.

The progress in ambulatory care has not always been a clear road. Many barriers have risen along the way that have prevented pharmacists from being accepted in the clinical community as a patient care provider. Some clinicians still view pharmacists as dispensers of medications and believe patient care is not within the scope of a pharmacists' practice. In some cases, this barrier has been surpassed in settings such as VAMCs and HMOs, where a capitated health care system is practiced. Pharmacists have saved these institutions money as well as improved health outcomes, acting not as dispensers of medication, but as clinicians. In addition, the pharmacy profession itself has in some respects inhibited its own growth. Large retail pharmacy chains whose salaries are significantly more than that of an ambulatory care pharmacist, absorb a large portion of graduates that may desire to pursue a career in ambulatory care but are attracted to a higher salary. However, the future for ambulatory care pharmacists appears brighter as legislative change is looking to recognize pharmacists as providers and reimburse them for providing pharmaceutical care.

CONCLUSION

As the need for change in the profession of pharmacy has evolved since the 1990s, pharmacy schools have responded by producing a well-rounded practitioner and provider of pharmaceutical care. More graduates are choosing to gain patient care skills and training in ambulatory care residency or fellowship programs, allowing them to be focused practitioners and teachers. The future for pharmacists in the area of ambulatory care looks bright as pharmacists lobby to be recognized as providers and to be reimbursed for providing pharmaceutical care. Finally, as pharmacists continue to demonstrate that their clinical services improve patient outcomes and decrease overall health care costs, jobs in the ambulatory care setting will continue to expand to

other venues, allowing pharmacists to accomplish what they were trained to do.

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American College of Clinical Pharmacy (ACCP)

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INTRODUCTION

The American College of Clinical Pharmacy (ACCP) was founded in 1979 when 29 clinical pharmacists—organized largely by Donald C. McLeod, M.S.—gathered in Kansas City, Missouri, with a common goal: to promote the rational use of medications in society by forming an organization dedicated to and focused on advancing the cutting-edge of clinical pharmacy practice and research. Those ideals held by ACCP's founding members still find themselves in the College's mission:

> ACCP is a professional and scientific society that provides leadership, education, advocacy, and other resources enabling clinical pharmacists to achieve excellence in practice and research.

ORGANIZATION

Only two years after its founding, ACCP created its Research Institute in 1981 to advance pharmacotherapy through support and promotion of research, training, and educational programs. Through 2000, this has largely taken the form of a number of Research Awards that support specific research projects conducted by College members in a variety of therapeutic areas, and Fellowships that provide for the stipends of postgraduate clinical pharmacists in an intensive research training experience. Both types of programs are available to ACCP members on a competitive basis.

Also in 1981, Russell R. Miller, Ph.D., founded the journal *Pharmacotherapy* as a publication dedicated to human pharmacology and drug therapy. When first established, *Pharmacotherapy* was not affiliated with any medical or pharmacy associations. In 1988, ACCP adopted *Pharmacotherapy* as its official journal, and in 1994, ACCP acquired the journal. Now a monthly publication, *Pharmacotherapy* publishes a complementary array of original clinical research and evidence-based reviews in the broad field of pharmacotherapy and clinical pharmacology.

Membership

As of the end of 2001, ACCP had approximately 7000 members, located mostly in the United States and Canada. ACCP members can be found in all practice venues, including ambulatory clinics and community pharmacies, community hospitals, the pharmaceutical industry, pharmacy and medical school faculties, university hospitals, and VA and military hospitals. More than 80% of ACCP members hold the Pharm.D. degree, 70% have completed a postgraduate residency, and 25% have completed a research fellowship training program. Approximately 25% of ACCP members are certified in one or more of the specialty practice areas recognized by the Board of Pharmaceutical Specialties (BPS; i.e., Nuclear Pharmacy, Nutrition Support, Oncology, Pharmacotherapy, Psychiatry). Consistent with one of ACCP's founding tenets—to promote the rational use of medications in society—College members directly assume responsibility for the drug therapy of individual patients through collaborative practice agreements with physicians; regularly consult with and advise physicians, other health professionals, and patients regarding drug therapy; serve on key institutional or other committees that oversee the medication use process; and teach pharmacy or other health profession students. In addition, many ACCP members are responsible for conducting basic, clinical, health services, economic, or other applied research. This research, for example, may involve clinical trials of new drug entities, pharmacokinetic and pharmacodynamic studies in normal volunteers and patients, pharmacoeconomic evaluations of drug therapies, and health services research to examine the impact of pharmacy services.

The practice and research interests of ACCP members span the broad array of pharmacotherapy. As one way to provide for the unique needs of clinical pharmacists with diverse interests, ACCP currently includes approximately 20 Practice and Research Networks (PRNs). The PRNs form special interest groups within the College in areas ranging from Ambulatory Care to Infectious Diseases to Women's Health.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006306

MAJOR PROGRAMS

Education

ACCP holds three major scientific and/or educational meetings each year. The ACCP Annual Meeting, held in late-October or early-November, and the Spring Practice and Research Forum, held in April, include a variety of educational symposia as well as poster or platform presentations of original research. Both meetings include educational and networking sessions conducted by the College's PRNs. The ACCP Recruitment Forum takes place at the Annual Meeting and provides an opportunity for employers and prospective applicants to interview. Recruitment On-Line, a year-round job listing service, is available on the College's web site.

Each year, ACCP also conducts its "Updates in Therapeutics," designed as both a comprehensive review of therapeutics and as a preparatory course for clinical pharmacists planning to sit for BPS specialty certification in Pharmacotherapy, Nutrition Support, Oncology, or Psychiatry. ACCP is expanding its use of technology to facilitate distance learning. ACCP educational programs will be increasingly available through the College's web site at www.accp.com.

In April 1999, ACCP partnered with the European Society of Clinical Pharmacy (ESCP) to co-host the first International Congress on Clinical Pharmacy in Orlando, Florida. With a theme of "Documenting the Value of Clinical Pharmacy Services," the Congress was attended by more than 1300 pharmacists from 51 countries.[1] ACCP and ESCP plan to organize a second International Congress in 2004.

Publications

In addition to *Pharmacotherapy*, publications produced by ACCP include the *Pharmacotherapy Self-Assessment Program* (PSAP) and the College's annual *Directory of Residencies and Fellowships*. In addition to its use as a general professional development tool, PSAP is approved by BPS for use by Board Certified Pharmacotherapy Specialists (BCPS) in obtaining their required recertification. With publication of its fourth edition (PSAP-IV) in 2001, this modular-based program is available in both hardcopy and Internet versions. The ACCP *Directory of Residencies and Fellowships* provides a comprehensive index and description of postgraduate training opportunities offered by ACCP members. It is published in the fall of each year to assist students and residents in their career development. Other publications available from ACCP are described on the College's web site.

Professional Leadership and Advocacy

ACCP participates in several coalitions with other national organizations, including the Council on Credentialing in Pharmacy, the Joint Commission of Pharmacy Practitioners, the Alliance for Pharmaceutical Care, and the Pharmaceutical Sciences Consortium. In general, ACCP's advocacy efforts are focused on the federal government, with the overall goal of better enabling clinical pharmacists to provide patient care and perform research.

A bibliography and reprints of ACCP white papers, position statements, and guidelines are available on the College's web site. These include two comprehensive reviews of published literature that document the value of clinical pharmacy services.[2,3]

GOVERNANCE

ACCP is governed by an 11-person Board of Regents, elected from and by the College's members. The President of the College serves as chair of the Board of Regents. Members of the 2001 Board of Regents include:

- President: Barry L. Carter, Pharm.D., FCCP, BCPS
- President-Elect: Bradley A. Boucher, Pharm.D., FCCP, BCPS
- Past President: Thomas C. Hardin, Pharm.D., FCCP, BCPS
- Secretary: J. Herbert Patterson, Pharm.D., FCCP, BCPS
- Treasurer: Marsha A. Raebel, Pharm.D., FCCP, BCPS
- Regents: Betty J. Dong, Pharm.D.; Julie A. Johnson, Pharm.D., FCCP, BCPS; Mary Lee, Pharm.D., FCCP, BCPS; Michael Maddux, Pharm.D., FCCP; Ralph H. Raasch, Pharm.D., FCCP, BCPS; and David R. Rush, Pharm.D., BCPS

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American Council on Pharmaceutical Education

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INTRODUCTION

The American Council on Pharmaceutical Education (ACPE), located at 311 W. Superior Street, Suite 512, Chicago, Illinois 60610-3537, is the national agency for accreditation of professional degree programs in pharmacy and providers of continuing pharmaceutical education including certificate programs in pharmacy. The ACPE was established in 1932 for accreditation of preservice (entry-level) pharmacy education. Accreditation standards reflect professional and educational qualities identified by ACPE as essential to quality professional programs at colleges and schools of pharmacy. Standards are established through a comprehensive and broadly based procedure that provides opportunities for contributions from the community of interests affected by the accreditation process.

OVERVIEW

Accreditation of Professional Degree Programs

The first ACPE standards, developed between 1932 and 1937, called for sweeping changes in pharmaceutical education. These standards required the completion of a four-year course of study in order to attain the baccalaureate degree in pharmacy. The standards were published in 1937 and were subsequently revised during the 1940s and early 1950s. In the 1960s, revision of the standards led to the incorporation of a five-year baccalaureate in pharmacy program and a doctor of pharmacy program which involved a four-year professional program that was preceded by two years of preprofessional studies. In the mid-1970s, standards for two separate entry-level, professional programs, the baccalaureate in pharmacy program and the doctor of pharmacy program were developed. In addition, professional practice experiences were incorporated into the curriculum for the first time. The revisions of the 1980s expanded upon curricular expectations for the doctor of pharmacy program leading to greater emphasis on curricular and programmatic outcomes. In 1989, ACPE issued its intention to propose new standards that would merge the two programmatic standards with a focus on a doctor of pharmacy program. The new accreditation standards and guidelines for the professional program in pharmacy leading to the Doctor of Pharmacy degree (Standards 2000) were adopted June 14, 1997. Implementation Procedures for these new accreditation standards became effective on July 1, 2000, in accord with a stated transition period.

Continuing Education Accreditation Program

Requirements for continued pharmaceutical education began in the early 1970s, when State Boards of Pharmacy began requiring licensed pharmacists to participate in continuing pharmaceutical education activities. Between 1972 and 1974, the American Association of Colleges of Pharmacy and the American Pharmaceutical Association convened a task force to discuss issues related to the continued competence in pharmacy practice. In 1974, the Board of the American Pharmaceutical Association recommended that ACPE initiate accreditation of continuing pharmaceutical education. Consequently, ACPE began the accreditation of providers of continuing pharmaceutical education in 1975. Participation in continuing education programs earned through an ACPE-accredited provider is accepted for licensure renewal by all state boards of pharmacy requiring continuing education. The symbol used by the ACPE to designate that a continuing education provider is accredited is

In 1998, the profession charged ACPE to develop standards for certificate programs. A certificate program is a structured continuing education experience that is narrower in focus and shorter in duration than a degree

DOI: 10.1081/E-ECP 120006199

program. Certificate programs are designed to instill, expand, or enhance practice competencies through the systematic acquisition of specified knowledge, skills, attitudes, and behaviors. In June 1999, Standards and Quality Assurance Procedures for Providers Offering Certificate Programs in Pharmacy were adopted. As of Fall 2000, 30 providers had been accredited to provider certificate programs. The symbol used by the ACPE to designate that a certificate training program is provided by an accredited provider is

Of note, the standards originally developed for the accreditation of providers of continuing pharmaceutical education were revalidated during development of the standards pertaining to providers of certificate programs. In addition, the new term "statements of credit" should be when documenting completion of a continuing education activity provided by an ACPE-accredited provider. The term "certificates of credit" should be reserved for use in conjunction with ACPE-accredited certificate programs only.

Annually, or more frequently if necessary, the ACPE publishes the Directory of Accredited Doctor of Pharmacy Programs of Colleges and Schools of Pharmacy and the Directory of Accredited Providers of Continuing Pharmaceutical Education.

The Pharmacists' Learning Assistance Network (P.L.A.N.®) is an information service developed by the ACPE to allow pharmacists to access information on continuing education programs. The P.L.A.N. service, which is operated by ACPE, maintains a database on all continuing pharmaceutical education programs offered by ACPE-approved providers. Pharmacists may request a computer search of continuing pharmaceutical education programs to suit their learning needs or conduct their own search on ACPE's web site.

ORGANIZATIONAL STRUCTURE AND GOVERNANCE

The Council is an autonomous and independent agency whose 10-member Board of Directors is derived through the American Association of Colleges of Pharmacy, the American Pharmaceutical Association, the National Association of Boards of Pharmacy (three appointments each), and the American Council on Education (one appointment). These organizations are not members of the ACPE, and appointees to the Board of Directors are not delegates of these organizations. The organizational structure of ACPE assures the integrity of the accreditation program through responsive, responsible, and independent operation. The Board of Directors has authority for management of corporate affairs and is responsible for establishing policies and procedures, setting standards for accreditation of professional programs of colleges and schools of pharmacy, establishing standards for accreditation of providers of continuing education, including certificate programs in pharmacy, and taking actions concerning accreditation. A Public Interest Panel serves in an advisory capacity. The ACE appointee and the Public Interest Panel assure a public perspective in policy- and decision-making processes.

Dr. Daniel A. Nona served as the Executive Director from 1975–2000. Dr. Peter H. Vlasses assumed the Executive Director position effective January 1, 2000.

MISSION

ACPE is organized for the purpose of promoting and encouraging educational, research, and scientific activities. The ACPE formulates educational, research, and scientific standards which an accredited professional program of a college or school of pharmacy or an accredited provider of continuing education will be expected to meet and maintain. The essential purpose of the professional degree program accreditation process is to provide a professional judgment of the quality of a college or school of pharmacy's professional program(s) and to encourage continued improvement thereof. Accreditation concerns itself with quality assurance and quality enhancement. The responsibilities of the ACPE's professional degree accreditation program are as follows:

- To advance the standards of pharmaceutical education in the United States and associated commonwealths.
- To formulate the educational, scientific, and professional principles and standards for professional programs in pharmacy which a college or school of pharmacy is expected to meet and maintain for accreditation of its programs, and to revise these principles and standards when deemed necessary or advisable.
- To formulate policies and procedures for the accreditation process.
- To evaluate the professional program(s) of any college or school of pharmacy within or beyond its national geographic scope that requests accreditation of its program(s).
- To publish a directory of accredited professional programs of colleges and schools of pharmacy for the use of state boards of pharmacy or appropriate

state licensing agencies in pharmacy, other interested agencies, and the public, and to revise such directory annually or as frequently as deemed desirable.
- To provide assurances to constituencies that the professional programs that have been accredited continue to comply with standards, and therefore, to conduct periodic evaluations in a manner similar to that for original accreditation.
- To assist the advancement and improvement of pharmacy education as well as prerequisites and procedures for licensure and to provide a basis for interinstitutional relationships.

The ACPE's Continuing Education Provider Accreditation Program is designed to assure pharmacists, boards of pharmacy, and other members of pharmacy's community of interests, of the quality of continuing pharmaceutical education programs. The purposes of the Continuing Education Provider Accreditation Program are to:

- Assure and advance the quality of continuing pharmaceutical education, including Certificate Programs in Pharmacy, thereby assisting in the advancement of the practice of pharmacy.
- Establish standards for accredited providers of continuing pharmaceutical education, including accredited providers offering Certificate Programs in Pharmacy.
- Provide pharmacists with a dependable basis for selecting accredited continuing education experiences.
- Provide a basis for uniform acceptance of continuing education credits among states.
- Provide feedback to providers about their continuing education programs through periodic comprehensive reviews and ongoing monitoring activities with a need toward continuous improvement and strengthening.

CURRENT INITIATIVES

The new accreditation standards and guidelines for the professional program in pharmacy leading to the Doctor of Pharmacy degree (Standards 2000) were adopted June 14, 1997. Implementation procedures for these new accreditation standards became effective on July 1, 2000, in accord with a stated transition period.

ACPE is a member of the Council on Credentialing in Pharmacy, a coalition consisting of 11 national pharmacy organizations, which was founded in 1999 to provide leadership, standards, public information, and coordination for voluntary professional credentialing programs in pharmacy.

In April 2000, ACPE developed a Web-based survey as part of a strategic planning initiative. The purpose of the Web-based survey was to:

- Assess current awareness of ACPE within the profession.
- Assess current effectiveness of ACPE activities.
- Identify opportunities for ACPE process improvement.
- Receive feedback and opinions on how else ACPE can serve pharmacy.

Data obtained from the Web-based survey will be used to develop a new strategic plan targeted for review by the profession and for approval by January 30, 2001.

MEETINGS

The Board of Directors meets twice a year. A regular annual meeting of the Board of Directors is held in January, while a second annual meeting is held every June.

American Journal of Health-System Pharmacy (ASHP)

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American Society of Health-System Pharmacists, Bethesda, Maryland, U.S.A.

INTRODUCTION

The *American Journal of Health-System Pharmacy* (*AJHP*) is the official publication of the American Society of Health-System Pharmacists (ASHP). *AJHP*'s mission is to facilitate communication among members and subscribers and to create an archive of publications that both reflect and lead contemporary pharmacy practice.

OBJECTIVES

In addition to publishing a substantial body of peer-reviewed scientific papers, *AJHP* provides extensive, timely, in-depth news coverage of pharmacy issues. Numerous columns feature advice on management and therapeutic problems. Current content priorities include contemporary drug therapy issues; descriptions of practice innovations in acute care, long-term care, ambulatory care, home care, and managed care; and outcomes research, including pharmacoeconomics. Content is also guided by ASHP's Leadership Agenda, which currently emphasizes creating fail-safe medication use in health systems, advancing the pharmacist's role in patient care, fostering pharmacy practice leadership, accelerating the adoption of high-level pharmaceutical services for patients across the continuum of care, and assisting pharmacists in applying advances in electronic technology and science to the care of patients.

HISTORY

Leo Mossman edited the first issue, published in June 1943. The periodical was originally entitled the *Official Bulletin of the American Society of Hospital Pharmacists* and was mimeographed on beige paper. Harvey A.K. Whitney became coeditor in September 1943, and Mossman and Whitney continued monthly publication through December 1943. Donald E. Francke and Mossman co-edited two issues, distributed in January and July of 1944, and Francke then assumed sole editorship, a responsibility he would hold for 22 years.

Because of financial difficulties in funding the production and mailing of the *Bulletin*, a decision was made to accept paid advertising to offset expenses. The first paid advertisement appeared in the January–February 1950 issue. The influx of advertising revenue allowed the use of commercial offset printing with this issue. Over the years, advertising income has far exceeded the production cost of *AJHP*. This margin has contributed to ASHP's ability to provide member services in excess of those possible through membership dues alone. Most other pharmacy association periodicals have been subsidized through other income sources.

By 1955 the *Bulletin* had achieved worldwide distribution. In 1958 the publication began monthly distribution and was renamed the *American Journal of Hospital Pharmacy*. When Francke resigned from ASHP in 1966 to pursue other publishing interests, George P. Provost succeeded him as editor and continued in that post until 1974. William A. Zellmer succeeded Provost as *AJHP*'s editor and provided a voice for pharmacy for more than 18 years in his widely read editorials. In 1992, when Zellmer's other ASHP obligations had expanded to the point where it was difficult for him to fulfill the responsibilities of *AJHP*'s editorship, C. Richard Talley succeeded to the post.

In 1982, in response to the growth of clinical pharmacy practice in hospitals and the increasing number of clinical papers being published in *AJHP*, ASHP created a new periodical entitled *Clinical Pharmacy*. This journal began as a bimonthly publication and attracted 7000 subscribers in its first year. It expanded to monthly distribution in 1986. ASHP's creation of this periodical is widely believed to have enhanced the growth of clinical pharmacy.

As the practice of clinical pharmacy became increasingly mainstream among ASHP members, more of them asked ASHP to provide the content of *Clinical Pharmacy* as a benefit to all members, not just subscribers. Through the persistent application of new publishing technology,

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DOI: 10.1081/E-ECP 120006272

the *AJHP* and *Clinical Pharmacy* staff was able to reduce production costs dramatically. That enabled ASHP to merge *Clinical Pharmacy* into *AJHP* in 1994, creating pharmacy's only peer-reviewed scientific journal to be published 24 times each year. *AJHP* has published more than 2000 pages annually for the past 20 years.

AJHP (Coden: AHSPEK; ISSN: 1079-2082) is published by the American Society of Health-System Pharmacists twice a month, on the 1st and 15th. Circulation in 2001 was 37,870; the 2001 subscription rate was $195 for nonmembers (USA). A subscription is included as a benefit to ASHP members. Editorial offices are located at 7272 Wisconsin Avenue, Bethesda, Maryland 20184, U.S.A. (Telephone: 301-657-3000, ext. 1200; Fax: 301-664-8857; E-mail: ajhp@ashp.org).

AJHP is abstracted and indexed by all the major secondary sources (e.g., *International Pharmaceutical Abstracts*, *Biological Abstracts*, *Chemical Abstracts*, *Cumulative Index to Nursing and Allied Health Literature*, *Current Contents: Clinical Medicine*, *Current Contents: Life Sciences*, *Excerpta Medica*, *Index Medicus*, and the Iowa Drug Information Service.

In 1997 some components of *AJHP* began appearing on ASHP's Web site. Starting in September 1999, the full text of *AJHP* was posted. Members and other subscribers can now read and print type-quality copies of *AJHP* content about 10 days before an issue is mailed. Furthermore, important scientific findings that affect patient safety can be conveyed to the public and the media the instant they have finished undergoing the traditional peer-review, editing, and composition steps, saving weeks or months of delay in many cases. No other pharmacy organization in the world is currently doing this.

Enhancements of *AJHP*'s Web-based distribution are in the works. The searchability of past issues is being improved, and new procedures and mechanisms for authors and reviewers to use in electronically submitting manuscripts, letters, and other communications are being developed.

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www.ashp.org.

American Journal of Pharmaceutical Education

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INTRODUCTION

The *American Journal of Pharmaceutical Education* is a service publication for the community of pharmacy educators. It publishes articles as a means of disseminating information, methods, and techniques concerning pharmacy education.

AIMS AND SCOPE

The Journal chronicles the numerous changes that have occurred in pharmacy education since its launch issue in 1937. During the most recent 25 years, many of changes that have occurred in pharmacy education have been described in this Journal. Pharmacy programs have incorporated the advent of physical pharmacy, biopharmaceutics, and pharmacokinetics courses in their curriculums. Changes in the pharmaceutical sciences of social and administrative sciences as well as medicinal chemistry have impacted the teaching of pharmacotherapy to pharmacy students. In addition, the role of the pharmacist as a health professional in the management of disease states through drug therapy has seen the development and teaching of clinical pharmacy in the pharmacy curriculum. The inclusion of an experiential component to pharmacy education has created a vast emphasis on the application of the science of pharmacy to the delivery of care to the patient. Current issues of the Journal continue to describe pharmacy education and also include a section based on the Innovations in Teaching Competition sponsored by the AACP Council of Faculties and a section called "Teachers' Topics" that features course content presented by the best instructors selected by their school or college.

The Journal is published quarterly, from its office at 1426 Prince Street, Alexandria, Virginia 22314–2841 (phone: 703-739-2330; fax: 703-839-8982; www.aacp.org) under the editorship of George H. Cocolas, School of Pharmacy, Chapel Hill, North Carolina.

HISTORY

The Journal is the official publication of the American Association of Colleges of Pharmacy (AACP). Its purpose is to document pharmacy education and to advance it. The Journal originated in 1937 from the efforts of Rufus A. Lyman, dean of the College of Pharmacy at the University of Nebraska. AACP had published a *Proceedings* since 1900 but these once-a-year volumes were not a useful mechanism to energize pharmaceutical education. With the support of the Executive Committee of AACP, the Journal began its publication as a quarterly to describe pharmaceutical education in the schools and colleges in the United States. In 2002, the Journal reached its 66th year and remains a quarterly. Since 1991 the Journal has added a winter supplement to archive committee reports and minutes of meetings in one single issue.

FUTURE DIRECTIONS

Pharmacy education is ever changing. The mission of the Journal is to continue to document current teaching methodologies and studies about pharmacy education in schools and colleges of pharmacy.

The technology of the Web is becoming more evident in the publication of printed journals. This Journal, in the near future, will be offering its publication online.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006273

American Pharmaceutical Association

A

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INTRODUCTION

The American Pharmaceutical Association (APhA) is the national professional society of pharmacists and is located at 2215 Constitution Avenue, NW, Washington, D.C. The main phone number is (202) 628-4410; the main fax line is (202) 783-2351; the primary web address is www.aphanet.org. APhA also hosts a site for consumers with the address www.pharmacyandyou.org. Since its founding, APhA has been a leader in the professional and scientific advancement of pharmacy, and in safeguarding the well-being of the individual patient.

HISTORY

The American Pharmaceutical Association was founded in Philadelphia, Pennsylvania, in 1852 by a group of pharmacists from across the young nation who were concerned about the quality of medicinal products and the standards of practice of those engaged in the apothecary, or pharmacy, trade.

The first permanent home for APhA was established through an act of Congress in 1932. Land on the national mall adjacent to the Lincoln Memorial in Washington, D.C., was identified as appropriate to be occupied by a national organization dedicated to the advancement of science and practice of pharmacy. To this day, APhA is the only nongovernmental organization with its operations on the national mall. The building itself was designed by noted architect John Russell Pope who, among other prominent buildings, designed the Jefferson Memorial and National Archives Building.

ORGANIZATIONAL STRUCTURE AND GOVERNANCE

A 19-member Board of Trustees elected by the membership governs APhA. The chief executive officer is John A. Gans, PharmD, who assumed his position as Executive Vice-President and a member of the APhA Board in 1989. The term of APhA President is three years (President-Elect, President, and Immediate Past-President). Nine trustees are elected for 3-year terms (three in each election cycle). The Board elects a Treasurer for a term of 3 years, and this individual serves with the presidential officers and another sitting Trustee on the APhA Executive Committee. Each of the three APhA Academy presidents serves a 1-year term as Trustee. The other two Trustees are the Speaker and Speaker-Elect of the APhA House. These officers are elected at the APhA Annual Meeting by delegates to the APhA House and serve for 2-year terms.

Policy for the Association, on issues important to the profession and the public health, is established by a nearly 400-member House of Delegates—the largest representative body of pharmacists in the United States. Eleven national pharmacy organizations have secured voting representation in the APhA House of Delegates and collaborate on the formation of policy for the Association and the profession. The Board of Trustees is empowered, if necessary, to make policy in the interim period between meetings of the House of Delegates and determines implementation strategies for House-adopted policies.

The membership of APhA exceeds 50,000 pharmacists, pharmacy students, pharmaceutical scientists, and pharmacy technicians. An active member must be licensed to practice pharmacy in the United States or hold a degree from a U.S.-accredited school or college of pharmacy. Nonpharmacists with an interest in the mission of APhA may become associate members.

Each member is served by one of three APhA Academies: The Academy of Pharmacy Practice and Management (APhA–APPM), the Academy of Pharmaceutical Research and Science (APhA–APRS), or the Academy of Students of Pharmacy (APhA–ASP). Each Academy annually elects officers to direct the development of programs, products, and services to meet the needs of members.

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DOI: 10.1081/E-ECP 120006280

MISSION AND KEY OBJECTIVES

APhA is dedicated to improving public health by assisting members and enhancing the profession of pharmacy. It accomplishes this mission by pursuing activities consistent with the following goals:

- Expand access to and promote the value of pharmacists' caregiving services in obtaining positive health outcomes through optimal use of medications.
- Equip pharmacists and others allied to the profession with information and education resources to support provision of patient care.
- Become the primary membership organization of choice for America's pharmacists and others allied to the profession.
- Develop the resource base necessary for successful achievement of the Association's mission.

CURRENT MAJOR INITIATIVES

APhA programs, products, and services are built in recognition of the dual roles of contemporary pharmacists: 1) to insure that the public has access to a safe, efficient, accurate, and patient-sensitive drug distribution system, and 2) that patients achieve optimal outcomes from medication use (prescription, nonprescription, and nontraditional therapies) with the assistance of pharmacists. Pharmacists may engage in one or both aspects of these roles, and APhA members practice in a wide variety of different settings, either directly or indirectly affecting patient care.

Publications and education are important elements of APhA program development. New product bulletins and special reports are aimed at equipping practitioners with timely and unbiased information for their practice. APhA periodical publications include *Journal of the American Pharmaceutical Association*, *Pharmacy Today*, *Journal of Pharmaceutical Sciences*, *Pharmacy Student*, and *Drug-Info Line*, the newest monthly newsletter which provides concise summaries of key pharmacotherapeutic issues.

APhA reference books include the *Handbook of Nonprescription Drugs*, 13th Edition, *Medication Errors*, *Handbook of Pharmaceutical Excipients*, *APhA Drug Treatment Protocols*, and several texts to guide those engaged in compounding practice.

APhA advocacy efforts aim principally at earning deserved recognition for pharmacists as practitioners involved in direct patient care and securing appropriate compensation for those services. This includes educating and lobbying legislative and regulatory officials at the state and national levels, in collaboration with other state and national pharmacy organizations. Private sector advocacy on these same issues extends to business leaders, colleagues in other health professions, insurers, and other decision makers involved with healthcare and the medication use process.

APhA has several affiliate organizations, and through the work of its Foundation and credentialing organizations, the Association has made a major commitment to research, quality measurement, and accountability. The APhA Foundation has sponsored and directed several significant research and demonstration projects to contribute to the body of evidence that pharmacists' services enhance patient health-seeking behavior and improve outcomes. Research on quality measurement and the development of tools to reduce medication use problems and errors is a priority of the Foundation.

Three credentialing organizations with APhA affiliations help pharmacists and technicians secure meaningful credentials to advance their careers. The Board of Pharmaceutical Specialties is a 25-year-old certification agency awarding specialty recognition to pharmacists in five board-recognized areas. The Pharmacy Technician Certification Board, founded by APhA, the American Society of Health-System Pharmacists, the Michigan Pharmacists Association, and the Illinois Council of Health-System Pharmacists in 1995, has certified over 75,000 pharmacy technicians. A disease-specific certification agency, the National Institute for Standards in Pharmacist Credentialing, was founded in 1997. APhA shares responsibility with the National Association of Boards of Pharmacy, the National Association of Chain Drug Stores, and the National Community Pharmacists Association for overseeing this credentialing program for pharmacists. Four disease states are currently certified by computer-based examination through NISPC.

MAJOR APhA MEETINGS

APhA hosts one national meeting annually. The meeting provides continuing education for pharmacists, pharmacy technicians, scientists, and numerous affiliated organizations. The Federal pharmacists hold meetings in conjunction with APhA, as do the American Institute on the History of Pharmacy, the American Society of Pharmacy Law, and several professional fraternities and honor societies. Dates for meetings in upcoming years are as follows:

- APhA2003—New Orleans, Louisiana, March 28–April 1.
- APhA2004—Seattle, Washington, March 26–30.
- APhA2005—Orlando, Florida, April 1–5.
- APhA2006—Phoenix, Arizona, March 24–28.

American Society of Consultant Pharmacists

A

Timothy Webster
Phylliss Moret
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INTRODUCTION

The American Society of Consultant Pharmacists (ASCP) is the international professional association that provides leadership, education, advocacy, and resources enabling senior care pharmacists to enhance quality of care and quality of life for older individuals through the provision of pharmaceutical care and the promotion of healthy aging. Consultant pharmacists specializing in senior care pharmacy are essential participants in the healthcare system, recognized and valued for the practice of pharmaceutical care for the senior population and people with chronic illness.

For millions of senior citizens and individuals with chronic illnesses, consultant pharmacists play a vital role in ensuring optimal drug therapy. In their role as medication therapy experts, consultant pharmacists take responsibility for their patients' medication-related needs; ensure that their patients' medications are the most appropriate, the most effective, the safest possible, and are used correctly; and identify, resolve, and prevent medication-related problems that may interfere with the goals of therapy. Consultant pharmacists manage and improve drug therapy and improve the quality of life of the senior population and other individuals residing in a variety of environments, including hospitals, nursing facilities, subacute care and assisted living facilities, psychiatric hospitals, hospice, and home- and community-based care.

SENIOR CARE PHARMACY

While medications are probably the single most important factor in improving the quality of life for older Americans, the nation's seniors are especially at risk for medication-related problems due to age-related physiological changes, higher incidence of multiple chronic diseases and conditions, and greater consumption of prescription and over-the-counter medications.

The economic impact of medication-related problems in persons over the age of 65 now rivals that of Alzheimer's disease, cancer, cardiovascular disease, and diabetes. Medication-related problems are estimated to be one of the top five causes of death in that age group, and a major cause of confusion, depression, falls, disability, and loss of independence.

For more than a generation, consultant pharmacists have dedicated themselves to protecting the health of some of our most vulnerable citizens—residents of nursing facilities. Today, the senior care pharmacists ASCP represents are patient advocates for all of our nation's seniors, wherever they reside.

CONSULTANT PHARMACY PRACTICE

Consultant pharmacists are committed to caring for the well-being of each individual, taking into account the complex interrelationships between disease states, nutrition, medications, and other variables. They are essential players on the healthcare team, and influential decision makers in all aspects of drug therapy. Consultant pharmacists counsel patients, provide information and recommendations to prescribers and caregivers, review patients' drug regimens, present in-service educational programs, and oversee medication distribution services.

In addition to these basic responsibilities, consultant pharmacists provide a wide range of other primary care services to the nation's seniors, including pain management counseling, pharmacokinetic dosing services, intravenous therapy, nutrition assessment and support, and durable medical equipment services.

A clear picture of the enormous impact being made by consultant pharmacists in achieving optimal therapeutic outcomes and reducing medication-related problems is emerging from the Fleetwood Project—ASCP Foundation's landmark three-phase study to document the value of pharmacists' services. The Fleetwood Phase I study found that consultant pharmacists' drug regimen

review services in the nation's nursing facilities improve the frequency of optimal drug therapy outcomes by 43% and save as much as $3.6 billion annually in costs associated with medication-related problems.[1] In Fleetwood Phase II, the Fleetwood model was developed and tested for feasibility. The Fleetwood model includes prospective drug regimen review, direct communication with prescribers to resolve therapeutic issues, patient assessment, and formalized pharmaceutical care planning for geriatric patients at highest risk for medication-related problems. The results of the Phase II pilot study were published in the October 2000 issue of *The Consultant Pharmacist*. The Fleetwood model will be further refined in Fleetwood Phase III, currently underway, by identifying and validating "pharmacist-sensitive outcomes"—those clinical outcomes most sensitive to pharmacist intervention for older patients at high risk for medication-related problems.

ASCP: SERVING THE NEEDS OF A DYNAMIC PROFESSION

The ASCP was founded in 1969 to represent the interests of its members and promote safe and effective medication therapy for the residents of nursing facilities—mostly frail elderly patients. The term "consultant pharmacists" is rooted in federal regulations, which requires a pharmacist to provide drug regimen reviews for nursing facility residents. The organization has grown dramatically over the past quarter century and its membership continues to diversify and expand their services to people who need them the most—America's seniors, wherever they reside (Tables 1 and 2).

Table 1 Percentage of ASCP members that provide the following services

Drug regimen review	64%
IV therapy	34%
Drug utilization review	34%
Pharmacokinetic monitoring	27%
Drug formulary management	23%
Pain management	20%
Drug research and studies	20%
Nutrition	18%
Compliance packaging	15%
Home care	13%
DME/surgical appliances	11%
Services for fees	7%
Laboratory testing	5%

Table 2 Percentage of ASCP pharmacists that provide services to the following sites

Nursing homes	76%
Counseling to long-term care facilities (LTCF)	70%
Dispensing to LTCF	54%
Administrative responsibility to LTCF	42%
Residential	41%
Subacute	31%
Hospice	30%
Mental health	28%
Home care	25%
Retail dispensing	19%
Acute care	15%
Correctional facilities	11%
Hospital LTCF	8%

The Executive Director of ASCP is Tim Webster; elected leadership consists of President (Mark Sey), President-elect (Stephen Feldman), Vice President (Ross Buckley), Secretary/Treasurer (Herb Langsam), and the Immediate Past President and Chairman of the Board. These officers and ten directors comprise the Board of Directors. The Board of Directors has full administrative authority in all Society matters, except as otherwise provided in ASCP bylaws.

ASCP has chapters in 20 states and Canada, 30 state affiliates, over 600 pharmacy student members, and hundreds of international members in 18 countries. As consultant pharmacists' practice activities expand and diversify, so does their need for innovative programs, information, and resources. ASCP is strongly committed to meeting these needs.

Education

ASCP offers many opportunities for ACPE-accredited continuing education at its annual meeting, midyear conference, and other regional and chapter-sponsored meetings, seminars, and workshops. ASCP also enables pharmacists to gain geriatric pharmacy knowledge thought its web-based education sites, which include geriatricpharmacyreview.com and scoup.net. (SCOUP is the acronym for Senior Care Online University for Professionals.)

The ASCP Research and Education Foundation also funds, coordinates, and conducts a wide range of traineeships and research programs in long-term care and geriatric healthcare.

Advocacy

ASCP protects the interests of consultant pharmacists and their patients in lobbying and congressional testimony on

Capitol Hill, with federal regulatory agencies, and with state legislatures. The Society tracks and analyzes hundreds of legislative and regulatory developments nationwide, and maintains an effective political presence through the ASCP-PAC (political action committee) and the Capitol Fund, a legislative lobbying fund.

Practice Resources

To help consultant pharmacists succeed in a demanding and changing healthcare environment, ASCP offers a broad array of manuals, texts, videotapes, and software programs. These include the widely used texts: *Drug Regimen Review: A Process Guide for Pharmacists*, *100% Immunization Campaign Resource Manual*, *The Medication Policy and Procedure Manual for Assisted Living*, and *Nursing Home Survey Procedures and Interpretive Guidelines: A Resource for the Consultant Pharmacist*. A multitude of resource directories are also available at ascp.com, which include *Medication-Related Problems in Older Adults*, *Geriatrics Resource Page*, and *Fact Sheet on Medication Use in Nursing Facilities*. Other ASCP-related web sites include ccgp.com, immunizeseniors.org, ascpfoundation.org, geriatricpharmacyreview.com, and scoup.net.

Publications

ASCP members receive several publications including *The Consultant Pharmacist*, the Society's award-winning monthly journal presenting peer-reviewed clinical research, news, and practice management information; *ASCP Update*, a monthly newsletter focusing on pharmacy news, ASCP programs and initiatives, and state and federal legislative and regulatory developments; and *Clinical Consult*, continuing education newsletter, providing in-depth information on a wide range of clinical topics.

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MISSION

ASCP is the international professional association that provides leadership, education, advocacy, and resources enabling senior care pharmacists to enhance quality of care and quality of life for older individuals through the provision of pharmaceutical care and the promotion of healthy aging.

ASCP's vision include:

- The senior population realizes improved quality of care and quality of life through the provision of pharmaceutical care.
- Senior care pharmacists are recognized and valued for their care of patients.
- Senior care pharmacists are professionals, essential in healthcare systems.
- ASCP is the acknowledged leader in Senior Care Pharmacy practice.

For more information, contact the American Society of Consultant Pharmacists, 1321 Duke Street, Alexandria, Virginia 22314-3563; Tel: 703-739-1300; Fax: 703-739-1321; e-mail: info@ascp.com; www.ascp.com.

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American Society of Health-System Pharmacists (ASHP)

C. Richard Talley
American Society of Health-System Pharmacists, Bethesda, Maryland, U.S.A.

INTRODUCTION

The American Society of Health-System Pharmacists (ASHP) is the 30,000-member national professional association representing pharmacists who practice in hospitals, health maintenance organizations, long-term care facilities, home care, and other components of the health-care system. ASHP believes that the mission of pharmacists is to help people make the best use of medicines, and assisting pharmacists in fulfilling this mission is ASHP's primary objective. The Society has extensive publishing and educational programs designed to help members improve their delivery of pharmaceutical care and is the national accrediting organization for pharmacy residency and pharmacy technician training programs. Among pharmacy associations, ASHP stands out as having the largest staff (more than 200), the largest budget (more than $34 million in 2001), the largest educational meeting (more that 21,000 attendees in 2001), and the largest variety of products and educational opportunities.

HISTORY AND ACHIEVEMENTS

Among ASHP's most important achievements are its successes in building practitioner consensus on the societal role of pharmacy. One of the landmark events in the emergence of clinical pharmacy was the ASHP invitational conference on "Directions for Clinical Practice in Pharmacy," held in 1985 in Hilton Head, South Carolina. In similar fashion, ASHP's involvement with the four "Pharmacy in the 21st Century" conferences (the second of four such meetings, conceived and presented through the Joint Commission of Pharmacy Practitioners), helped establish the clinical roles of pharmacists.

ASHP further established new direction for clinical pharmacy by being one of the creators—along with the American Pharmaceutical Association, the Michigan Pharmacists Association, and the Illinois Council of Health-System Pharmacist—of the Pharmacy Technician Certification Board (PTCB). It is widely believed that standardized education for pharmacy technicians, enabled by PTCB, will facilitate pharmacists in delegating more distributive roles to technicians and in expanding clinical roles for pharmacists.

ASHP provides services and products to members in ten practice domains: acute care, ambulatory care, clinical specialist, home care, long-term and chronic care, managed care, new practitioner, pharmacy practice management, student, and technician. Pharmacy students receive all member services plus the special services of the ASHP Student Forum—all at greatly reduced rates.

MEMBERSHIP

Membership in ASHP includes a wide variety of benefits. For example, members have full access to all components of ashp.org, ASHP's content-rich, interactive Web site that provides information and e-commerce opportunities 24 hours a day, 7 days a week. Membership includes subscriptions to two periodicals: the *American Journal of Health-System Pharmacy* (*AJHP*), a peer-reviewed, scientific journal published 24 times each year, and ASHP *News and Views*, a newsletter addressing practice issues and upcoming events that is published 12 times each year. Members can attend ASHP's major continuing education meetings—The ASHP Annual Meeting and the ASHP Midyear Clinical Meeting—at rates discounted by an amount equal to ASHP's annual dues. Members can take advantage of more than 150 self-study courses, publications, videos, and software at an average saving of 20% compared with nonmember rates. In addition to the networking opportunities available at ASHP meetings and seminars and similar events conducted by ASHP's Affiliated State Chapters, members can enroll in the ASHP Practice Advancement Links (PALs) program to expand their interconnections with other practitioners. ASHP members can achieve recognition as Fellows of ASHP by applying

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DOI: 10.1081/E-ECP 120006370

to the Practitioner Recognition Program. National and international recognition can be achieved through authorship in *AJHP* and through presentations at ASHP's educational meetings. Members qualify for financial benefits through ASHP's MemberCard program, available at low rates and with no annual fee. There is also an ASHP Member loan program, and members are eligible for insurance benefits, including group insurance plans for family term life, short-term medical, catastrophic major medical, accident, and disability income protection and in-hospital care.

PUBLICATIONS AND EDUCATIONAL RESOURCES

ASHP is the leading publisher of pharmacy information. The best-known products include:

- *American Journal of Health-System Pharmacy.*
- *AHFS Drug Information*, the print product; *AHFS first*, the electronic database, and eBookman, the hand-held multimedia content player version.
- *International Pharmaceutical Abstracts.*
- *Handbook on Injectable Drugs.*
- *Clinical Skills Programs*, for acute care and ambulatory care.
- *Medication Teaching Manual*, the print product; MedTeach, the customizable electronic database; and safemedication.com, the Web-based consumer medication guide.

Over several decades, ASHP has worked with members to develop *Best Practices for Health-System Pharmacy*, a compilation of statements, guidelines, therapeutic position statements, and residency accreditation standards. In addition to its ongoing creation of practice standards, the Office of Professional Practice and Scientific Affairs at ASHP monitors professional practice needs, works with other major health organizations, works toward the prevention of medication misadventures, and communicates with federal and state regulatory bodies that define pharmacy practice in hospitals and other components of health systems.

ASHP is the sole accrediting body for postgraduate residency training programs and pharmacy technician training programs. In 2001 there were 536 ASHP-accredited programs for pharmacists and 83 ASHP-accredited programs for technicians throughout the United States.

ASHP's Government Affairs Division staff provides substantial advocacy for public policy on behalf of ASHP members before the U.S. Congress, federal agencies (e.g., FDA and HCFA), state legislators, and boards of pharmacy.

The ASHP Section of Clinical Specialists focuses on "bringing science to practice" through 17 specialty networks, dedicated Web-site content, and section-specific electronic listservs and an online membership directory available only to section members.

The ASHP Section of Home Care Practitioners provides home infusion providers in alternative sites with special programming at the Midyear Clinical Meeting, advocacy on reimbursement and JCAHO issues, dedicated Web-site content, section-specific listserv news services, and an online membership directory available only to section members.

ASHP's Center on Pharmacy Practice Management monitors, analyzes, and reports on trends in pharmacy practice management. It conducts and publishes an annual national survey of pharmacy practice in health systems, conducts a leadership conference on pharmacy practice management, and coordinates other educational sessions at ASHP meetings.

ASHP's Center on Managed Care Pharmacy monitors, analyzes, and reports on trends in managed care pharmacy, creates specialized programming at ASHP's national meetings, conducts conferences and workshops, conducts surveys, monitors and influences quality-related measures, and coordinates networking opportunities.

ASHP's Center on Patient Safety helps pharmacists lead implementation of proven medication-use safety practices, fosters best practices, identifies training opportunities, promotes pharmacy's role, facilitates alliances, and collaborates with the ASHP Research and Education Foundation to achieve its goals.

To better support the success of its members, ASHP works with other pharmacy organizations, such as the Joint Commission of Pharmacy Practitioners, the Pharmacy Technician Certification Board, the Board of Pharmaceutical Specialties, the Institute for Safe Medication Practices, and the International Pharmaceutical Federation.

On a broader scale, ASHP's Public Relations Division works to influence the image of pharmacy with the U.S. Congress and regulatory bodies, other healthcare associations, hospital and health-system organizations, groups concerned with scientific issues, accrediting and licensing bodies, groups concerned with consumer and patient safety issues, key health-system decision-makers, and the news media.

Antibiotic Rotation

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INTRODUCTION

Antimicrobial resistance is secondary to a variety of variables (Fig. 1).[1] The link between drug use and the development of resistance is one that has been explored by many investigators resulting in common themes. The Society of Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) have authored a joint publication.[2] Their observations include the following: 1) changes in antimicrobial use are paralleled by changes in the prevalence of resistance; 2) antimicrobial resistance is more prevalent in nosocomial bacterial strains than in those from community-acquired infections; 3) during outbreaks of nosocomial infection, patients infected with resistant strains are more likely than control patients to have received antimicrobials previously; 4) areas within hospitals that have the highest rates of antimicrobial resistance also have the highest rates of antimicrobial use; and 5) increasing duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms.

As a result of these observations, a variety of methods have been utilized to modify antimicrobial use in an effort to combat resistance. These include the use of an antimicrobial formulary, restriction of agents, requirement of prior approval to obtain specific agents, multidisciplinary antibiotic management teams, and the use of computerized support systems. The impact of these programs on resistance is reviewed elsewhere,[3,4] and one or more of these methods is being employed in many institutions.

ANTIMICROBIAL ROTATION

One method that has seen only limited use is antimicrobial rotation. Defined as the prospective and purposeful altering of antimicrobial selection in an effort to prevent or delay the emergence and spread of bacterial resistance, this technique has evolved over the last several decades. Although antimicrobial rotation is simply a variation of antimicrobial control, its motive is focused on resistance prevention and reduction and not specifically on decreasing expenditures related to antimicrobial use.

It is implicit in this type of strategy that one uses a drug for a defined period of time, changes to another agent, and then reuses the original agent. In addition, what is *not* implied is a reactive alteration in antimicrobial selection due to an established epidemic of resistance. These definitions are quite important in evaluating the impact that antibiotic rotation may have, as many individuals have described the later scenario, and these reports do not meet the criteria for an evaluation of rotating drugs.

Several assumptions must be made in order for rotation to be a potentially effective strategy: 1) resistance to Drug A is independent from Drug B; 2) resistant organisms are "less fit" and will go away when selective pressure is decreased or removed (Fig. 2);[5] and 3) the environment in which rotation is being employed is a closed system. In addition, it must be understood that several pathways have been described for the appearance or spread of resistance (Table 1).

Given these assumptions and pathways, clearly, changes in antimicrobial use in a facility or part of a facility will only have potential impact on selection and to some extent on the likelihood of mutations to occur.

ESSENTIAL ELEMENTS OF AN OPTIMAL ANTIMICROBIAL ROTATION PROGRAM

Implementation of an antimicrobial rotation program into any setting is a daunting task. There are many practical issues that currently remain unanswered, including what agents should be included in the rotation, how frequently should rotation occur, what part(s) of an institution would be most likely to benefit from rotation and how to achieve buy-in from the medical staff so as to result in a high level of compliance with the program. Resolutions for these issues that will be broadly applicable to a variety of health care settings are unlikely. It is vital to prospectively answer these questions in a variety of institutions in order

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006403

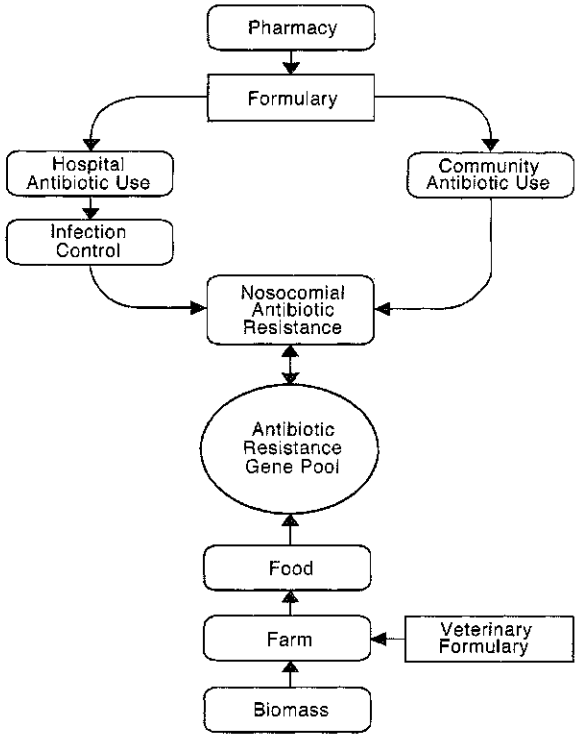

Fig. 1 Variables involved in antimicrobial resistance.

to be able to draw any conclusions about the success or failure of antibiotic rotation.

The impact of such a system will be measured in large part based on the changes in bacterial susceptibility, so

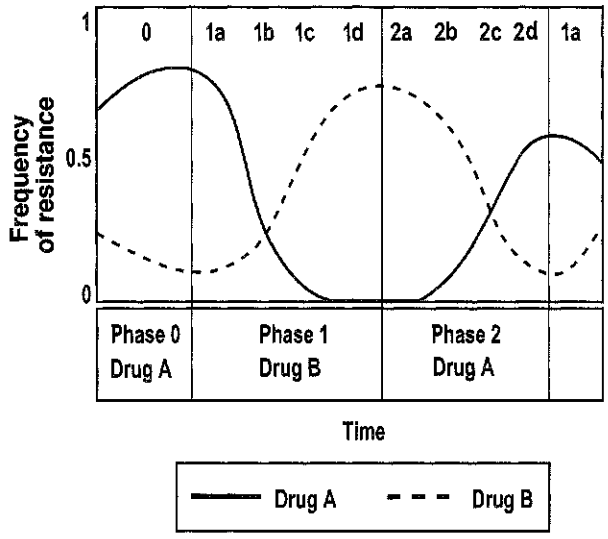

Fig. 2 Resistance assumptions.

Table 1 Pathways for the appearance or spread of resistance

Pathway	Issue
Introduction of a newly resistant organism	Patient, health care worker Other facility (hospital, etc.)
Mutation	Reservoir of high density of organisms with a high likelihood for random selection of resistance mutation
Selection of resistant organism	Selective pressure of antimicrobial use
Dissemination	Poor infection control

(From Ref. [6].)

one must prospectively define what organisms are of interest and what "resistance" is for each key organism. A system must be in place to monitor the presence or lack of resistance. This should include both clinical as well as environmental isolates. Organisms need to be able to be stratified based on site of infection, location within the hospital, and whether they are community or nosocomially acquired. As has been outlined above, antimicrobial agents are only one of the variables related to antimicrobial resistance, and antibiotic rotation should be seen as one of several modalities that will achieve antibiotic stewardship. A stable and effective infection control program must be in place, as well as a mechanism to optimize antimicrobial prescribing and track all antimicrobial use. This needs to include the ability to type organisms, identify genetic markers of resistance, and measure antimicrobial use in each area of an institution per unit of time. Lastly, an evaluation of clinical outcomes needs to be performed to insure that such a strategy does no harm to patients.

EVIDENCE-BASED REVIEW OF THE IMPACT OF ANTIMICROBIAL ROTATION

The first description of rotating antibiotics was conducted by Gerding et al.[7] In an effort to improve susceptibility to gentamicin, a shift to amikacin as the aminoglycoside of choice was conducted. During each period of amikacin use (on average 26 months duration), the susceptibility to gentamicin improved over baseline. Unfortunately, this project was reactive in that the switch was performed as a result of poor susceptibility to gentamicin. The duration of the cycles was not predetermined, there was no differ-

entiation between nosocomial and community isolates, there was no specific infection control documentation, nonaminoglycoside antimicrobial use was not monitored, and clinical outcomes were not assessed.

Various investigators have conducted several other studies involving switches within the same class or a cessation of the use of one agent within a class.[8,9] Most have demonstrated improved antimicrobial susceptibility that was maintained as long as the original agent with which poor susceptibility had been seen, was not reintroduced into the environment. A recent study by Seppala et al. in Finland showed that by reducing the use of erythromycin, the susceptibility of Group A streptococci to macrolides significantly improved.[10] Unfortunately, as newer macrolides penetrated the marketplace in Finland and began to be utilized, this trend was quickly reversed (Fig. 3).[10]

Kollef et al. conducted a single switch study where they treated patients in a cardiothoracic intensive care unit empirically for 6 months with ceftazidime and then in the second 6-month period, treated patients with ciprofloxacin.[11] They showed a significant reduction in ventilator-associated pneumonia (VAP), mostly due to a decrease in the number of patients infected with resistant Gram-negative bacteria. This study did not employ true rotation in that a second 6-month rotation of each therapy was not conducted and, as outlined above, did not meet most of the criteria for an ideal rotation program.

Gruson et al. conducted a study in a 16-bed medical intensive care unit in patients mechanically ventilated for greater than 2 days.[12] During the first phase of the study, ciprofloxacin and ceftazidime were used empirically to treat Gram-negative infections. During the second phase of the study, these agents were restricted, and other antibiotics (including other beta-lactams with or without an aminoglycoside) were utilized. The authors noted a significant reduction in all VAP, but an increase in VAP caused by methicillin-sensitive *Staphylococcus aureus*. Susceptibility patterns for *Pseudomonas aeruginosa* and *Burkholderia cepacia* were evaluated and showed improvements over the baseline period.

Raymond et al. reported on a rotation study in a surgical intensive care unit with a different twist.[13] Patients were stratified as either having sepsis/peritonitis or pneumonia, and empiric therapy was cycled every 3 months by syndrome. Fourteen hundred fifty-six admissions and 540 infections were treated over a 2-year period. With similar severity of illness during the before and after periods (mean APACHE II = 19), the authors demonstrated a reduction of length of stay from a mean of 62 days to 39 days, a reduction of vancomycin-resistant enterococcal and methicillin-resistant staphylococcal infection from 14 per 100 admissions to 8 per 100 admissions and death due to any cause dropped from 25 in the before period to 18 in the rotation period. Antimicrobial susceptibility and several other key parameters needed to evaluate the effectiveness of this program were not reported.

Gelone et al. conducted a 3-year prospective study of antimicrobial rotation in three intensive care units at Temple University (the START trial).[14] This study, like those described above, used a before and after approach. Daily rounds were performed, and the following were assessed on every patient: 1) demographics; 2) antibiotic regimen and dosing; 3) the presence of infection (based on predefined criteria); and 4) organ-

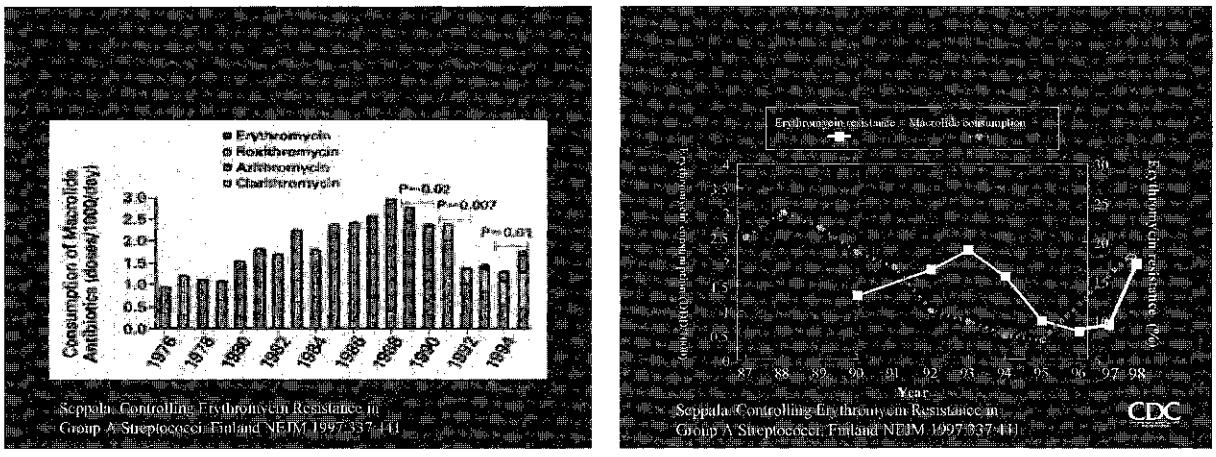

Fig. 3 Effect of erythromycin on Group A streptococci.

ism susceptibility. All definitions were developed prospectively. Criteria for bloodstream, skin and skin-structure, and urinary tract infection were defined based on modified Center's for Diseases Control and Prevention (CDC) criteria. Pneumonia was defined using the American Thoracic Society's criteria. Resistant organisms/infections were defined as resistance to two or more antibiotics typically used to empirically treat the above infection in these units (including aminoglycosides, ceftazidime, ciprofloxacin, imipenem–cilastatin, and piperacillin). Baseline data were collected for a 1-year period, and subsequently, a 2-year rotation period was carried out. Four regimens for empiric therapy of Gram-negative infection were rotated on a monthly basis (cefepime, imipenem–cilastatin, piperacillin–tazobactam, and ciprofloxacin). The addition of an aminoglycoside was left to the discretion of the primary care physician. Susceptibility to studied antimicrobials improved significantly for *Klebsiella pneumoniae*, *Enterobacter species*, *Pseudomonas aeruginosa*, and *Enterococcus species*. Susceptibility remained stable for *Staphylococcus aureus*. Susceptibility significantly decreased for *Acinetobacter species* to imipenem–cialstatin. Resistant bloodstream infection decreased significantly (11% versus 4%) as did resistant pneumonias (15% versus 5.4%). Overall, antimicrobial expenditures remained stable comparing before and after periods ($1.5 before and $1.3 million dollars after). Significant increases were seen in piperacillin–tazobactam (23%), imipenem–cilastatin (21%), and ciprofloxacin (18%) use, while cefepime use decreased by 34%. Review of crude mortality rates for bloodstream infections and pneumonia cases showed no significant differences.

The CDC has funded a 2-$^1/_2$ year, three-center study to evaluate antimicrobial rotation in adult intensive care units.[15] This trial will utilize 4-month cycles of the following drugs: cefepime, a fluoroquinolones, imipenem–cilastatin or meropenem, and piperacillin–tazobactam. Investigators will evaluate the acquisition of antibiotic-resistant Gram-negative organisms as gastrointestinal tract colonizers, those associated with clinical infection, changes in organism susceptibility over time, and adverse events and death. At the time of this publication, this project was just underway, and results were unavailable.

ROLE OF ANTIBIOTIC ROTATION

As stated above, antibiotic rotation should be viewed as one method of antibiotic control. As with most methods of antibiotic control, definitive evidence of its impact in a variety of health care settings is lacking. The available evidence does suggest that antibiotic rotation is associated with improvements in bacterial susceptibility and a decrease in the incidence of resistant infections. Many questions remain unanswered, including which agents to rotate, how long to rotate, and what settings would most benefit from this strategy.

The development of new or novel agents active against resistant pathogens is time consuming and at times lags behind new microbial threats. Strategies that enable the use of currently available agents for extended periods of time are exciting and necessary. Although antibiotic rotation is promising, there are currently gaps in knowledge regarding this method of antibiotic control. In addition, the data generated to date may not be generalizable across various health care settings. Caution should be exercised in establishing such a program. Individuals are encouraged to apply as many of the essential elements noted above in an effort to assess the impact of this strategy. Documentation of results (both positive and negative) is essential to define the ultimate role of antibiotic rotation.

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PROFESSIONAL DEVELOPMENT

Anticoagulation Clinical Pharmacy Practice

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INTRODUCTION

Anticoagulation clinics serve the purpose of a coordinated clinic that oversees the management of oral anticoagulants (blood thinners), specifically, the medication warfarin. These anticoagulation clinics may also employ the use of intravenous or subcutaneous administration and monitoring of unfractionated heparin and low-molecular-weight heparin (LMWH). Anticoagulants in anticoagulation clinics are used for treatment and prevention of blood clots in the deep venous system and lungs, prevention of systemic blood clots in patients with atrial fibrillation, and prosthetic mechanical heart valves. They are also used in peripheral vascular disease, prior strokes, congestive heart failure, heart attacks, and hypercoagulable states.

Anticoagulation clinics are based in the inpatient or outpatient units of a hospital or managed-care organization, or in a community setting. They have been in existence since at least 1968, when they were managed solely by physicians.[1] Pharmacists have been involved with such clinics since the 1970s, both in the United States and in Europe.[2–7] The role of the pharmacist in an anticoagulation clinic varies widely. The pharmacist may be part of a multidisciplinary team, including physicians, physician assistants, and/or nurses, or the pharmacist may be directly responsible for the management of the clinic. In the winter of 1999, a survey by the Anticoagulation Forum elicited 233 responses out of 531 anticoagulation clinics contacted.[8] Anticoagulation clinics had a patient panel size ranging from 1 to 1000+ patients, with a median of 250 patients per clinic.[8] The majority of these clinics received referrals from cardiologists and general internists.[8] A little more than 50% of the staffing consisted of pharmacists, another 40% consisted of nurses.[8]

A variety of factors influence the safety of anticoagulation therapy, given the narrow therapeutic range of anticoagulation therapy and the risk of an adverse event versus the benefit of therapy. These factors include the following:

- Patient understanding of the medications.
- Patient compliance with medications and appointments.
- The need for frequent International Normalizing Ratio (INR) testing.
- Medications, diet, and illnesses.
- The need for careful assessment of results.
- The need for increased communication with patients.
- The need for coordination of care with other providers and services, such as laboratories.[9]

The majority of patients who are placed on oral anticoagulation are followed by their personal primary-care provider.[9] These providers often have an inadequate system for tracking patients and ensuring follow-up, and lack the time for thorough patient counseling.[9] Often practitioners are not aware of the multitude of drug interactions. These factors have deprived many patients of proper follow-up, or many times patients simply are not put on oral anticoagulation because of the complexity of monitoring.[9] Increasingly, patients are being placed on therapy with oral anticoagulation medications when there is a coordinated system in place to monitor them and thus improve overall patient care.[9] Anticoagulation clinics allow for a systemized approach to monitoring, evaluating, and adjusting appropriate anticoagulation therapy.[9] Pharmacists have been able to develop their role as an anticoagulation practitioner due to the significant role they play in counseling and educating patients about their medications. Pharmacists also possess the advanced drug knowledge and education in pharmacology and pharmacokinetics required in managing these patients.

The prothrombin time (PT) test is the most common method for monitoring oral anticoagulation.[10] Standardization of this test using the INR has improved reliability of warfarin monitoring in North America.[10] Findings from two pharmacist-managed anticoagulation clinics

DOI: 10.1081/E-ECP 120006223

showed how unstandardized PT tests could lead to significant error and misjudgment.[11] The adoption of the INR is considered one of the most significant advances in anticoagulation therapy.

CLINICAL PHARMACY OPPORTUNITIES

Anticoagulation Clinics in the United States

There have been many articles published concerning pharmacist involvement with anticoagulation clinics. Typically, such anticoagulation clinics are in hospital-based, outpatient settings. In the United States, the majority of these clinics are in the outpatient units of the Department of Veterans Affairs Medical Centers (VAMC) and other teaching hospitals.[2–4,6,7,12–27] These anticoagulation clinics are usually responsible for the management and coordination of warfarin therapy. The first report of a pharmacist-managed anticoagulant clinic was published in 1979.[2] This report described a pharmacist-managed anticoagulation clinic at McGuire VAMC in Richmond, VA, that began in the Department of Cardiology. Although the majority of anticoagulation clinics exist in VAMC or university-affiliated teaching hospitals, there have been descriptions of an outpatient anticoagulation clinic in a private community hospital[28] and in managed-care settings.[29–31] There is a growing network of private practice-based, for-profit clinics.[32] Anticoagulation clinics can also be found in the inpatient setting.[33–35]

Outpatient Treatment of Deep Vein Thrombosis with LMWH

With the advent of LMWH, anticoagulation clinics are now using LMWH, by use of which patients can avoid being admitted into a hospital or shorten the length of hospitalization.[22–24,30,31] Patients can have their injections done at home. Patients with a confirmed diagnosis of deep vein thrombosis (DVT) are evaluated to determine eligibility to receive LMWH via outpatient. Once the patient is eligible, a nurse typically administers the first dose, and the pharmacist begins the counseling and evaluates the patient's ability to self-inject. The anticoagulation clinic then follows up with the patient until determining that anticoagulation therapy is no longer required.

Anticoagulation Clinics in the United Kingdom

In the United Kingdom, pharmacists have also managed anticoagulation clinics.[5,36–40] They can be found in hospital clinics, general practitioner surgery clinics, and community pharmacy-based clinics. In a year 2000 survey, approximately 20% of the 250 National Health Service hospitals had a pharmacist-led anticoagulation clinic; these anticoagulation clinics are now working together to develop a master protocol for the initiation of DVT treatment, management of anticoagulation treatment in outpatients, training of anticoagulation personnel, and research opportunities.[41] Pharmacists have also been involved in a pharmacist-led outpatient DVT clinic.[38] At Neath General Hospital, it was determined that there was a potential savings of 268 inpatient-bed days annually by employing the outpatient DVT clinic.[38] A former senior general practitioner at Downfield surgery in Dundee explained how working with a team, specifically with pharmacists, led to improved patient care, innovation, and development.[42] He noted that pharmacists are playing a major role in implementing national evidence-based guidelines to improve the quality of patient care.[42]

Description of Anticoagulation Clinics

There may not be such a thing as a typical anticoagulation clinic. Generally, however, a physician will serve as a director or consultant for the clinic. The physician may directly oversee each plan the pharmacist formulates, or the pharmacist may follow some type of protocol without being directly supervised by the physician. In many clinics, the pharmacist has responsibility for designing an appropriate anticoagulant regime for the patient. The pharmacist is normally responsible for the day-to-day operations of the clinic. Pharmacists are also responsible for enrolling patients in the anticoagulation clinic by obtaining medication and medical histories, and by assessing factors that may affect the control of the therapy. The pharmacist is responsible for counseling patients about the signs and symptoms of bleeding and clotting, compliance with medications and follow-up appointments, drug interactions, food interactions, and how health status affects warfarin. Generally, the patient presents for a blood draw either via venous puncture or via point-of-care testing. Point-of-care testing is currently being used in a few clinic sites and is done via portable machine. It measures the INR from a fingerstick sample of whole blood and provides results within minutes. If the patient has blood drawn from a venous puncture, the patient will have to wait for results, or some clinics will call or mail them to the patient. With modern technology, an efficient lab can provide INR results within 15 minutes of a blood draw. If blood is drawn from a finger stick, the patient will receive the results immediately and will be given instructions on dosing of warfarin and follow-up instructions for returning to the clinic. Regardless of the means of testing, patients are assessed for compliance

with the anticoagulant, signs or symptoms of bleeding or clotting, recent changes in diet, appetite, medications, alcohol consumption, and illnesses. Based on the patient's INR and assessment of the previous factors, the anticoagulant may be continued or adjusted. A follow-up appointment is then made.

Safety

Table 1 summarizes nonrandomized, mainly retrospective studies that compare frequency of hemorrhage and thromboembolism prior to being enrolled into a pharmacy-managed anticoagulation clinic and after enrollment. These studies demonstrate a decrease in adverse events when patients are followed in a pharmacist-managed anticoagulation clinic. Many of these reports compare adverse events before there was an anticoagulation clinic versus after an anticoagulation clinic was instituted. The study by Chiquette et al. was unique in that it compared results with three different inception groups.[17] All the patients were newly started on warfarin, two groups were in a pharmacy-managed anticoagulation clinic, and one group was managed by routine medical care.[17]

Cost Effectiveness

The cost effectiveness of pharmacy-managed anticoagulation clinics has been addressed in a few studies.[13,15,17] Usually the benefits are determined from decreased adverse events and decreased hospitalization and emergency visits. In one study, hospitalizations and emergency room visits were reduced by 50 to 80%.[17] Savings have been estimated between $860 and $4072 per patient per year of therapy for patients on oral anticoagulation therapy.[13,15,17] Anticoagulation clinics that have used LMWH for DVT treatment in the outpatient setting have estimated cost-avoidance savings between $1800 and $2470 per patient treated.[24,31] These savings not only reflect improved anticoagulation management, but also reflect pharmacists identifying and intervening with other medical conditions. Chiquette et al. described $300 savings per patient per year in regards to other interventions besides anticoagulation management.[17]

Patient and Physician Satisfaction

Three surveys have been published on patients' perceptions of a pharmacy-managed anticoagulation clinic.[19,25,29] Generally, patients found pharmacists to be caring and competent.[19] Patients perceived that they were at a decreased risk of having problems with warfarin and blood clotting due to pharmacist involvement, and they believed that frequent monitoring of their warfarin would mean less chance of bleeding or clotting.[25] Overall, patients were highly satisfied with the care they received from a pharmacist-managed anticoagulation clinic.[29] A survey of physicians published in the United States elicited 21 out of 41 responses and showed that physicians were positive about the care their patients were receiving from a pharmacy-managed anticoagulation clinic.[29]

Future

The future for anticoagulation clinics is bright. Every year there is evidence of increased interest in this area. The

Table 1 Frequency of hemorrhage and thromboembolism with routine medical care versus pharmacist-managed anticoagulation clinics

Study[b]	Type of care	No. of patients	Patient years	Major hemorrhage[c]	Minor hemorrhage[c]	Thromboembolism[c]
Cohen et al. 1985[6]	RMC	17	NA[a]	9.0[d]	NA[a]	NA[a]
	AC	18		6.9[d]	NA[a]	NA[a]
Garbedia-Ruffalo et al. 1985[12]	RMC	26	64.3	12.4	NA[a]	6.2
	AC	26	41.9	2.4	NA[a]	0
Wilt et al. 1995[15]	RMC	NA[a]	28	28.6	14.3	48.6
	AC		60	0	13.7	0
Chiquette et al. 1998[17]	RMC	142	102	3.9	62.8	11.8
	AC	176	123	1.6	26.1	3.3

AC, Pharmacist-managed anticoagulation clinic; RMC, routine medical care.
[a]NA, not available.
[b]Mix indications for warfarin (venous and arterial disease).
[c]Results expressed as percent per patient year of therapy.
[d]Combined major and minor hemorrhage.
Adapted from Ref. [9].

biggest problem facing anticoagulation clinics today is reimbursement. Pharmacists currently can only bill for a minimal visit, whereas other practitioners such as nurse practitioners and physician's assistants can charge three to five times as much per visit due to their provider status. Oral anticoagulation monitoring may become more common in the community setting as pharmacists learn more about anticoagulation and as more states allow pharmacists to adjust medications. Patients may find it to be more convenient due to proximity of local pharmacies, and with the availability of portable point-of-care testing, patients can receive results quickly.[43] Many patients may ultimately perform testing at home with portable machines.[44] Home testing can be performed in a couple of ways. Either the patient tests the blood at home and calls in the results to the anticoagulation clinic, or the patient follows a protocol to adjust the warfarin dosage at home.[44] There will always be some patients not capable of performing their own testing. Even if the patient is monitoring his or her blood at home, pharmacists will still need to be involved by providing education and making dosage change recommendations, especially when confounding factors exist, such as drug interactions and illnesses. Currently, the disadvantages of the portable machines are that they are expensive and that follow-up management is not billable. Recently, Roche Diagnostics withdrew its point-of-care testing machine for patient's home use due to insurance companies, hospitals, and clinics not willing to pay for such machines. Results of portable machine monitors versus routine lab results may diverge at high INRs; however, this also can occur between two different routine laboratories. Two studies reported that the portable monitor was more reliable, less variable, more reproducible, and less likely to give clinically misleading and erroneously high INR results than the laboratory of a major medical center.[45]

CERTIFICATION, TRAINING, AND CREDENTIALING

Certification

Pharmacists in anticoagulation clinics should be able to demonstrate advanced knowledge of anticoagulation. More recently, the importance of credentialing anticoagulation providers has come to the forefront. This may become more important in the future for pharmacy practitioners who want reimbursement for their services. The National Certification Board for Anticoagulation Providers (NCBAP) has a mission to optimize patient care through a multidisciplinary national certification process for registered nurses, advanced practice nurses, pharmacists, physician's assistants, or physicians. Any credentialed individual who is a Certified Anticoagulant Care Provider (CACP) should possess advanced antithrombotic/anticoagulant knowledge. Practitioners are required to submit evidence of their practice experience and obtain a passing score on a comprehensive examination. CACP providers must possess a valid U.S. professional license, as well as the knowledge and skills to provide high-quality care to patients. The certification and examination began in 1999; as of the spring of 2000, there were 68 CACP providers, 44 of these being pharmacists.[46] (To obtain more information, contact the NCBAP through www.acforum.org or write to NCBAP, c/o Anticoagulation Forum, Boston University Medical Center, Room E-113, 88 E. Newton Street, Boston, Massachusetts 02118-2395, phone 716-638-7265.) The National Institute for Standards in Pharmacists Credentialing (NISPC) was formed in 1998 by the American Pharmaceutical Association, the National Association of Boards of Pharmacy, the National Association of Chain Drug Stores, and the National Community Pharmacists Association. The NISPC provides a nationally recognized credentialing process that establishes appropriate standards of care and facilitates recognition of the value of disease state management services such as anticoagulation provided by pharmacists. (To obtain more information, contact the NISPC Testing Center through www.nispcnet.org, or write to NISPC Testing Center, 700 Busse Highway, Park Ridge, Illinois 60068-2402, phone 847-698-6227.)

Training

The Anticoagulant Therapy Management Certificate Program is an internet-delivered program developed by the University of Southern Indiana, School of Nursing and Health Professionals. This program is a collaborative effort among regional health care providers, members of the NCBAP, and the University of Southern Indiana School of Nursing and Health Professionals. Their goal is to prepare health professionals for monitoring and managing outpatient anticoagulation therapy. This program will also prepare health professionals for the National Certified Anticoagulation Care Provider Examination. (For information, visit the web site at http://healthusi.edu or call 1-877-874-4584.)

The American Society of Health-Systems Pharmacist (ASHP) Foundation provides a 5-day, experience-based certificate program called the Anticoagulation Management Service Traineeship Program. This program is designed to train pharmacy practitioners to establish and

maintain specialized services for the management of patients undergoing long-term anticoagulant therapy. The program is intended to provide individualized, intensive didactic and clinical training for selected candidates. Trainees will observe and participate in the activities of an established anticoagulation management service. This program provides 35 hours of continuing education. (Applications and additional information may be obtained by calling the ASHP Fax-on-demand system at 301-664-8888 and requesting documents 702 and 703, or by logging on to their web site at www.ashpfoundation.org.)

The American College of Clinical Pharmacy (ACCP) Research Institute, University of Texas (UT), and Anticoagulation Clinics of North America (ACNA) provides a minimum 4-week, intensive traineeship that includes a structured didactic component, extensive clinical experience in several ACNA practice sites in San Antonio, TX, and surrounding communities; and participation in ongoing clinic research. The program is targeted primarily to PharmD students in their final year of professional study, but pharmacy residents and fellows as well as practicing pharmacists are encouraged. Applicants have also come from other countries. Arrangements can be made with ACNA/UT faculty for students to receive academic credit from their home institution for the experience. (Applications can be obtained through www.accp.com/ClinNet/Research.html or by calling 816-531-2177.)

The University of Illinois at Chicago offers an Antithrombosis Management Service Certificate Program via the Internet. It is a 9-week certificate program and offers 40 contact hours. This program covers a wide array of topics, including pharmacotherapy, patient assessment, protocol development, and business planning. (Applications can be obtained through conted@uic.edu or by calling 866-742-7623.)

Credentialing

A 1996 survey conducted nationwide in the United States elicited 110 responses out of 177 pharmacist-managed anticoagulation clinics contacted.[47] As per the results, 23% offered some type of anticoagulation training program and 29% had at least one pharmacist who completed the ASHP Research and Education Foundation's Anticoagulation Service Traineeship.[47] At the McClellan Memorial VAMC in Little Rock, Arkansas, the anticoagulation clinic has specific guidelines on how their pharmacists should be trained and credentialed.[21] Pharmacists are required to have the following:

- Advanced knowledge of the pharmacology and pharmacokinetics of anticoagulants.
- Advanced knowledge of the pathophysiology of thromboembolic disease states.
- Experience with physical assessment and interviewing patients.
- Experience preparing and providing in-service education to other health care professionals and patients.
- A working knowledge of basic hospital and clinic policies and quality assurance practices.[21]

These requirements were met through reading review and research articles, observing patient interviews and conducting patient interviews under direct observation of a privileged anticoagulation clinic pharmacist, presenting an in-service, and passing a credentialing examination.[21]

RESOURCES

There are a few critical papers or publications that a practitioner should have available in the clinic:

- *Consensus Conferences on Antithrombotic Therapy* sponsored by the American College of Chest Physicians.[48] This provides a comprehensive review and recommendations performed by international experts on antithrombotic therapy.
- *British Committee for Standards in Haematology Guidelines.*[49] This document tends to be the guideline used in Europe. It contains information on indications for oral anticoagulation and management of an anticoagulation service.
- *The Consensus Guidelines for Coordinated Outpatient Oral Anticoagulation Therapy Management.*[50] This guideline contains information on the organization and management of anticoagulation clinics.
- *Managing Oral Anticoagulation Therapy, Clinical and Operational Guidelines.*[9] Written by a multidisciplinary group of health care providers. This is an excellent resource that covers the development and implementation of an anticoagulation management service and management of patients receiving oral anticoagulants. The chapters contain examples of actual policies, procedures, guidelines, algorithms, charts, and flow sheets used in anticoagulation clinics across the United States.
- The NCBAP puts forth competency statements for certified anticoagulation care providers. There are five domains:
  - Applied physiology and pathophysiology of thromboembolic disease.
  - Patient assessment and management.

- Patient education.
- Applied pharmacology of antithrombotic agents.
- Operation (administrative) procedures.
- Extensive recommendations on resources and references.

Pharmacy organizations or web sites that practitioners may find helpful are as follows:

- The ACCP's Practice and Research Networks (PRNs) are for members with common practice and research interests. An interactive e-mail group allows members to exchange information on a daily basis.
- ASHP:
  - ASHP Foundation provides an example of an anticoagulation clinic protocol.
  - Drug-use evaluation criteria that have been put forth by ASHP.[51] These criteria serve as guidelines for quality assurance.
- The web site of the Anticoagulation Forum (www.acforum.org) has links to continuing education, news and events, newsletters, and clinic locations.[52]
- The Department of Health in the United Kingdom provides an anticoagulant booklet, which provides patients with information on anticoagulation [obtained from DHSS Stores, No. 2 site, Manchester Road, Heywood, Lancashire OL10 2PZ, or SHHD (Div. IIID), Room 9, St. Andrews House, Edinburgh EH1 3DE].[49]

PROFESSIONAL NETWORKING OPPORTUNITIES

The Anticoagulation Forum, founded in 1991, is an excellent avenue for professional networking. It brings together three health care disciplines—medicine, nursing, and pharmacy. This organization has global membership and is interested in anticoagulation management in the setting of a coordinated anticoagulation management service. It is supported by the pharmaceutical and diagnostics industry. Currently, the organization's web site contains information about news and events, articles, meetings, and continuing education.[52] It can be accessed through the following web site address: www.acforum.org.[52] There are currently more than 2300 members representing 25 countries and more than 800 anticoagulation clinics.[52] These countries include the United States, Canada, Panama, Netherlands, Scotland, Germany, Brazil, Slovenia, Denmark, Holland, Sweden, Switzerland, Argentina, Iran, Uruguay, France, Italy, Korea, Saudi Arabia, Australia, United Kingdom, Singapore, Israel, Spain, and China.[53] This forum holds a conference biannually.

Another networking opportunity is the University of Wisconsin–Madison-sponsored Pharmacy Invitational Conference on Anticoagulation Therapy. This conference is held yearly, immediately preceding the ASHP Midyear Clinical Meeting in December. This event includes a full day of anticoagulation topics and qualifies for continuing education credit.

LEGAL ISSUES

Although important, only limited information is available in the literature concerning the legal issues of operating an anticoagulation clinic. Legal issues are mentioned briefly in the 2001 Chest supplement.[54] It describes strength in unanimity among anticoagulation clinics.[54] As the number of anticoagulation clinics increases and as more studies show that anticoagulation clinics improve patient care, anticoagulation clinics are becoming the standard of care. Other means of managing anticoagulated patients may have to demonstrate services that are equal or superior to an anticoagulation clinic.[54]

Another issue that may impact pharmacist-managed anticoagulation clinics will be collaborative drug therapy management (CDTM) based on legislated statute. Anticoagulation clinics are a good example of CDTM.[55] It is officially recognized in 25 states and by the federal government (i.e., U.S. armed forces, VAMCs, Indian Health Service).[55] Typically, the physician delegates management authority to the pharmacist with the terms of a formal agreement.[55] It allows pharmacists to order laboratory tests, assess patients, initiate and modify drug therapy, monitor patients, and administer medications.[55] States without CDTM may limit the pharmacist's role in an anticoagulation clinic.[55] To avoid litigation, pharmacists should be well trained, act within protocol framework, document thoroughly, and always be sure patients are aware that a pharmacist is providing care.[55]

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Association of Faculties of Pharmacy of Canada

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INTRODUCTION

The Association of Faculties of Pharmacy of Canada (AFPC) was originally constituted as the Canadian Conference of Pharmaceutical Faculties in 1944. At that time there were seven pharmacy schools in Canada and this organization was formed to enhance pharmacy education in Canada. The name was changed to the Association of Faculties of Pharmacy of Canada in 1969 and the organization currently includes all pharmacy teaching faculty in the nine faculties of pharmacy in Canada.

ORGANIZATION STRUCTURE AND GOVERNANCE

The organization includes the nine faculties of pharmacy in Canada and all faculty members who have the equivalent of 20% FTE appointments within those institutions. There are currently 215 active members, 12 associate members, and 13 affiliate members within the organization.

The organization has a four person executive and a nine member council with each member representing one of the faculties of pharmacy. The executive director serves on a half time basis; the current executive and council members appear in the appendix.

SUMMARY OF MISSION AND KEY OBJECTIVES

The mission statement currently under review) is to develop and implement policies and programs which will provide a forum for exchange of ideas, ensure a liaison with other organizations, and foster and promote excellence in pharmaceutical education and research in Canada.

Primary Objectives

- To foster and promote progress in pharmaceutical education and research.
- To stimulate and provide opportunity for exchange of ideas and discussion among pharmaceutical educators with a view to improving curricula and teaching methods.
- To encourage high and uniform standards of education in pharmacy throughout Canada by assuming an advisory role for development of policies and standards used for the accreditation of programs of pharmaceutical education.
- To establish and maintain liaison with pharmacy and appropriate educational associations, other health professionals, government agencies and members of the pharmaceutical industry that may further the development, support, and improvement of pharmaceutical education, practice, and research.
- To represent, support, and protect the interests of members and to give recognition for achievement.

Current Initiatives

The AFPC has directed resources and energies to a number of activities that are designed to assist faculty become better teachers, to help schools with curricular planning, and to inform the academy of developments in education and learning. Educational outcomes have been established for both the baccalaureate and doctor of pharmacy programs. Recent annual conferences have focused on new teaching methods and means of evaluation of both students and the educational programs. The AFPC has also participated in several initiatives and position papers that were intended to serve the broader interests of the profession in the health care system. One very important issue—the human resource needs within the pharmacy profession—is currently being addressed. This not only includes the number of pharmacy personnel, but also the educational requirements for different levels of those personnel.

Major Meetings

The Association convenes an annual conference in late May or June of each year. The Executive and Council also

DOI: 10.1081/E-ECP 120006279

hold a mid-year meeting in February with the primary purpose of conducting internal business and meeting with external pharmacy and related organizations.

APPENDIX: AFPC COUNCIL AND EXECUTIVE DIRECTORY (EFFECTIVE SEPTEMBER 12, 2000)

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Australian Adverse Drug Reaction Advisory Committee

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INTRODUCTION

In common with many other nations around the world, in Australia the Commonwealth Department of Health and Aged Care maintains an infrastructure that deals with issues relating to the safety and efficacy of pharmaceutical drug products. The Australian Drug Evaluation Committee (ADEC) was established in 1964 to address this role, and in 1970 a subcommittee known as the Adverse Drug Reactions Advisory Committee (ADRAC) was formed to facilitate the monitoring of medicinal drug safety in Australia. In this regard, ADRAC performs similar functions to those of the U.S. Food and Drug Administration (FDA) and the U.K. Committee on Safety of Medicines (CSM).

ADRAC MEMBERSHIP

The Executive Secretary of ADRAC is Dr. Ian Boyd (Ian.Boyd@health.gov.au), who administers the affairs of the committee. The Chair of the ADRAC committee is Dr. Timothy Mathew, a nephrologist based in Adelaide, South Australia. The current membership of the committee is constituted entirely of senior medical practitioners from locations around Australia. Each member has an extensive background in clinical and academic medicine, and all are highly respected by their peers. The Society of Hospital Pharmacists has recently lobbied without success for the addition of one or more senior clinical pharmacists to the committee. This request has been based on the sizable proportion of reports from the Australian hospital pharmacy sector and the unique skills and training that an appropriate pharmacist could bring to the committee.

REPORTING OF SUSPECTED ADVERSE DRUGS REACTIONS TO ADRAC

ADRAC utilizes a spontaneous, voluntary reporting system to identify suspected adverse reactions to drugs in hospitals and community-based settings. A standard reporting form (sometimes referred to as the "blue card") is widely promulgated by ADRAC by dissemination with commonly used Australian drug information resources such as the *Australian Medicines Handbook*, and it can also be downloaded from the Web site www.health.gov.au/tga/docs/html/adr.htm. The form is used to document information about all drug therapy at the time of the suspected adverse drug reaction (ADR), as well as basic demographic and clinical information such as age, gender, height, and weight. There is also space to record other relevant information, such as laboratory indices, relevant history, or previous exposure to the drug. Other information recorded on the form includes the details of any treatment administered and the outcome of the reaction (including sequelae). Completed forms are sent to the ADRAC secretariat in Australia's national capital city, Canberra, where the information is collated and analyzed in the ADRAC secretariat.

The last 10 years have seen substantial growth in the number of ADRs reported to ADRAC. Most recently, ADRAC has received some 13,000 reports per annum, and although the absolute number of reports may appear modest by international comparison, it is important to note that the proportionate rate of reporting (when adjusted for Australia's population) is higher than that of most other developed nations. Recent data suggests that approximately 1% of reports received have a fatal outcome. Approximately 50% of reports received by ADRAC now originate from the pharmaceutical industry, with a further 25% submitted by primary care physicians (also referred to in Australia as general medical practitioners). On the order of 20% of all submissions are received from Australian hospitals, and of these reports the majority are from hospital pharmacists. A small proportion of reports is also received from community-based pharmacists. Unlike the case in other parts of the world, submissions from nurses do not contribute significantly to the total number of reports received by ADRAC each year.

DOI: 10.1081/E-ECP 120006371

Although ADRAC clearly encourages reporting of all suspected adverse drug reactions in Australia (including those to alternative medicines, including herbal and homeopathic products), the committee has provided guidance in relation to reactions of particular interest. Reactions that result in death, danger to life, admission to hospital, prolongation of hospitalization, absence from productive activity, or increased investigational or treatment costs have been identified as priority areas for ADRAC. In addition to these reports, the committee also requests the reporting of all suspected drug interactions, as well as all reactions thought to have been implicated as a cause of birth defects. Naturally, reaction reports are also sought for drugs that have been newly released onto the Australian market.

ANALYSIS AND USAGE OF ADR DATA BY ADRAC

The information received in ADR reports is considered by the ADRAC committee during its meetings, conducted eight times each year. After analyzing the clinical circumstances and ancillary data described in the report, assignment of a causality rating (in accordance with predefined criteria) is generally the next step. In a relatively small proportion of cases, the ADRAC secretariat may make further contact with the health practitioner who made the original report, seeking to gain additional clarifying information or to ascertain the outcome or sequelae of the suspected reaction. Once processed, the information is entered into a relational database that now stores details of many thousands of ADR reports. Health professionals such as clinical pharmacists can contact the ADRAC secretariat for information about possible reactions. Data available on request include the number of reactions (including reactions of a particular type) that have been received for any drug, as well as causality ratings assigned by the committee for individual reports. Upon further request, it is possible to access detailed clinical information about individual ADR reports. This service is provided in a very timely fashion, with the turnaround time for the feedback of information routinely less than 24 hours.

In addition to providing access to the information stored in the database, ADRAC also utilizes the information received in reports for a range of other purposes. The ADRAC bulletin is published four times each year and is widely distributed to medical practitioners and pharmacists free of charge. The bulletin, which is also available on the Internet (www.health.gov.au/tga/docs/html/aadrbidx.htm), summarizes details of common or important drug reactions and interactions and in this way serves an important educative function. Information from ADR reports is also summarized into reports that are published up to three times a year in the *Medical Journal of Australia*. ADR data from ADRAC are also forwarded to the Collaborating Centre for International Drug Monitoring of the World Health Organization in Uppsala, Sweden.

CONCLUSION

In summary, the ADRAC committee performs a unique and important public health role in Australia. The work of the committee and the secretariat provides vital support for Australian health care workers seeking information about the adverse effects of drugs. In return, ADRAC enjoys strong support from doctors, pharmacists, and the pharmaceutical industry in the form of voluntary, spontaneous reports of ADRs. In this way, ADRAC works with other stakeholders to make a positive contribution to the quality use of medicines in Australia.

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Australian Medicines Handbook

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INTRODUCTION

The Australian Medicines Handbook (AMH) is a compendium of drug and therapeutic information. It was developed to provide pharmacists, doctors, other health professionals, and their students with concise, independent and comparative information about drugs and quality drug use in Australia.

PHILOSOPHY

A compendium of drug and therapeutic information, the AMH is an initiative of Australia's National Health Policy in response to professional, consumer, and government concerns about the lack of independent drug information resources in Australia. AMH was developed to provide pharmacists, doctors, other health professionals, and their students with independent and comparative information about drugs.

AMH was initially modeled on the British National Formulary (BNF), and evolved to incorporate further comparative and therapeutic information. The best available evidence is used to support recommendations, thus discouraging drug use where evidence is lacking or poor.

AMH publications are designed as practice, teaching, and learning tools, and aim to promote Quality Use of Medicines (QUM) by providing readily accessible, concise, up-to-date, clinically relevant information that facilitates effective, rational, safe, and economical prescribing and dispensing.

AMH complements other independent Australian publications about drugs and therapeutics including Australian Prescriber, the Therapeutic Guideline series, and National Prescribing Service publications. It provides a different focus to drug information compendia based on government-approved Product Information.

KEY HISTORY

The concept of a "national formulary" modeled on the BNF was recommended in 1991 following a meeting convened by the Australian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) and the Consumers' Health Forum. In June 1995, money was granted by the Australian Government to develop a drug information database suitable for publishing printed and electronic versions of an Australian Medicines Handbook. The publishing phase was not initially funded. First staff were appointed in December 1995.

In May 1998, the first edition, AMH 1998, was published. The second edition, AMH 2000, was published in February 2000. CD-ROM and Internet products, based on second edition content, were released in May 2000, with upgrades released in April 2001. A set of third edition products is planned for release in early 2003.

Australian Medicines Handbook Pty Ltd., the business entity that owns the content and publishes the products, was established with Australian government funding. It received its final funding in March 1999, and now operates on a fully commercial basis. The three shareholders of the company are the Royal Australian College of General Practitioners, the Pharmaceutical Society of Australia, and the Australasian Society for Clinical and Experimental Pharmacologists and Toxicologists.

UPTAKE IN MAJOR TARGET GROUPS

The first edition was available only in print version (book) and sold approximately 9500 copies. The second edition, AMH 2000, is expected to at least match this figure in print version sales. CD-ROM and Internet versions based on the second edition have made a significant impact on uptake.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006366

Uptake by community and hospital pharmacists and undergraduate pharmacy training is very high. Most medical students in Australia now use AMH. In teaching hospitals, uptake by nurses and doctors is moderate to high but varies by state. Although uptake in general practice is moderate (about 10 to 20%), it appears to be steadily increasing (1).

CONTENT FEATURES

In Australia, the most commonly utilized and accessible information sources about prescription drugs are based on a drug's Product Information, the document approved by Australia's drug regulation authority, the Therapeutic Goods Administration (TGA).

AMH content is written after consideration of best available scientific evidence, the Product Information, standard international reference sources, and Australian evidence-based and consensus guidelines from government and nongovernment agencies. Information is concise and clinically relevant for Australian practice, providing comparisons between drugs and between drug classes, with a focus on comparative efficacy, safety, and cost. Key advice for patients about how to use medicines safely and effectively is included.

Types of Information Presented

Information in the AMH is organized into 20 chapters, according to organ-system (e.g., neurological drugs). Each chapter contains brief disease treatment summaries (e.g., hypertension), which incorporate discussion of various treatments, including nondrug and complementary therapies, and comparison of different classes of drugs. Treatment summaries also include advice for appropriate management for specific groups of patients or stages of disease.

Drug profiles are arranged by generic drug name and listed under drug class profiles (e.g., ACE inhibitors); this allows for comparison across a class to be made, and minimizes repetition of information common to all members of the class. Indications listed in monographs are generally those that are approved by TGA. Additional accepted clinical uses such as minor indications for which there are few or no other alternative drugs and there is evidence to support such use are also included. Dosage information is clear and concise; interactions information is limited to those likely to be important clinically, together with advice on management. Information and recommendations regarding use of a particular drug in pregnancy, breastfeeding, renal or hepatic impairment, children, and the elderly are included. AMH documents frequently include "Practice points," which include brief information, advice, and tips that are important for the safe and effective use of a particular drug or drug class.

General principles of drug use for groups of drugs, such as anti-infectives, antineoplastics, and ocular drugs, are also provided.

BENEFITS

Although passive provision of this high-quality targeted information alone is unlikely to change prescribing behavior and improve health outcomes, access to impartial drug information is recognized as a component of the WHO/INRUD drug use indicators (2) and is an identified strategy in the implementation plan of Australia's National Prescribing Service.

The perceived benefits of AMH are:

- It is a good starting point for drug-related questions, and can save time by providing reliable up-to-date information in a user-friendly format.
- It provides practical knowledge and advice that is independent of government and acts as a balance to promotional information provided by the pharmaceutical industry.
- It is written in minimally technical language and can be used as an aid to patient consultations.
- It is suited to both hospital and community use.

AMH has been credentialed by key health professional organizations such as the Australian Medical Association Council of General Practice, the Society of Hospital Pharmacists of Australia, the Australian Divisions of General Practice, and the National Prescribing Service. Consumer groups such as Consumers Health Forum and government advisory groups such as the Pharmaceutical Health and Rational Use of Medicines committee and the Australian Pharmaceutical Advisory Committee have also given support.

CONTENT

Creation

AMH content is derived in-house by a small team of highly skilled and experienced editors, most of whom are pharmacists. Editors possess postgraduate training and experience in areas such as drug information and critical appraisal, pharmacoepidemiology, pharmacoeconomics,

and editing. Work experiences are broad and include the pharmaceutical industry, academic detailing, hospital-based clinical pharmacy, and medical writing. In addition, a small number of paid external contributing writers help expand and update specific parts of the content. In addition to regular surveillance of published pharmacotherapeutics literature, spontaneous feedback from readers assists in developing and refining content.

Review

The review process for the scientific aspects of the content involves four steps. After initial drafting or updating by an AMH editor or external contributor, a second AMH editor will review material for adherence to house style and for scientific content. Content is modified based on this review. The draft material is then sent out in parallel to members of the Editorial Advisory Board, and a Review Panel (external reviewers) who are specifically recruited to look at particular sections. Information regarding drug use in renal impairment and pregnancy or breastfeeding is reviewed by external specialist clinical pharmacists. After consideration of all reviewers' comments, a final draft is created and sent to the Editorial Advisory Board for approval.

In this way, a combination of experts and end-users review AMH content. At present, a team of about 150 external reviewers assist in the Review Panel process. They include general practitioners and specialist physicians and surgeons, academics and researchers, hospital and community pharmacists, specialist nurses, and educators from organizations that support consumers with chronic illnesses. Each Review Panel contains expert specialist clinicians, a clinical pharmacologist with an interest in the specific area, hospital-based clinical pharmacists, community pharmacists, general practitioners (urban and rural), and allied health workers when relevant (e.g., diabetes and asthma nurses and educators). These reviewers are not remunerated, but they receive a complimentary copy of AMH, and their contribution is acknowledged in the publications.

AMH Editorial Advisory Board

The Editorial Advisory Board contains academics and practitioners in pharmacy, clinical pharmacology, and general practice. Some members have substantial experience in medical editing and publishing. They are asked to declare any potential conflicts of interest.

As well as assisting in the review process, the Editorial Advisory Board helps set editorial policy and approve plans for new content or major update.

FUTURE DEVELOPMENTS

Although a traditional publishing process was used in the creation of the first two editions of AMH books, the need to provide users with multiple formats has required the work environment to be re-engineered and editors now work in an SGML environment. This allows production of reports such as a print-ready file (from which the book is published); an HTML version that serves as the current CD-ROM and web-based products; and potentially other formats or subsets of AMH data, from one set of source files.

Future developments include adding a production pathway to allow a personal digital assistant version of AMH to be produced, and incorporation of an XML database into the work environment, which will allow for complex queries to be performed on the data set.

Best-Practices Documents (ASHP)

B

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INTRODUCTION

The American Society of Health-System Pharmacists (ASHP) develops and publishes professional Best-Practices documents that cover a wide range of clinical practice and therapeutic topics. There is a range of detail among types of Best-Practices documents: Statements documents express basic philosophy and Guidelines offer programmatic advice. Of the two types of therapeutic documents, Therapeutic Guidelines are thorough discussions of drug use, whereas Therapeutic Position Statements are concise responses to specific therapeutic issues.

TOPICS

The topics covered among the types of Best-Practices documents are varied and dynamic. Documents are continuously developed, reviewed, updated, and discontinued on the basis of assessments of relevance to contemporary clinical practices and trends. Currently, a sampling of active, clinically related documents includes the following topics summarized by document type:

- *ASHP Statement*: A declaration and explanation of basic philosophy or principle, as approved by the Board of Directors and the House of Delegates. ASHP Statements cover such topics as the pharmacist's role in clinical pharmacokinetic monitoring, infection control, and primary care.
- *ASHP Guideline*: Advice on the implementation or operation of pharmacy practice programs, as approved by the Board of Directors. ASHP Guidelines include, among other topics, pharmacists' activities in adverse drug-reaction monitoring and reporting, medication-use evaluation, patient education and counseling, development of clinical care plans, provision of medication information, and surgery and anesthesiology pharmaceutical services.
- *ASHP Therapeutic Guideline*: Thorough, systematically developed advice for healthcare professionals on appropriate use of medications for specific clinical circumstances, as approved by the Board of Directors. ASHP Therapeutic Guidelines cover surgical and nonsurgical antimicrobial prophylaxis, stress ulcer prophylaxis, pharmacologic management of nausea and vomiting caused by chemotherapy or radiation therapy, and the use of angiotensin-converting enzyme inhibitors in patients with left ventricular dysfunction.
- *ASHP Therapeutic Position Statement*: Concise statements that respond to specific therapeutic issues of concern to healthcare consumers and pharmacists, as approved by the Board of Directors. ASHP Therapeutic Position Statements include such topics as identifying and preventing pneumococcal resistance, preventing and treating multidrug-resistant tuberculosis, use of aspirin for prophylaxis of myocardial infarction, recognition and treatment of depression in older adults, smoking cessation, and optimizing treatment of hypertension.

PURPOSE OF ASHP BEST-PRACTICES DOCUMENTS

ASHP's Best-Practices documents represent a consensus of professional judgment, expert opinion, and documented evidence. They provide guidance and direction to ASHP members and pharmacy practitioners and to other audiences related to pharmacy practice. Their use may help with compliance to federal and state laws and regulations, to meet accreditation requirements, and to improve pharmacy practice and patient care. Best-Practices documents are written to establish goals that are progressive and challenging yet attainable in applicable health-system settings. They generally do not represent minimum levels of practice, unless titled as such, and should not be viewed as ASHP requirements. The use of ASHP's documents by members and other practitioners is strictly voluntary. Their content should be assessed and adapted to the needs of local health-system settings on the basis of independent judgment.

DEVELOPMENT OF BEST-PRACTICES DOCUMENTS

The processes used to draft and review new or revised Best-Practices documents vary, depending on the body responsible for their development and on the type of document. These processes are described in the following. Once approved, documents become official ASHP policy and are published in the *American Journal of Health-System Pharmacy*, added to ASHP's Web site, and incorporated into the next edition of *Best-Practices for Health-System Pharmacy*.

ASHP Statements and Guidelines

Any of the ASHP policy-recommending bodies (councils and commissions) may initiate and oversee the development of ASHP Statements and Guidelines; however, most of them are initiated by the Council on Professional Affairs. The development of these documents generally includes the following steps:

- A team of up to five individuals is selected from volunteers on the basis of their demonstrated knowledge of the topic and practice settings. The team develops a preliminary draft. Drafters are usually ASHP members; however, depending on the subject, the team may include nonmember pharmacists and representatives of other healthcare disciplines.
- ASHP distributes drafts to reviewers who have interest and expertise in the topic. Reviewers consist of members, various ASHP bodies, and representatives of other health care disciplines and professional organizations. A draft may be presented at an open hearing or in a network forum during an ASHP Annual or Midyear Clinical Meeting, or may be posted on ASHP's Web site for comment.
- Drafts are revised on the basis of comments and a review of the literature, evaluated for content and quality, and submitted to the appropriate ASHP policy-recommending body for action. That body may suggest further revisions or recommend approval by the ASHP Board of Directors.

ASHP Therapeutic Guidelines and Position Statements

The Commission on Therapeutics has responsibility for the development of ASHP Therapeutic Guidelines and ASHP Therapeutic Position Statements.

ASHP therapeutic guidelines

The development of these documents generally includes the following steps:

- When the Commission on Therapeutics (COT) identifies a topic for Therapeutic Guideline development, ASHP formally solicits proposals for a contractual arrangement with an individual, group, or organization to draft the Guidelines document and coordinate its review. The contractor will work with a panel of six to ten experts appointed by ASHP who have diverse backgrounds relevant to the topic.
- A systematic analysis of the literature is performed, and scientific evidence is evaluated on the basis of predetermined criteria. Recommendations in the document rely on scientific evidence or expert consensus. When expert judgment must be used, the document indicates the scientific reasoning that influenced the decision. Scientific evidence takes precedence over expert judgment. Each recommendation is accompanied by projections of the relevant health and cost outcomes that could result.
- The expert panel and COT review every draft of the Guidelines document and provide comments. This process is repeated until the expert panel and COT are satisfied with the content.
- ASHP solicits multidisciplinary input on the final draft. Reviewers consist of members and selected individuals knowledgeable in the content area, representatives of various ASHP bodies, and other professional organizations.
- Once the above processes are completed, COT recommends that the ASHP Board of Directors approve the Guideline.

ASHP therapeutic position statements

The development of these documents generally includes the following steps:

- One or more experts on a given topic is assigned to draft the Therapeutic Position Statement. Drafters are selected on the basis of demonstrated knowledge of the topic and practice setting. Most often, the drafters are ASHP members.
- The proposed draft document is reviewed by COT, which may suggest modifications. This process is repeated until COT is satisfied with the content.
- ASHP solicits multidisciplinary input on the draft. Reviewers consist of members and selected indivi-

duals knowledgeable in the content area, representatives of various ASHP bodies, and other professional organizations.
- Once the above processes are completed, COT finalizes the draft and recommends that the ASHP Board of Directors approve it.

Timeliness

The goal is to have an approvable draft within one year of the initial decision to develop a new or revised practice standard. Development usually takes one to three years, depending on the availability of drafters, the strength of the evidence, the accumulated practice experience, and the extent of the reviews and revisions. ASHP Best-Practices documents are dynamic: Therapeutic documents are reviewed every three years, and Practice Statements and Guidelines every five years and are revised as needed.

ACCESS TO BEST-PRACTICES DOCUMENTS

Besides being published in *AJHP* and the *Best Practices for Health-System Pharmacy*, Best-Practice documents are available through ASHP's Fax On-Demand service by calling (301)664-8888 and on ASHP's Web site at www.ashp.org/bestpractices/index.html.

FURTHER READING

www.ashp.org/bestpractices/index.html.

Biopharmaceutics

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INTRODUCTION

Biopharmaceutics is the study of the interrelationship of the physicochemical properties of the drug [active pharmaceutical ingredient, (API)] and the drug product (dosage form in which the drug is fabricated) based on the biological performance of the drug (Table 1).

Biopharmaceutics also considers the impact of the various manufacturing methods and technologies on the intended performance of the drug product. Biopharmaceutics uses quantitative methods and theoretical models (1) to evaluate the effect of the drug substance, dosage form, and routes of drug administration on the therapeutic requirements of the drug and drug product in a physiological environment.

Bioavailability is often used as a measure of the biological performance of the drug and is defined as a measure of the rate and extent (amount) to which the active ingredient or active moiety becomes available at the site of action. Bioavailability is also a measure of the rate and extent of therapeutically active drug that is systemically absorbed.

Biopharmaceutics allows for rational design of drug products to deliver the drug at a specific rate to the body in order to optimize the therapeutic effect and minimize any adverse effects. As shown in Table 1, biopharmaceutics is based on the physicochemical characteristics of the active drug substance, the desired drug product, and considerations of the anatomy and physiology of the human body (1). Inherent in the design of a suitable drug product is knowledge of the pharmacodynamics of the drug, including the desired onset time, duration, and intensity of clinical response, and the pharmacokinetics of the drug including absorption, distribution, elimination, and target drug concentration.

Thus, biopharmaceutics involves factors that influence the: 1) protection and stability of the drug within the drug product; 2) the rate of drug release from the drug product; 3) the rate of dissolution of the drug at the absorption site; and 4) the availability of the drug at its site of action (Fig. 1).

BIOPHARMACEUTIC CONSIDERATIONS IN DRUG PRODUCT DESIGN

Drugs are generally given to a patient as a manufactured drug product (finished dosage form) that includes the active drug and selected ingredients (excipients) that make up the dosage form. Common pharmaceutical dosage forms include liquids, tablets, capsules, injections, suppositories, transdermal systems, and topical drug products. The formulation and manufacture of a drug product requires a thorough understanding of the biopharmaceutics.

Each route of drug application presents special biopharmaceutic considerations in drug product design (Table 2). Systemic drug absorption from an extravascular site is influenced by the anatomic and physiologic properties of the site and the physicochemical properties of the drug and the drug product. The anatomy, physiology, and the contents of the gastrointestinal tract (GI) are considered in the design of a drug product for oral administration. For example, considerations in the design of a vaginal tablet formulation for the treatment of a fungus infection include whether the ingredients are compatible with vaginal anatomy and physiology, whether the drug is systemically absorbed from the vagina and how the vaginal tablet is to be properly inserted and placed in the appropriate area for optimum efficacy. Requirements for an eye medication include pH, isotonicity, sterility, local irritation to the cornea, draining of the drug by tears, and concern for systemic drug absorption. An additional consideration might be the contact time of the medication with the cornea. Although, increased eye contact time might be achieved by an increase in viscosity of the ophthalmic solution, the patient may lose some visual acuity when a viscous product is administered. Biopharmaceutic considerations for a drugs administered

[a]The content in this article reflects the view of the authors and does not represent the view of FDA.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006419

Table 1 Biopharmaceutic considerations in drug product design

Active pharmaceutical ingredient (API)		
	Stability	Impurities
	Solubility	Salt form
	pH and pKa	Particle size
	Crystalline form (polymorph)	Complexation
	Excipient interaction and compatability	
Drug product		
	Type of drug product (capsule, tablet, solution, etc.)	Stability
	Immediate or modified release	Excipients
	Dosage strength	Manufacturing variables
	Bioavailability	
Physiologic factors		
	Route of administration	Blood flow
	Permeation of drug across cell membranes	Surface area
	Binding to macromolecules	Biotransformation
Pharmacodynamic and pharmacokinetic considerations		
	Bioavailability	Pharmacokinetics
	Therapeutic objective	Dose
	Adverse reactions	Toxic effects
Manufacturing considerations		
	Production methodology and technology	Cost
	Quality control/quality assurance	Stability testing
	Specification of raw materials	
Patient considerations	Compliance, labeling, and product acceptance	Cost

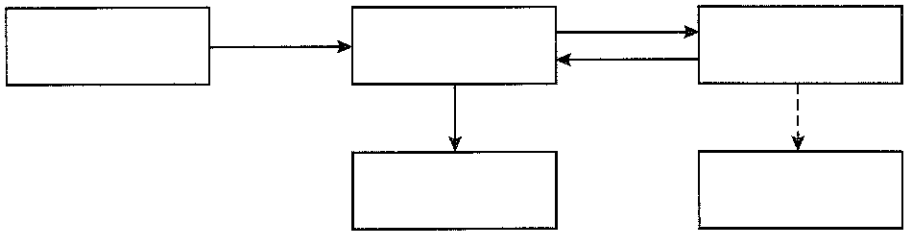

Fig. 1 Scheme demonstrating the dynamic relationships among the drug, the product, and pharmacologic effect. (From Ref. 1.)

by intramuscular injection include, local irritation, drug dissolution, and drug absorption from the injection site.

Biopharmaceutic studies may be performed using in vitro or in vivo methods (Table 3). In vitro methods are useful (2–6) to understand the physico-chemical properties of the drug and drug product and to evaluate the quality of the manufacturing process. Ultimately, the drug must be studied in vivo, in humans to assess drug efficacy, including the pharmacodynamic, pharmacokinetic, therapeutic and toxic profiles. Drug dissolution, absorption, metabolism, and potential interaction with food and other components in the GI tract are major biopharmaceutic topics for research and regulatory considerations in drug development.

A drug given by intravenous administration is considered complete or 100% bioavailable because the drug is placed directly into the systemic circulation. By carefully choosing the route of drug administration and proper design of the drug product, drug bioavailability can be varied from rapid and complete systemic drug absorption to a slow, sustained rate of absorption or even virtually no absorption, depending on the therapeutic objective. Once the drug is systemically absorbed, normal physiologic processes for distribution and elimination occur, which usually is not influenced by the specific formulation of the drug. The rate of drug release from the product, and the rate of drug absorption, are important in determining the onset, intensity, and duration of drug action of the drug.

RATE-LIMITING STEPS IN ORAL DRUG ABSORPTION

Systemic drug absorption from a drug product consists of a succession of rate processes (Fig. 2). For solid oral, immediate release drug products (e.g., tablet, capsule), the rate processes include 1) disintegration of the drug product and subsequent release of the drug; 2) dissolution of the drug in an aqueous environment; and 3) absorption across cell membranes into the systemic circulation. In the process of drug disintegration, dissolution, and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence.

The slowest step in a kinetic process is the rate-limiting step. Except for controlled release products, disintegration of a solid oral drug product is usually more rapid than drug dissolution and drug absorption. For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step, and therefore exerts a rate-limiting effect on drug bioavailability. In contrast, for a drug that has a high aqueous solubility, the dissolution rate is rapid and the rate at which the drug crosses or permeates cell membranes is the slowest or rate-limiting step.

PHYSIOLOGIC FACTORS AFFECTING DRUG ABSORPTION

Passage of Drugs Across Cell Membranes

For systemic absorption, a drug must pass from the absorption site through or around one or more layers of cells to gain access into the general circulation. The permeability of a drug at the absorption site into the systemic circulation is intimately related to the molecular structure of the drug and the physical and biochemical properties of the cell membranes. For absorption into the cell, a drug must traverse the cell membrane. Transcellular absorption is the process of a drug movement across a cell. Some polar molecules may not be able to traverse the cell membrane, but instead, go through gaps or "tight junctions" between cells, a process known as paracellular drug absorption. Some drugs are probably absorbed by a mixed mechanism involving one or more processes.

Passive diffusion

Passive diffusion is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration. This process is passive because no external energy is expended. Drug

Table 2 Common routes of drug administration

Route	Bioavailability	Advantages	Disadvantages
Parenteral routes			
Intravenous bolus (IV)	Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous.	Drug is given for immediate effect.	Increased chance for adverse reaction. Possible anaphylaxis.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption.	Plasma drug levels more precisely controlled. May inject large fluid volumes.	Requires skill in insertion of infusion set.
	Rate of drug absorption controlled by infusion pump.	May use drugs with poor lipid solubility and/or irritating drugs.	Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
Intramuscular injection (IM)	Rapid from aqueous solution.	Easier to inject than intravenous injection.	Irritating drugs may be very painful.
	Slow absorption from nonaqueous (oil) solutions.	Larger volumes may be used compared to subcutaneous solution.	Different rates of absorption depending upon muscle group injected and blood flow.
Subcutaneous injection (SC)	Prompt from aqueous solution.	Generally, used for insulin injection.	Rate of drug absorption depends upon blood flow and injection volume.
	Slow absorption from repository formulations.		
Enteral Routes			
Buccal or sublingual (SL)	Rapid absorption from lipid-soluble drugs.	No "first-pass" effects.	Some drug may be swallowed. Not for most drugs or drugs with high doses.
Oral (PO)	Absorption may vary. Generally slower absorption rate compared to IV bolus or IM injection.	Safest and easiest route of drug administration. May use immediate-release and modified-release drug products.	Some drugs may have erratic absorption, be unstable in the gastointestinal tract, or be metabolized by liver prior to systemic absorption.
Rectal (PR)	Absorption may vary from suppository.	Useful when patient cannot swallow medication.	Absorption may be erratic. Suppository may migrate to different position.
	More reliable absorption from enema (solution).	Used for local and systemic effects.	Some patient discomfort.
Other routes			
Transdermal	Slow absorption, rate may vary.	Transdermal delivery system (patch) is easy to use.	Some irritation by patch or drug. Permeability of skin variable with condition, anatomic site, age, and gender.
	Increased absorption with occlusive dressing.	Used for lipid-soluble drugs with low dose and low MW.	Type of cream or ointment base affects drug release and absorption.
Inhalation	Rapid absorption. Total dose absorbed is variable.	May be used for local or systemic effects.	Particle size of drug determines anatomic placement in respiratory tract. May stimulate cough reflex. Some drug may be swallowed.

(From Ref. 1.)

Table 3 Examples of in vitro and in vivo biopharmaceutic studies

Biopharmaceutic studies (in vivo)	Bioavailability study	Measurement of drug in plasma, urine or other tissues
	Acute pharmacologic effect	Measurement of a pharmacodynamic effect, e.g., FEV_1, blood pressure, heart rate, skin blanching
	Clinical study	Measurement of drug efficacy
Biopharmaceutic studies (in vitro)	Drug release/dissolution	Measurement of the rate of drug dissolved under specified conditions
	Drug permeability	Use of CACO2 cells (an isolated colon cell line) are grown into membranes to study the intestinal permeability and gut metabolism of drugs.
	Drug biotransformation (metabolism)	Use of liver cells, homogenates or isolated cytochrome P450 isozymes to drug study biotransformation.

molecules move randomly forward and back across a membrane (Fig. 3). If the two regions have the same drug concentration, forward-moving drug molecules will be balanced by molecules moving back, resulting in no net transfer of drug. For a region that has a higher drug concentration, the number of forward-moving drug molecules will be higher than the number of backward-moving molecules, resulting in a transfer of molecules to the region with the lower drug concentration, as indicated by the big arrow. Flux is the rate of drug transfer and is represented by a vector to show its direction. Molecules tend to move randomly in all directions because molecules possess kinetic energy and constantly collide with each another in space. Only left and right molecule movements are shown in Fig. 3, because movement of molecules in other directions would not result in concentration changes because of the limitation of the container wall.

Passive diffusion is the major transmembrane process for most drugs. The driving force for passive diffusion is the difference in drug concentrations on either side of the cell membrane. According to Fick's Law of Diffusion, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration

$$dQ/dt = \{DAK/h\}(C_{GI} - C_p)$$

where dQ/dt = rate of diffusion; D = diffusion coefficient; K = partition coefficient; A = surface area

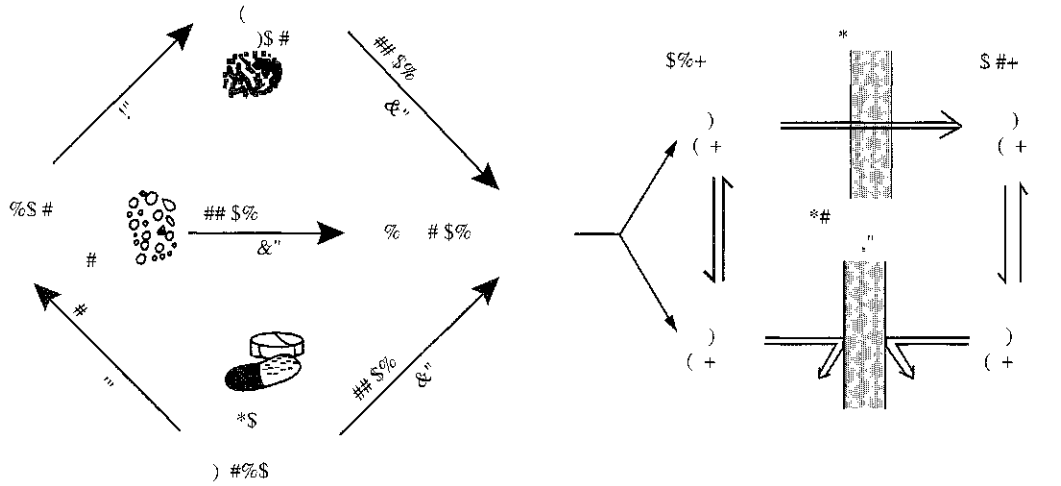

Fig. 2 Summary of processes involved following the oral administration of a drug in tablet or capsule form. (From Blanchard, J. Gastrointestinal absorption. II. Formulation factors affecting bioavailability. Am. J. Pharm. **1978**, *150*, 132–151.)

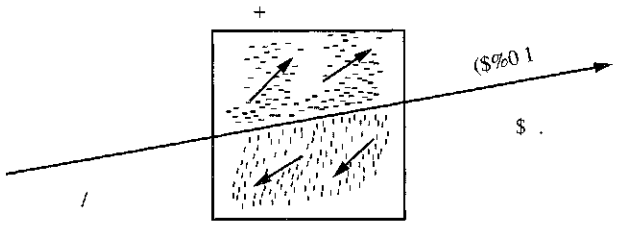

Fig. 3 Passive diffusion of molecules. Molecules in solution diffuse randomly in all directions. As molecules diffuse from left to right and vice versa (small arrows), a net diffusion from the high-concentration side to the low-concentration side results. This results in a net flux (J) to the right side. Flux is measured in mass per unit area (e.g., mg/cm^2). (From Ref. 1.)

of membrane; h = membrane thickness; and $C_{GI} - C_p$ = difference between the concentrations of drug in the GI tract and in the plasma.

Drug distributes rapidly into a large volume after entering the blood resulting in a very low plasma drug concentration with respect to the concentration at the site of drug administration. Drug is usually given in milligram doses, whereas plasma drug concentrations are often in the microgram per milliliter or nanogram per milliliter range. For drugs given orally, $C_{GI} \gg C_p$. A large concentration gradient is maintained driving drug molecules into the plasma from the GI tract.

As shown by Fick's Law of Diffusion, lipid solubility of the drug and the surface area and the thickness of the membrane influence the rate of passive diffusion of drugs. The partition coefficient, K, represents the lipid–water partitioning of a drug. More lipid soluble drugs have larger K values that theoretically increase the rate of systemic drug absorption. In practice, drug absorption is influenced by other physical factors of the drug, limiting its practical application of K. The surface area of the membrane through which the drug is absorbed directly influences the rate of drug absorption. Drugs may be absorbed from most areas of the GI tract. However, the duodenal area of the small intestine shows the most rapid drug absorption due to such anatomic features as villi and microvilli, which provide a large surface area. These villi are not found in such numbers in other areas of the GI tract.

The membrane thickness, h, is a constant at the absorption site but may be altered by disease. Drugs usually diffuse very rapidly into tissues through capillary cell membranes in the vascular compartments. In the brain, the capillaries are densely lined with glial cells creating a thicker lipid barrier (blood–brain barrier) causing a drug to diffuse more slowly into brain. In certain disease states (e.g., meningitis) the cell membranes may be disrupted or become more permeable to drug diffusion.

Many drugs have lipophilic and hydrophilic substituents. More lipid soluble drug molecules traverse cell membranes more easily than less lipid-soluble (i.e., more water-soluble) molecules. For weak electrolyte drugs (i.e, weak acids, bases), the extent of ionization influences drug solubility and the rate of drug transport. Ionized drugs are more water soluble than nonionized drugs which are more lipid soluble. The extent of ionization of a weak electrolyte depends on the pKa of the drug and the partition hypothesis (pH) of the medium in which the drug is dissolved. The Henderson and Hasselbalch equation describes the ratio of ionized (charged) to unionized form of the drug and is dependent on the pH conditions and the pKa of the drug:

For weak acids,

$$\text{Ratio} = -\frac{(\text{salt})}{(\text{acid})} = \frac{(A^-)}{(HA)} = 10^{(pH-pKa)}$$

For weak bases,

$$\text{Ratio} = -(\text{base})\,(\text{salt}) = (RNH)2\,(RNH^{+3}) = 10^{(pH-pKa)}$$

According to the pH, a weak acid (e.g., salicylic acid) should be rapidly absorbed from the stomach (pH 1.2) due to a favorable concentration gradient of the unionized (more lipid soluble) drug from the stomach to the blood, because practically all the drug in the blood compartment is dissociated (ionized) at pH 7.4. A weak base (e.g., quinidine) is highly ionized in acid pH and is poorly absorb from the stomach. Although many drugs obey by the pH, in practice, the major site of absorption of most drugs is usually in the small intestine (duodenum) due presence of a large surface area and high blood flow.

The drug concentration on either side of a membrane is also influenced by the affinity of the drug for a tissue component, which prevents the drug from freely moving back across the cell membrane. For example, drug that binds plasma or tissue proteins causes the drug to concentrate in that region. Dicumarol and sulfonamides strongly bind plasma proteins; whereas, chlordane, a lipid-soluble insecticide, partitions and concentrates into adipose (fat) tissue. Tetracycline forms a complex with calcium and concentrates in the bones and teeth. Drugs may concentrate in a tissue due to a specific uptake or active transport process. Such processes have been demonstrated for iodide in thyroid tissue, potassium in the intracellular water, and certain catecholamines in adrenergic storage sites.

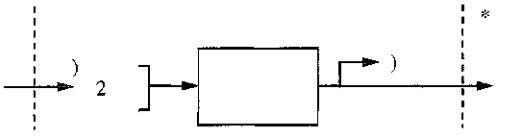

Fig. 4 Hypothetical carrier-mediated transport process. (From Ref. 1.)

Carrier-mediated transport

Theoretically, a lipophilic drug may pass through the cell or go around it. If drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption. In the intestine, molecules smaller than 500 MW may be absorbed by paracellular drug absorption. Numerous specialized carrier-mediated transport systems are present in the body especially in the intestine for the absorption of ions and nutrients required by the body.

Active transport: Active transport is a carrier-mediated transmembrane process that is important for GI absorption of some drugs and also involved in the renal and biliary secretion of many drugs and metabolites. A carrier binds the drug to form a carrier–drug complex that shuttles the drug across the membrane and then dissociates the drug on the other side of the membrane (Fig. 4). Active transport is an energy-consuming system characterized by the transport of drug against a concentration gradient, that is, from regions of low drug concentrations to regions of high concentrations.

A drug may be actively transported, if the drug molecule structurally resembles a natural substrate that is actively transported. A few lipid-insoluble drugs that resemble natural physiologic metabolites (e.g., 5-fluorouracil) are absorbed from the GI tract by this process. Drugs of similar structure may compete for adsorption sites on the carrier. Because only a certain amount of carrier is available, the binding sites on the carrier may become saturated at high drug concentrations. In contrast, passive diffusion is not saturable.

Facilitated diffusion: Facilitated diffusion is a non-energy requiring, carrier-mediated transport system in which the drug moves along a concentration gradient (i.e., moves from a region of high drug concentration to a region of low drug concentration). Facilitated diffusion is saturable, structurally selective for the drug and shows competition kinetics for drugs of similar structure. Facilitated diffusion seems to play a very minor role in drug absorption.

Carrier-mediated intestinal transport: Various carrier mediated systems (transporters) are present at the intestinal brush border and basolateral membrane for the absorption of specific ions and nutrients essential for the body. Many drugs are absorbed by these carriers because of the structural similarity to natural substrates. An intestinal transmembrane protein, *P*-Glycoprotein (*P*-Gp) appears to reduce apparent intestinal epithelial cell permeability from lumen to blood for various lipophilic or cytotoxic drugs. Other transporters are present in the intestines. For example, many oral cephalosporins are absorbed through the amino acid transporter.

Vesicular transport

Vesicular transport is the process of engulfing particles or dissolved materials by the cell. Pinocytosis refers to the engulfment of small solutes or fluid, whereas phagocytosis refers to the engulfment of larger particles or macromolecules generally by macrophages. Endocytosis and exocytosis are the processes of moving macromolecules into and out of a cell, respectively.

During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material, and then engulfs the material into the cell. Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell. Vesicular transport is the proposed process for the absorption of orally administered sabin polio vaccine and various large proteins. An example of exocytosis is the transport of a protein such as insulin from insulin-producing cells of the pancreas into the extracellular space. The insulin molecules are first packaged into intracellular vesicles, which then fuse with the plasma membrane to release the insulin outside the cell.

ORAL DRUG ABSORPTION

Physiologic Considerations

Drugs may be administered by various routes of administration (Table 2). Except for intravenous drug administration, drugs are absorbed into the systemic circulation from the site of administration and are greatly affected by conditions at the administration site.

Oral administration is the most common route of drug administration. Major physiologic processes in the GI system include secretion, digestion, and absorption. Secretion includes the transport of fluid, electrolytes, peptides, and proteins into the lumen of the alimentary canal. Enzymes in saliva and pancreatic secretions are involved in the digestion of carbohydrates and proteins. Other secretions such as mucus protect the linings of the lumen of the GI tract. Digestion is the breakdown of food

constituents into smaller structures in preparation for absorption. Both drug and food constituents are mostly absorbed in the proximal area (duodenum) of the small intestinal. The process of absorption is the entry of constituents from the lumen of the gut into the body. Absorption may be considered as the net result of both lumen-to-blood and blood-to-lumen transport movements.

Drugs administered orally pass through various parts of the enteral canal including the oral cavity, esophagus, and various parts of the GI tract. Residues eventually exit the body through the anus. Drugs may be absorbed by passive diffusion from all parts of the alimentary canal including sublingual, buccal, GI, and rectal absorption. For most drugs, the optimum site for drug absorption after oral administration is the upper portion of the small intestine or duodenum region. The unique anatomy of the duodenum provides an immense surface area for the drug to passively diffuse (Table 4). In addition, the duodenal region is highly perfused with a network of capillaries, which helps to maintain a concentration gradient from the intestinal lumen and plasma circulation.

The total transit time, including gastric emptying, small intestinal transit, and colonic transit ranges from 0.4 to 5 days. Small intestine transit time (SITT) ranges from 3 to 4 h for most healthy subjects. If absorption is not completed by the time a drug leaves the small intestine, drug absorption may be erratic or incomplete. The small intestine is normally filled with digestive juices and liquids, keeping the lumen contents fluid. In contrast, the fluid in the colon is reabsorbed, and the lumen content in the colon is either semisolid or solid, making further drug dissolution erratic and difficult.

Gastrointestinal motility

Once the drug is given orally, the exact location and/or environment of the drug product within the GI tract is difficult to discern. GI motility tends to move the drug through the alimentary canal so that it may not stay at the absorption site. For drugs given orally, an anatomic absorption window may exist within the GI tract in which the drug is efficiently absorbed. Drugs contained in a nonbiodegradable controlled-release dosage form must be completely released into this absorption window prior to the movement of the dosage form into the large bowel. The transit time of the drug in the GI tract depends upon the pharmacologic properties of the drug, type of dosage form, and various physiologic factors. Physiologic movement of the drug within the GI tract depends upon whether the alimentary canal contains recently ingested food (digestive or fed state) or is in the fasted or interdigestive state.

Gastric emptying time

After oral administration, the swallowed drug rapidly reaches the stomach. Because the duodenum has the greatest capacity for the absorption of drugs from the GI tract, a delay in the gastric emptying time will slow the rate and possibly the extent of drug absorption from the duodenum, thereby prolonging the onset time for the drug. Drugs, such as penicillin, that are unstable in acid, may decompose if stomach emptying is delayed. Other drugs, (e.g., aspirin) may irritate the gastric mucosa during prolonged contact.

Factors that tend to delay gastric emptying include consumption of meals high in fat, cold beverages, and anticholinergic drugs. Liquids and small particles less than 1 mm are generally not retained in the stomach. These small particles are believed to be emptied due to a slightly higher basal pressure in the stomach over the duodenum. Different constituents of a meal will empty from the stomach at different rates. For example, liquids are generally emptied faster than digested solids from the stomach. Large particles, including tablets and capsules, are delayed from emptying for 3–6 h by the presence of food in the stomach. Indigestible solids empty very slowly, probably during the interdigestive phase, a phase in which food is not present and the stomach is less motile but periodically empties its content due to housekeeper wave contraction.

Intestinal motility

Normal peristaltic movements mix the contents of the duodenum, bringing the drug particles into intimate contact with the intestinal mucosal cells. The drug must have a sufficient time (residence time) at the absorption site for optimum absorption. In the case of high motility in the intestinal tract, as in diarrhea, the drug has a very brief residence time and less opportunity for adequate absorption.

Blood perfusion of the gastrointestinal tract

The blood flow is important in carrying the absorbed drug from the absorption site to the systemic circulation. A large network of capillaries and lymphatic vessels perfuse the duodenal region and peritoneum. The splanchnic circulation receives about 28% of the cardiac output and is increased after meals. Drugs are absorbed from the small intestine into the mesenteric vessels which flows to the hepatic-portal vein and then to the liver prior to reaching the systemic circulation. Any decrease in mesenteric blood flow, as in the case of congestive heart failure, will decrease the rate of systemic drug absorption from the intestinal tract.

Table 4 Drug absorption in the gastrointestinal tract

Anatomic area	Function	Affect on drug absorption
Oral cavity	Saliva, pH 7, contains ptyalin (salivary amylase), digests starches. Mucin, a glycoprotein, lubricates food and may interact with drugs.	Buccal and sublingual absorption occurs for lipid-soluble drugs.
Esophagus	The esophagus connects the pharynx and the cardiac orifice of the stomach. The pH is 5–6. The lower part of the esophagus ends with the esophageal sphincter, which prevents acid reflux from the stomach.	Tablets or capsules may lodge in this area, causing local irritation. Very little drug dissolution occurs in the esophagus.
Stomach	The fasting stomach pH is about 2 to 6. In the fed state, the stomach pH is about 1.5 to 2, due to hydrochloric acid secreted by parietal cells. Stomach acid secretion is stimulated by gastrin and histamine. Mixing is intense and pressurized in the antral part of the stomach, a process of breaking down large food particles described as antral milling. Food and liquid are emptied by opening the pyloric sphincter into the duodenum.	Drugs are not efficiently absorbed in the stomach. Basic drugs are solubilized rapidly in acid. Stomach emptying influences the time for drug reaching the small intestine. The food content and osmolality influenced by stomach emptying. Fatty acids delay gastric emptying. High-density foods generally are emptied more slowly from the stomach.
Duodenum	A common duct from the pancreas and gall bladder enters the duodenum. Duodenal pH is 6 to 6.5 due to the presence of bicarbonate that neutralizes the acidic chyme emptied from the stomach. The pH is optimum for enzymatic digestion of protein and peptide food. Pancreatic juice containing enzymes is secreted into the duodenum from the bile duct. Trypsin, chymotrypsin, and carboxypeptidase are involved in the hydrolysis of proteins into amino acids. Amylase is involved in the digestion of carbohydrates. Pancreatic lipase secretion hydrolyzes fats into fatty acids.	The main site for drug absorption. An immense surface area for the passive diffusion of drug to due to the presence of villi and microvilli forming a brush border. A high blood perfusion maintains a drug concentration gradient from the intestinal lumen and plasma circulation. The complex fluid medium in the duodenum dissolves many drugs with limited aqueous solubility. Ester prodrugs are hydrolyzed during absorption. Proteolytic enzymes degrade many protein drugs in the duodenum, preventing adequate absorption. Acid drugs dissolve in the alkaline pH. Bile secretion helps to dissolve fats and hydrophobic drugs
Jejunum	The jejunum is the middle portion of the small intestine in between the duodenum and the ileum. Digestion of protein and carbohydrates continues after receiving pancreatic juice and bile in the duodenum, this portion of the small intestine generally has less contraction than the duodenum and is preferred for in vivo drug absorption studies.	Drugs generally absorbed by passive diffusion.
Ileum	The ileum, pH about 7, with the distal part as high as 8, is the terminal part of the small intestine and has fewer contractions than the duodenum. The ileocecal valve separates the small intestine with the colon.	Drugs generally absorbed by passive diffusion.
Colon	The colon, pH 5.5–7, is lined with mucin functioning as lubricant and protectant. The colon contains both aerobic and anaerobic micro-organisms that may metabolize some drugs. Crohn's disease affects the colon and thickens the bowel wall. The microflora may also become more anaerobic. Absorption of clindamycin and propranolol are increased, whereas other drugs have reduced absorption with this disease (Rubinstein et al. 1988).	Very limited drug absorption due to the lack of microvilli and the more viscous and semisolid nature of the lumen contents. A few drugs such as theophylline and metoprolol are absorbed in this region. Drugs that are absorbed well in this region are good candidates for an oral sustained-release dosage form.

(Continued)

Table 4 Drug absorption in the gastrointestinal tract (*Continued*)

Anatomic area	Function	Affect on drug absorption
Rectum	The rectum is about 15 cm long, ending at the anus. In the absence of fecal material, the rectum has a small amount of fluid, (about 2 m) with a pH about 7. The rectum is perfused by the superior, middle, and inferior hemorrhoidal veins. The inferior hemorrhoidal vein (closest to the anal sphincter) and the middle hemorrhoidal vein feed into the vena cava and back to the heart. The superior hemorrhoidal vein joins the mesenteric circulation, which feeds into the hepatic portal vein and then to the liver.	Drug absorption may be variable depending upon the placement of the suppository or drug solution within the rectum. A portion of the drug dose may be absorbed via the lower hemorrhoidal veins, from which the drug feeds directly into the systemic circulation; some drug may be absorbed via the superior hemorrhoidal veins, which feeds into the mesenteric veins to the hepatic portal vein to the liver, and metabolized prior to systemic absorption.

Some drugs may be absorbed into the lymphatic circulation through the lacteal or lymphatic vessels under the microvilli. Absorption of drugs through the lymphatic system bypasses the first-pass effect due to liver metabolism, because drug absorption through the hepatic portal vein is avoided. The lymphatics are important in the absorption of dietary lipids and may be partially responsible for the absorption for some lipophilic drugs such as bleomycin or aclarubicin which may dissolve in chylomicrons and be systemically absorbed via the lymphatic system.

Effect of food and other factors on GI drug absorption

Digested foods may affect intestinal pH and solubility of drugs. Food effects are not always predictable. The absorption of some antibiotics (e.g., penicillin, tetracycline) is decreased with food, whereas other drugs (e.g., griseofulvin) are better absorbed when given with food containing a high fat content. Food in the GI lumen stimulates the flow of bile. Bile contains bile acids. Bile acids are surfactants are involved in the digestion and solubilization of fats, and increases the solubility of fat-soluble drugs through micelle formation. For some basic drugs (e.g., cinnarizine) with limited aqueous solubility, the presence of food in the stomach stimulates hydrochloric acid secretion, which lowers the pH, causing more rapid dissolution of the drug and better absorption.

Generally, the bioavailability of drugs is better in patients in the fasted state and with a large volume of water (Fig. 5). However, to reduce GI mucosal irritation, drugs such as erythromycin, iron salts, aspirin, and nonsteroidal anti-inflammatory agents (NSAIDs) are given with food. The rate of absorption for these drugs may be reduced in the presence of food, but the extent of absorption may be the same.

The drug dosage form may also be affected by food. For example, enteric-coated tablets may stay in the stomach for a longer period of time because food delays stomach emptying. If the enteric-coated tablet does not reach the duodenum rapidly, drug release and subsequent systemic drug absorption are delayed. In contrast, enteric-coated beads or microparticles disperse in the stomach, are less affected by food, and demonstrate more consistent drug absorption from the duodenum.

Food may also affect the integrity of the dosage form, causing an alteration in the release rate of the drug. For example, theophylline bioavailability from Theo-24 controlled-release tablets is much more rapid (7) when given to a subject in the fed rather than fasted state (Fig. 6).

Some drugs, such as ranitidine, cimetidine, and dipyridamole, after oral administration produce a blood concentration curve consisting of two peaks. This double-peak phenomenon is generally observed after the administration of a single dose to fasted patients. The rationale for the double-peak phenomenon has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic recycling, or failure of a tablet dosage form. For a drug with high water solubility, dissolution of the drug occurs in the stomach, and partial emptying of the drug into the duodenum will result in the first absorption peak. A delay in stomach emptying results in a second absorption peak as the remainder of the dose is emptied into the duodenum.

Diseases such as Crohn's disease that alter GI physiology and corrective surgery involving peptic ulcer, antrectomy with gastroduodenostomy and selective vagotomy may potentially affect drug absorption. Drug absorption may be unpredictable in many disease conditions. Drugs or nutrients or both may also affect the absorption of other drugs. For example, propantheline

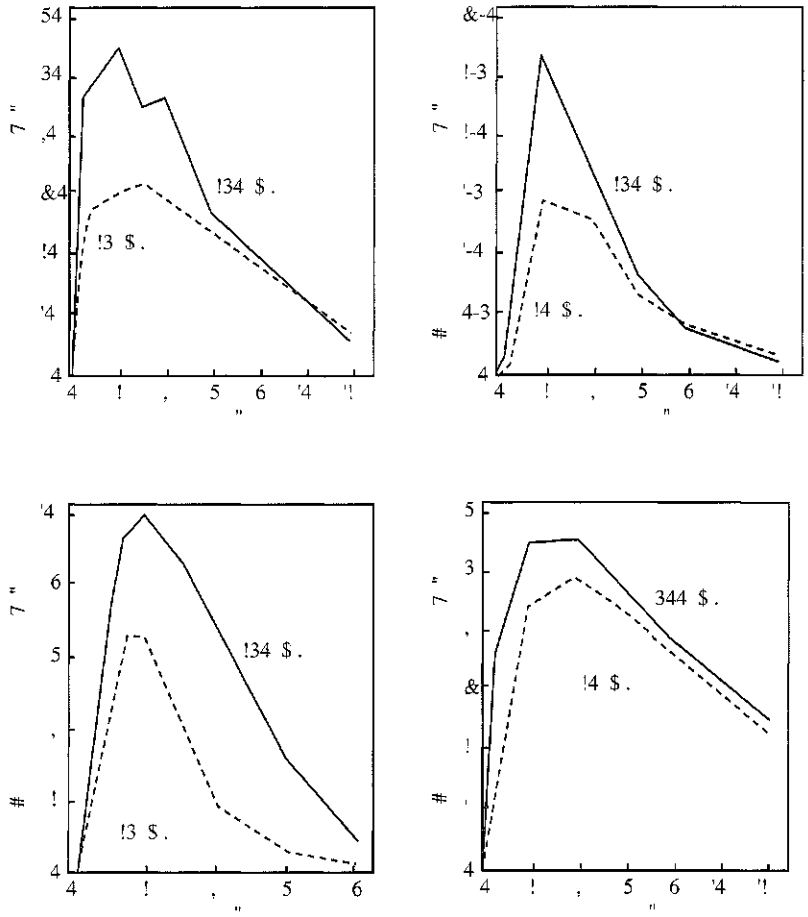

Fig. 5 Mean plasma or serum drug levels in healthy, fasting human volunteers ($n = 6$ in each case) who received single oral doses of aspirin (650 mg) tablets, erythromycin stearate (500 mg) tablets, amoxicillin (500 mg) capsules, and theophylline (260 mg) tablets, together with large. (From Welling P.G.; Drug Bioavailability and Its Clinical Significance. *Progress in Drug Metabolism*, Vol. 4; Bridges K.W.; Chassea, VD LF. Eds.; Wiley; London, 1980.)

bromide is an anticholinergic drug that slows stomach emptying and motility of the small intestine and may reduce stomach acid secretion. Grapefruit juice was found to increase the plasma level of many drugs due to inhibition of their metabolism in the liver.

PHARMACEUTICAL FACTORS AFFECTING DRUG BIOAVAILABILITY

Biopharmaceutic considerations in the design and manufacture of a drug product to deliver the active drug with the desired bioavailability characteristics include: 1) the type of drug product (e.g., solution, suspension, suppository), 2) the nature of the excipients in the drug product, 3) the physicochemical properties of the drug molecule, and 4) the route of drug administration.

Disintegration

Immediate release, solid oral drug products must rapidly disintegrate into small particles and release the drug. The United States Pharmacopoeia (USP) describes an official tablet disintegration test. The process of disintegration does not imply complete dissolution of the tablet and/or the drug. Complete disintegration is defined by the USP as "that state in which any residue of the tablet, except fragments of insoluble coating, remaining on the screen of

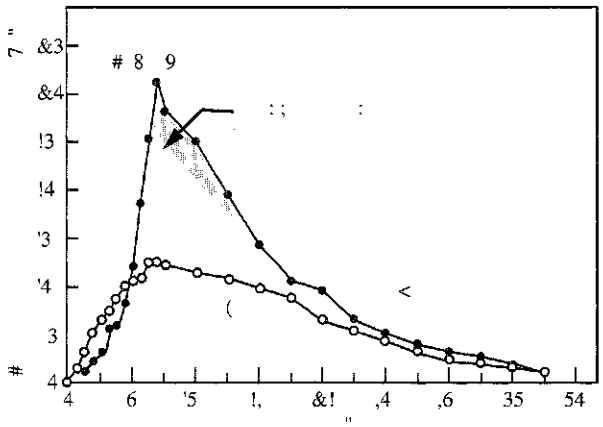

Fig. 6 Theophylline serum concentration in an individual subject after a single 1500 mg dose of Theo-24 taken during fasting, period during which this patient experienced nausea, repeated vomiting, or severe throbbing headache. The pattern of drug release during the food regimen is consistent with "dose-dumping." (From Ref. 7.)

the test apparatus in the soft mass have no palpably firm core." The USP provides specifications for uncoated tablets, plain coated tablets, enteric tablets, buccal tablets, and sublingual tablets. Exempted from USP disintegration tests are troches, tablets which are intended to be chewed, and drug products intended for sustained release or prolonged or repeat action.

Disintegration tests allow for precise measurement of the formation of fragments, granules, or aggregates from solid dosage forms, but do not provide information on the dissolution rate of the active drug. The disintegration test serves as a component in the overall quality control of tablet manufacture.

Dissolution

Dissolution is the process by which a chemical or drug becomes dissolved in a solvent. In biologic systems, drug dissolution in an aqueous medium is an important prior condition of systemic absorption. The rate at which drugs with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the GI tract often controls the rate of systemic absorption of the drug. Thus, dissolution tests are discriminating of formulation factors that may affect drug bioavailability.

As the drug particle dissolves, a saturated solution (stagnant layer) is formed at the immediate surface around the particle. The dissolved drug in the saturated solution gradually diffuses to the surrounding regions. The overall rate of drug dissolution may be described by the Noyes–Whitney equation which models drug dissolution in terms of the rate of drug diffusion from the surface to the bulk of the solution. In general, drug concentration at the surface is assumed to be the highest possible, i.e., the solubility of the drug in the dissolution medium. The drug concentration C is the homogeneous concentration in the bulk solution which is generally lower than that in the stagnant layer immediate to the surface of the solid. The decrease in concentration across the stagnant layer is called the diffusion gradient

$$dC/dt = DA(CS - C)h$$

where, dC/dt = rate of drug dissolution, D = diffusion rate constant, A = surface area of the particle, CS = drug concentration in the stagnant layer, C = drug concentration in the bulk solvent, and h = thickness of the stagnant layer.

The rate of dissolution, $(dC/dt) \times (1/A)$, is the amount of drug dissolved per unit area per time (e.g., g/cm^2 per min).

The Noyes–Whitney equation shows that dissolution rate is influenced by the physicochemical characteristics of the drug, the formulation, and the solvent. In addition, the temperature of the medium also affects drug solubility and dissolution rate.

PHYSICOCHEMICAL NATURE OF THE DRUG

Solubility, pH, and Drug Absorption

The natural pH environment of the GI tract varies from acidic in the stomach to slightly alkaline in the small intestine. Drug solubility may be improved with the addition of acidic or basic excipients. Solubilization of aspirin, for example, may be increased by the addition of an alkaline buffer. Controlled release drug products are nondisintegrating dosage forms. Buffering agents may be added to slow or modify the release rate of a fast-dissolving drug in the formulation of a controlled release drug product. The buffering agent is released slowly rather than rapidly so that the drug does not dissolve immediately in the surrounding GI fluid. Intravenous drug solutions are difficult to prepare with drugs that have poor aqueous solubility. Drugs that are physically or chemically unstable may require special excipients, coating or manufacturing process to protect the drug from degradation.

Stability, pH, and Drug Absorption

The pH-stability profile is a plot of reaction rate constant for drug degradation versus pH and may help to predict if

some of the drug will decompose in the GI tract. The stability of erythromycin is pH-dependent. In acidic medium, erythromycin decomposition occurs rapidly, whereas at neutral or alkaline pH the drug is relatively stable. Consequently, erythromycin tablets are enteric coated to protect against acid degradation in the stomach. In addition, less soluble erythromycin salts that are more stable in the stomach have been prepared.

Particle Size and Drug Absorption

The effective surface area of the drug is increased enormously by a reduction in the particle size. Because drug dissolution is thought to take place at the surface of the solute, the greater the surface area, the more rapid the rate of drug dissolution. The geometric shape of the drug particle also affects the surface area, and during dissolution the surface is constantly changing. In dissolution calculations, the solute particle is usually assumed to have retained its geometric shape.

Particle size and particle size distribution studies are important for drugs that have low water solubility. Particle size reduction by milling to a micronized form increased the absorption of low aqueous solubility drugs such as griseofulvin, nitrofurantoin, and many steroids. Smaller particle size results in an increase in the total surface area of the particles, enhances water penetration into the particles, and increases the dissolution rates. With poorly soluble drugs, a disintegrant may be added to the formulation to ensure rapid disintegration of the tablet and release of the particles.

Polymorphic Crystals, Solvates, and Drug Absorption

Polymorphism refers to the arrangement of a drug in various crystal forms (polymorphs). Polymorphs have the same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics. Some polymorphic crystals may have much lower aqueous solubility than the amorphous forms, causing a product to be incompletely absorbed. Chloramphenicol (9), for example, has several crystal forms, and when given orally as a suspension, the drug concentration in the body depended on the percentage of β-Polymorph in the suspension. The β-form is more soluble and better absorbed (Fig. 7). In general, the crystal form that has the lowest free energy is the most stable polymorph. Polymorphs that are metastable may convert to a more stable form over time. A crystal form change may cause problems in manufacturing the product. For example, a

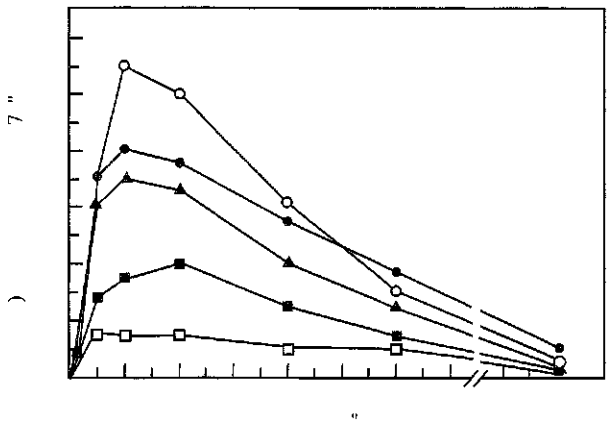

Fig. 7 Comparison of mean blood serum levels obtained with chloramphenicol palmitate suspensions containing varying ratios of α and β polymorphs, following single oral dose equivalent. (From Ref. 9.)

change in crystal structure of the drug may cause cracking in a tablet or even prevent a granulation to be compressed into a tablet requiring reformulation of the product. Some drugs interact with solvent during preparation to form a crystal called solvate. Water may form a special crystal with drugs called hydrates, for example, erythromycin forms different hydrates (8) which may have quite different solubility compared to the anhydrous form of the drug (Fig. 8). Ampicillin trihydrate, for example, was reported

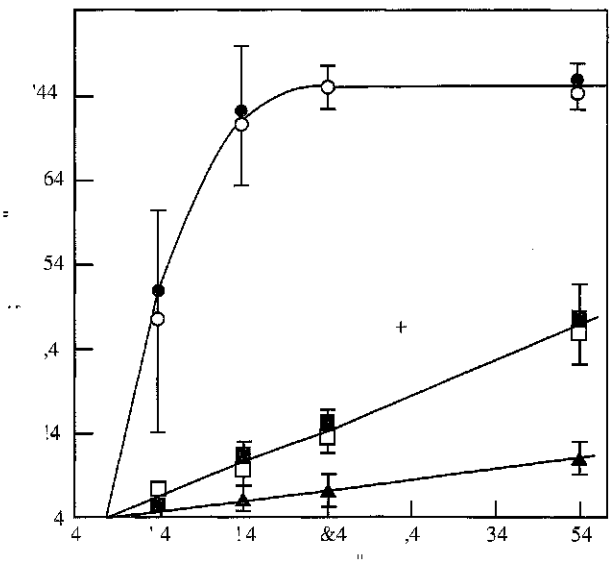

Fig. 8 Dissolution behavior of erythromycin dihydrate, monohydrate, and anhydrate in phosphate buffer (pH 7.5) at 37°C. (From Ref. 8.)

Table 5 Common excipients used in solid drug products

Excipient	Property in dosage form
Lactose	Diluent
Dibasic calcium phosphate	Diluent
Starch	Disintegrant, diluent
Microcrystalline cellulose	Disintegrant, diluent
Magnesium stearate	Lubricant
Stearic acid	Lubricant
Hydrogenated vegetable oil	Lubricant
Talc	Lubricant
Sucrose (solution)	Granulating agent
Polyvinyl pyrrolidone (solution)	Granulating agent
Hydroxypropylmethylcellulose	Tablet-coating agent
Titinium dioxide	Combined with dye as colored coating
Methylcellulose	Coating or granulating agent
Cellulose acetate phthalate	Enteric coating agent

(From Ref. 1.)

Table 6 Common excipients used in oral liquid drug products

Excipient	Property in dosage form
Sodium carboxymethylcellulose	Suspending agent
Tragacanth	Suspending agent
Sodium alginate	Suspending agent
Xanthan gum	Thixotropic suspending agent
Veegum	Thixotropic suspending agent
Sorbitol	Sweetener
Alcohol	Solubilizing agent, preservative
Propylene glycol	Solubilizing agent
Methyl propylparaben	Preservative
Sucrose	Sweetener
Polysorbates	Surfactant
Sesame oil	For emulsion vehicle
Corn oil	For emulsion vehicle

(From Ref. 1.)

to be less absorbed than the anhydrous form of ampicillin due to faster dissolution of the latter.

FORMULATION FACTORS AFFECTING DRUG DISSOLUTION

Excipients are pharmacodynamically inactive substances that are added to a formulation to provide certain functional properties to the drug and dosage form. Excipients may be added to improve the compressibility of the active drug, stabilize the drug from degradation, decrease gastric irritation, control the rate of drug absorption from the absorption site, increase drug bioavailability, etc. Some excipients used in the manufacture of solid and liquid drug products are listed in Tables 5 and 6. For solid oral dosage forms such as compressed tablets, excipients may include 1) diluent (e.g., lactose), 2) disintegrant (e.g., starch), 3) lubricant (e.g., magnesium stearate), and 4) other components such as binding and stabilizing agents. When improperly used in the formulation, excipients may alter drug bioavailability and possibly pharmacodynamic activity.

Excipients may affect the drug dissolution rate by altering the medium in which the drug is dissolving or by reacting with the drug itself. Some common manufacturing problems that affect drug dissolution and bioavailability are listed in Table 7. For example,

Table 7 Effect of excipients on the pharmacokinetic parameters of oral drug product[a]

Excipients	Example	k_a	t_{max}	AUC
Disintegrants	Avicel, Explotab	↑	←	↑/—
Lubricants	Talc, hydrogenated vegetable oil	←	↑	←/—
Coating agent	Hydroxypropylmethyl cellulose	—	—	—
Enteric coat	Cellulose acetate phthalate	←	↑	←/—
Sustained-release agents	Methylcellulose, ethylcellulose	←	↑	←/—
Sustained-release agents (waxy agents)	Castorwax, Carbowax	←	↑	←/—
Sustained-release agents (gum/viscous)	Veegum, Keltrol	←	↑	←/—

[a]This may be concentration and drug dependent.
↑ = Increase, ← = decrease, — = no effect. k_a = absorption rate constant, t_{max} = time for peak drug concentration in plasma, AUC = area under the plasma drug concentration time curve.
(From Ref. 1.)

suspending agents increase the viscosity of the drug vehicle, but may decrease the drug dissolution rate from the suspension. An excessive quantity of magnesium stearate (a hydrophobic lubricant) in the formulation may retard drug dissolution and slow the rate of drug absorption. The total amount of drug absorbed may also be reduced. To prevent this problem, the lubricant level should be decreased or a different lubricant selected. Sometimes, increasing the amount of disintegrant may overcome the retarding effect of lubricants on dissolution. However, with some poorly soluble drugs an increase in disintegrant level has little or no effect on drug dissolution because the fine drug particles are not wetted. The general influence of some common excipients on drug bioavailability parameters for typical oral drug products is summarized in Table 7.

Excipients may enhance or diminish the rate and extent of systemic drug absorption. Excipients that increase the aqueous solubility of the drug generally increase the rate of drug dissolution and absorption. For example, sodium bicarbonate in the formulation may change the pH of the medium surrounding the active drug substance. Aspirin, a weak acid, in an alkaline medium will form a water-soluble salt in which the drug rapidly dissolves. This process is known as dissolution in a reactive medium. The solid drug dissolves rapidly in the reactive solvent surrounding the solid particle. As the dissolved drug molecules diffuse outward into the bulk solvent, the drug may precipitate out of solution with a very fine particle size. The small particles have enormous collective surface area and disperse and redissolve readily for more rapid absorption on contact with the mucosal surface.

Excipients may interact directly with the drug to form a water-soluble or water-insoluble complex. If tetracycline is formulated with calcium carbonate, an insoluble complex of calcium tetracycline is formed that has a slow rate of dissolution and poor absorption.

Excipients may increase the retention time of the drug in the GI tract and therefore increase the amount of drug absorbed. Excipients may act as carriers to increase drug diffusion across the intestinal wall. The addition of surface-active agents may increase wetting as well as solubility of drugs. In contrast, many excipients may retard drug dissolution and thus reduce drug absorption.

Shellac used as a tablet coating, upon aging, can slow the drug dissolution rate. Surfactants may affect drug dissolution in an unpredictable fashion. Low concentrations of surfactants lower the surface tension and increase the rate of drug dissolution, whereas higher concentrations of surfactants tend to form micelles with the drug and thus decrease the dissolution rate. High tablet compression without sufficient disintegrant may cause poor disintegration in vivo of a compressed tablet.

IN VITRO DISSOLUTION TESTING

A dissolution test in vitro measures the rate and extent of dissolution of the drug in an aqueous medium in the presence of one or more excipients contained in the drug product. A potential bioavailability problem may be uncovered by a suitable dissolution method. The optimum dissolution testing conditions differ with each drug formulation. Different agitation rates, different medium (including different pH), and different dissolution apparatus should be tried to distinguish which dissolution method is optimum for the drug product and discriminating for drug formulation changes. The appropriate dissolution test condition for the drug product is then used to determine acceptable dissolution specifications.

The size and shape of the dissolution vessel may affect the rate and extent of dissolution. For example, the vessel may range in size from several milliliters to several liters. The shape may be round-bottomed or flat, so that the tablet might lie in a different position in different experiments. The amount of agitation and the nature of the stirrer affect the dissolution rate. Stirring rates must be controlled, and specifications differ between drug products. Low stirring rates (50–100 rpm) are more discriminating of formulation factors affecting dissolution than higher stirring rates. The temperature of the dissolution medium must be controlled and variations in temperature must be avoided. Most dissolution tests are performed at 37°C.

The nature of the dissolution medium, the solubility of the drug and the amount of drug in the dosage form will affect the dissolution test. The dissolution medium should not be saturated by the drug. Usually, a volume of medium larger than the amount of solvent needed to completely dissolve the drug is used in such tests. The usual volume of the medium is 500–1000 ml. Drugs that are not very water soluble may require use of a very-large-capacity vessel (up to 2000 ml) to observe significant dissolution. Sink conditions is a term referring to an excess volume of medium that allows the solid drug to continuously dissolve. If the drug solution becomes saturated, no further net drug dissolution will take place. According to the USP, "the quantity of medium used should be not less than three times that required to form a saturated solution of the drug substance."

Which medium is best is a matter of considerable controversy. The preferred dissolution medium in USP dissolution tests is deaerated water or if substantiated by the solubility characteristics of the drug or formulation, a buffered aqueous solution (typically pH 4–8) or dilute HCl may be used. The significance of dearation of the medium should be determined. Various investigators have used 0.1 *N* HCl, 0.01 *N* HCl, phosphate buffer, simulated gastric juice, water, and simulated intestinal juice, depending on the nature of the drug product and the location in the GI tract where the drug is expected to dissolve. No single apparatus and test can be used for all drug products. Each drug product must be tested individually with the dissolution test that best correlates to in vivo bioavailability.

The dissolution test usually states that a certain percentage of the labeled amount of drug in the drug product must dissolve within a specified period of time. In practice, the absolute amount of drug in the drug product may vary from tablet to tablet. Therefore, a number of tablets from each lot are usually tested to get a representative dissolution rate for the product. The USP provides several official (compendia) methods for carrying out dissolution tests of tablets, capsules and other special products such as transdermal preparations. The selection of a particular method for a drug is usually specified in the monograph for a particular drug product.

BIOAVAILABILITY AND BIOEQUIVALENCE

Bioavailability and bioequivalence may be determined directly using plasma drug concentration vs. time profiles, urinary drug excretion studies, measurements of an acute pharmacologic effect, clinical studies, or in vitro studies. Bioavailability studies are performed for both approved active drug ingredients or therapeutic moieties not yet approved for marketing by the FDA. New formulations of active drug ingredients or therapeutic moieties must be approved, prior to marketing, by the FDA. In approving a drug product for marketing, the FDA must ensure that the drug product is safe and effective for its labeled indications for use. To ensure that the drug product meets all applicable standards of identity, strength, quality, and purity, the FDA requires bioavailability/pharmacokinetic studies and where necessary bioequivalence studies for all drug products.

For unmarketed drugs which do not have full New Drug Application (NDA) approval by the FDA, in vivo bioavailability studies must be performed on the drug formulation proposed for marketing. Essential pharmacokinetic parameters of the active drug ingredient or therapeutic moiety is also characterized. Essential pharmacokinetic parameters include the rate and extent of systemic absorption, elimination half-life, and rates of excretion and metabolism should be established after single- and multiple-dose administration. Data from these in vivo bioavailability studies are important to establish recommended dosage regimens and to support drug labeling.

In vivo bioavailability studies are performed also for new formulations of active drug ingredients or therapeutic moieties that have full NDA approval and are approved for marketing. The purpose of these studies is to determine the bioavailability and characterize the pharmacokinetics of the new formulation, new dosage form, or new salt or ester relative to a reference formulation. After the bioavailability and essential pharmacokinetic parameters of the active ingredient or therapeutic moiety are established, dosage regimens may be recommended in support of drug labeling.

Bioequivalent Drug Products

Bioequivalent drug products are pharmaceutical equivalents whose bioavailability (i.e., rate and extent of systemic drug absorption) does not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single or multiple dose. Some pharmaceutical equivalents or may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied [21 CFR 320.1(e)].

Generic Drug Products

A generic drug product is considered bioequivalent to the reference listed drug product (generally the currently marketed, brand-name product with a full (NDA) approved by the FDA) if both products are pharmaceutical equivalents and its rate and extent of systemic drug absorption (bioavailability) do not show a statistically significant difference when administered in the same dose of the active ingredient, in the same chemical form, in a similar dosage form, by the same route of administration, and under the same experimental conditions.

Pharmaceutical equivalents are drug products that contain the same therapeutically active drug ingredient(s), same salt, ester, or chemical form; are of the same dosage form; and are identical in strength and concentration and route of administration. Pharmaceutical equivalents may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, and excipients (including colors, flavoring, preservatives).

Therapeutic equivalent drug products are pharmaceutical equivalents that can be expected to have the same clinical effect and safety profile when administered to patients under the same conditions specified in the labeling. Therapeutic equivalent drug products have the following criteria: 1) The products are safe and effective; 2) The products are pharmaceutical equivalents containing the same active drug ingredient in the same dosage form, given by the same route of administration, meet compendia or other applicable standards of strength, quality, purity, and identity and meet an acceptable in vitro standard; 3) The drug products are bioequivalent in that they do not present a known potential problem and are shown to meet an appropriate bioequivalence standard; 4) The drug products are adequately labeled; 5) The drug products are manufactured in compliance with current good manufacturing practice (GMP) regulations.

The generic drug product requires an abbreviated new drug application (ANDA) for approval by the FDA and may be marketed after patent expiration of the reference listed drug product. The generic drug product must be a therapeutic equivalent to the Reference drug product but may differ in certain characteristics including shape, scoring configuration, packaging, and excipients (includes colors, flavors, preservatives, expiration date, and minor aspects of labeling).

Pharmaceutical alternatives are drug products that contain same therapeutic moiety but are different salts, esters or complexes (e.g., tetracycline hydrochloride versus tetracycline phosphate) or are different dosage forms (e.g., tablet versus capsule; immediate release dosage form versus controlled release dosage form) or strengths.

In summary, clinical studies are useful in determining the safety and efficacy of the drug product. Bioavailability studies are used to define the affect of changes in the physico chemical properties of the drug substance and the affect of the drug product (dosage form) on the pharmacokinetics of the drug; whereas, bioequivalence studies are used to compare the bioavailability of the same drug (same salt or ester) from various drug products. If the drug products are bioequivalent and therapeutically equivalent, then the clinical efficacy and safety profile of these drug products are assumed to be similar and may be substituted for each other.

DRUG PRODUCT PERFORMANCE IN VITRO AS A MEASURE OF IN VIVO DRUG BIOAVAILABILITY

The best measure of a drug product's performance is to give the drug product to human volunteers or patients and then determine the in vivo bioavailability of the drug using a pharmacokinetic or clinical study. For some well characterized drug products and for certain drug products where bioavailability is self-evident (e.g., sterile solutions for injection), in vivo bioavailability studies may be unnecessary. In these cases, the performance of the drug product in vitro is used as a surrogate to predict the in vivo drug bioavailability. Because these products have predictable in vivo performance as judged by the in vitro characterization of the drug and drug product, the FDA may waive the requirement for performing an in vivo bioavailability study (Table 8).

Drug Products for which Bioavailability is Self-Evident

Drug bioavailability from a true solution is generally considered self-evident. Thus, sterile solutions, lyophilized powders for reconstitution, opthalmic solutions do not need bioequivalence studies but still must be manufactured according to current GMPs. However, highly viscous solutions may have bioavailability problems due to slow diffusion of the active drug.

In Vitro–In Vivo Correlation (IVIVC)

In vitro bioavailability data may be used to predict the performance of a dosage provided that the dissolution method selected is appropriate for the solid oral dosage form and prior information has been collected showing that the dissolution method will result in optimum drug absorption from the drug product. In general, IVIVC is best for well absorbed drugs for which the dissolution rate is the rate-limiting step. Some drugs are poorly absorbed and dissolution is not predictive of absorption (1). The objectives of IVIVC are to use rate of dissolution as a discriminating (i.e., sensitive to changes in formulation or manufacturing process), as an aid in setting dissolution specifications. When properly applied, IVIVC may be used to facilitate the evaluation

Table 8 Examples of drug products for which in vivo bioavailability studies may be waived

Condition	Example	Comment
Drug products for which bioavailability is self-evident	Drug solution (e.g., parenteral ophthalmic, oral solutions)	Drug bioavailability from a true solution is considered self-evident. However, highly viscous solutions may have bioavailability problems.
In vivo–in vitro correlation (IVIVC)	Modified release drug products	The dissolution of the drug from the drug product in vitro must be highly correlated to the in vivo bioavailability of the drug.
Biopharmaceutic classification (BCS) system	Immediate release solid oral drug products	Drug must be a highly soluble and highly permeable substance that is in a rapidly dissolving dosage form.
Biowaiver	Drug product containing a lower dose strength	Drug product is in the same dosage form, but lower strength and is proportionally similar in its active and inactive ingredients.

of drug products with manufacturing changes including minor changes in formulation, equipment, process, manufacturing site, and batch size. (see section on SUPAC) (2, 3, 10).

Three levels of IVIVC are generally recognized by the FDA (10). Level A correlation is usually estimated by deconvolution followed by comparison of the fraction of drug absorbed to the fraction of drug dissolved. A correlation of this type is the highest level of correlation and best predictor of bioavailability from the dosage form. A Level A correlation is generally linear and represents a point-to-point relationship between in vitro dissolution rate and the in vivo input rate. The Level A correlation should predict the entire in vivo time course from the in vitro dissolution data. Level B correlation utilizes the principles of statistical moment analysis, Various dissolution IVIVC methods were discussed by Shargel and Yu in 1985, 1993, 1999 (1). The mean in vitro dissolution time is compared to either the mean residence time or the mean in vivo dissolution time. Level B correlation, like Level A correlation, uses all of the in vitro and in vivo data but is not considered to be a point-to-point correlation and does not uniquely reflect the actual in vivo plasma level curve, since several different in vivo plasma level-time curves will produce similar residence times. A Level C correlation is the weakest IVIVC and establishes a single point relationship between a dissolution parameter (e.g., time for 50% of drug to dissolve, or percent drug dissolved in two hours, etc.) and a pharmacokinetic parameter (e.g., AUC, Cmax, Tmax). Level C correlation does not reflect the complete shape of the plasma drug concentration-time curve of dissolution profile.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

The FDA may waive the requirement for performing an in vivo bioavailability or bioequivalence study for certain immediate release solid oral drug products that meets very specific criteria, namely, the permeability, solubility, and dissolution of the drug. These characteristics include the in vitro dissolution of the drug product in various media, drug permeability information, and assuming ideal behavior of the drug product, drug dissolution and absorption in the GI tract. For regulatory purpose, drugs are classified according to BCS in accordance the solubility, permeability and dissolution characteristics of the drug (FDA Draft Guidance for Industry, January, 1999, see FDA website for guidance) (11). Based on drug solubility and permeability, Amidon et al. (10, 12) recommended the following BCS in 1995 (Table 9).

This classification can be used as a basis for setting in vitro dissolution specifications and can also provide a basis for predicting the likelihood of achieving a successful in IVIVC. The solubility of a drug is determined by dissolving the highest unit dose of the drug in 250 ml of buffer adjusted between pH 1.0 and 8.0. A drug substance is considered highly soluble when the dose/solubility volume of solution are less than or equal to 250 ml. High-permeability drugs are generally those with an extent of absorption that is greater than 90%.

Solubility

An objective of the BCS approach is to determine the equilibrium solubility of a drug under approximate

Table 9 Biopharmaceutics classification system (BCS)

Condition	Comments
Solubility	A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of water over a pH range of 1–8.
Dissolution	An immediate release (IR) drug product is considered rapidly dissolving when not less than 85% of the label amount of the drug substance dissolves within 30 min using the USP apparatus I at 100 rpm (or apparatus II at 50 rpm) in a volume of 900 ml or less.[a]
Permeability	A drug substance is considered highly permeable when the extent of absorption in humans is to be >90% of an administered dose based on mass balance determination.

[a]Media include: acidic media (e.g., 0.1 N HCl) or simulated gastric fluid, USP without enzymes, pH 4.5 buffer and pH 6.8 buffer of simulated intestinal fluid, USP without enzymes (From FDA Draft Guidance, Jan, 1999.)

physiological conditions. For this purpose, determination of pH-solubility profiles over a pH range of 1–8 is suggested. Preferably eight or more pH conditions should be evaluated. Buffers that react with the drug should not be used. An acid or base titration method can also be used for determining drug solubility. The solubility class is determined by calculating what volume of an aqueous media is sufficient to dissolve the highest anticipated dose strength. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1–8. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (8 ounces) of water.

Solution stability of a test drug in selected buffers (or pH conditions) should be documented using a validated stability-indicating assay. Data collected on both pH-solubility and pH-stability should be submitted in the biowaiver application along with information on the ionization characteristics, such as pKa(s), of a drug.

Determining Permeability Class

Studies of the extent of absorption in humans, or intestinal permeability methods, can be used to determine the permeability class membership of a drug. To be classified as highly permeable, a test drug should have an extent of absorption >90% in humans. Supportive information on permeability characteristics of the drug substance should also be derived from its physical–chemical properties (e.g., octanol:water partition coefficient).

Some methods to determine the permeability of a drug from the GI tract include 1) in vivo intestinal perfusion studies in humans, 2) in vivo or in situ intestinal perfusion studies in animals, 3) in vitro permeation experiments using excised human or animal intestinal tissues, and 4) in vitro permeation experiments across a monolayer of cultured human intestinal cells. When using these methods, the experimental permeability data should correlate with the known extent-of-absorption data in humans.

Table 10 Postapproval change levels

Change level	Example	Comment
Level 1	Deletion or partial deletion of an ingredient to affect the color or flavor of the drug product	Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.
Level 2	Quantitative change in excipients greater that allowed in a Level 1 change.	Level 2 changes are those that could have a significant impact on formulation quality and performance
Level 3	Qualitative change in excipients	Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. A Level 3 change may require in vivo bioequivalence testing.

Dissolution

The dissolution class is based on the in vitro dissolution rate of an immediate release drug product under specified test conditions and is intenended to indicate rapid in vivo dissolution in relation to the average rate of gastric emptying in humans under fasting conditions. An immediate release drug product is considered rapidly dissolving when not less than 85% of the label amount of drug substance dissolves within 30 min using the USP apparatus I at 100 rpm or apparatus II at 50 rpm in a voluume of 900 ml or less in each of the following media 1) acidic media such as 0.1 *N* HCl or Simulated Gastric Fluid USP without enzymes; 2) a pH 4.5 buffer; and 3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

BIOWAIVERS

In addition to routine quality control tests, comparative dissolution tests have been used to waive bioequivalence requirements (biowaivers) for lower strengths of a dosage form. The drug products containing the lower dose strengths should be compositionally proportional or qualitatively the same as the higher dose strengths and have the same release mechanism. For biowaivers, a dissolution profile should be generated and evaluated using one of the methods described under Section V in this guidance, "Dissolution Profile Comparisons." Biowaivers are generally provided for multiple strengths after approval of a bioequivalence study performed on one strength, using the following criteria: For multiple strengths of IR products with linear kinetics, the bioequivalence study may be performed at the highest strength and waivers of in vivo studies may be granted on lower strengths, based on an adequate dissolution test, provided the lower strengths are proportionately similar in composition [21 CFR 320.22(d)(2)]. Similar may also be interpreted to mean that the different strengths of the products are within the scope of changes permitted under the category "Components and Composition," discussed in the SUPAC-IR guidance.

SCALE-UP AND POSTAPPROVAL CHANGES (SUPAC)

After a drug product is approved for marketing by the FDA, the manufacturer may want to make a manufacturing change. The pharmaceutical industry, academia and the FDA developed (2, 3, 5, 3, 10, 3, 12–17) a series of guidances for the industry that discuss scale-up and postapproval changes, generally termed, SUPAC guidances (11). The FDA SUPAC guidances are for manufacturers of approved drug products who want to change 1) a component and composition of the drug product; 2) the batch size; 3) the manufacturing site; 4) the manufacturing process or equipment; and/or 5) packaging. These guidances describe various levels of postapproval changes according to whether the change is likely to impact on the quality and performance of the drug product. The level of change as classified by the FDA as to the likelihood that a change in the drug product might affect the quality of the product (Table 10).

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Board of Pharmaceutical Specialties

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INTRODUCTION

The Board of Pharmaceutical Specialties (BPS) was established in 1976 under the auspices of the American Pharmaceutical Association (APhA). The overriding concern of BPS is to ensure that the public receives the highest possible quality pharmacy services, contributing toward outcomes that improve a patient's quality of life. The BPS has four primary responsibilities:

- To recognize specialties in pharmacy practice.
- To set standards for certification and recertification.
- To objectively evaluate individuals seeking certification and recertification.
- To serve as a source of information and coordinating agency for pharmacy specialties.

The BPS is located at 2215 Constitution Avenue, NW, Washington, D.C. 20037-2985, phone: (202) 429-7591; fax: (202) 429-6304; www.bpsweb.org.

OVERVIEW

Certification is a voluntary process by which a practitioner's education, experience, knowledge, and skills are confirmed by one's profession as meeting or surpassing a standard beyond that required for licensure. The standards and processes for certification (unlike those for licensure) are established by a professional, nongovernmental agency. BPS certification is at the specialty level and signifies that an individual has met a national professional standard and demonstrated mastery of a body of knowledge, skills, and abilities in an advanced level in a specialized area of practice.

Today, BPS functions as an agency of APhA with its own governing Board structure. The board is composed of six pharmacist members, two health care practitioners outside of pharmacy, and one public member. The chair of each Specialty Council and the BPS Executive Director serve as nonvoting members of the Board. The Executive Director of BPS is Richard J. Bertin, Ph.D., R.Ph. and the current Chair of BPS is Roger W. Anderson, R.Ph., DrPH, who is Director of Pharmacy at M.D. Anderson Cancer Center.

To date, five specialties have been recognized by BPS: 1) nuclear pharmacy; 2) nutrition support pharmacy; 3) oncology pharmacy; 4) pharmacotherapy; and 5) psychiatric pharmacy. As of August, 2002, 3414 pharmacists are certified as specialists in one or more of these specialties. Added Qualification is a process for providing recognition of pharmacists with further training and experience in areas of concentration within an existing specialty.

MISSION AND OBJECTIVES

The mission of BPS was refined in 1997 and is reviewed by the Board semiannually. The mission is to improve public health through recognition and promotion of specialized training, knowledge, and skills in pharmacy and certification of pharmacist specialists. The organization achieves its mission through accomplishment of six strategic objectives including 1) providing leadership for the profession of pharmacy in the discussion, evolution, direction, and recognition of specialties in pharmacy; 2) establishing the standards for identification and recognition of specialties in consultation with the profession; 3) establishing standards of training, knowledge, and skills as the basis for certification of individuals; 4) developing and administering objective and valid means to evaluate the knowledge and skills of pharmacist specialists; 5) evaluating areas of specialization for their value and

viability; and 6) communicating the value of specialization and specialty certification in pharmacy.

THE SPECIALTIES

BPS has recognized five specialty practice areas. They are 1) nuclear pharmacy (1978); 2) nutrition support pharmacy (1988); 3) pharmacotherapy (1988); 4) psychiatric pharmacy (1992); and 5) oncology pharmacy (1996).

Nuclear pharmacy seeks to improve and promote public health through the safe and effective use of radioactive drugs for diagnosis and therapy. A nuclear pharmacist, as a member of the nuclear medicine team, specializes in procurement, compounding, quality assurance, dispensing, distribution, and development of radiopharmaceuticals. In addition, the nuclear pharmacist monitors patient outcomes and provides information and consultation regarding health and safety issues.

Nutrition support pharmacy addresses the care of patients receiving specialized parenteral or enteral nutrition. The nutrition support pharmacist is responsible for promoting restoration and maintenance of optimal nutritional status and designing and modifying treatment in accordance with patient needs. These specialists have responsibility for direct patient care and often function as members of multidisciplinary nutrition support teams.

Pharmacotherapy is the specialty responsible for ensuring the safe, appropriate, and economical use of drugs in patient care. The pharmacotherapy specialist has responsibility for direct patient care and often functions as a member of a multidisciplinary treatment team. These specialists may conduct clinical research and are frequently primary sources of drug information for other health care professionals.

Psychiatric pharmacy addresses the pharmaceutical care of patients with psychiatric disorders. As a member of a multidisciplinary treatment team, the psychiatric pharmacist specialist is often responsible for optimizing drug treatment and patient care by conducting patient assessments; recommending appropriate treatment plans; monitoring patient response; and preventing, identifying, and correcting drug-related problems.

Oncology pharmacy addresses the pharmaceutical care of patients with cancer. The oncology pharmacist specialist promotes optimal care of patients with various malignant diseases and their complications. These specialists are closely involved in recognition, management, and prevention of unique morbidities associated with cancer and cancer treatment; recognition of the balance between improved survival and quality of life as primary outcome indicators; and provision of safeguards against drug misadventures in a treatment area where novel and experimental drug therapies are frequently employed.

ADDED QUALIFICATIONS

Added Qualifications is the mechanism used by BPS to recognize further differentiation within a specialty which the Board has already recognized. This distinction may be granted to a BPS-certified specialist on the basis of a structured portfolio review process, administered by the Specialty Council responsible for the specialty. The first petition for Added Qualifications was in Infectious Diseases and was approved by the Pharmacotherapy Specialty Council and BPS in 1999. The first candidates were conferred the "Added Qualifications in Infectious Diseases" credential in 2000. A petition for Added Qualifications in Cardiology was approved in 2000, and the first candidates were conferred the Added Qualifications in Cardiology Pharmacotherapy credential in 2001.

THE CERTIFICATION PROCESS

When a group of interested pharmacists wishes to have a new specialty considered for recognition by the BPS, they submit a petition to the Board. The petition is evaluated against seven criteria: 1) need of the profession and the public for specifically trained practitioners in the specialty practice area to fulfill the responsibilities of the profession in improving the health and welfare of the public; 2) clear, significant demand for the specialty by the public and health care system; 3) presence of a reasonable number of pharmacist specialists practicing in and devoting significant time in the specialty area; 4) specialized knowledge of pharmaceutical sciences required by those practicing in the specialty area; 5) specialized functions provided by pharmacists in the specialty practice area that require education and training beyond the basic level attained by licensed pharmacists; 6) education and training in the specialty area provided by pharmacy colleges and other organizations; and 7) transmission of knowledge in the specialty practice area occurring through books, journals, symposia, professional meetings, and other media.

After a new specialty is recognized by BPS, a Specialty Council of content experts is appointed to work with the BPS and a professional testing firm to develop a psychometrically sound and legally defensible certification process. The Specialty Council is composed of six pharmacists practicing in the specialty area and three other pharmacists. Certification examinations consisting of 200 multiple choice questions are administered an-

nually at designated sites throughout the United States and in other countries. Each BPS-certified specialist must recertify every seven years. Approved professional development programs are available as an alternative to sitting for a 100-item recertification examination in nuclear pharmacy and pharmacotherapy. BPS continually evaluates and updates its certification and recertification processes. Approximately every five years, a new role delineation study is conducted for each specialty, and examination specifications are modified accordingly.

VALUE AND RECOGNITION OF CERTIFICATION

Specialty certification in pharmacy offers numerous potential benefits of significant value to patients, other health professionals, employers, health care systems, and the public. Specialty certification denotes that specialists are highly trained and skilled and have demonstrated the ability to identify, resolve, and prevent drug therapy problems. They have taken the initiative to seek additional education and experience in a specialized pharmacy field and exhibit a high level of commitment to patients and the profession. Certified pharmacist specialists function as valued members of treatment teams, optimizing and individualizing drug therapy. Employers can feel assured that the knowledge and skills of certified pharmacist specialists have been tested through a rigorous, objective, and peer-determined process.

Certification also provides a personal reward for pharmacist specialists. Specialty certification communicates to others that the specialist's educational and practice accomplishments differentiate the specialist from colleagues. Many specialists feel that they have a competitive edge in applying for positions, and some have received reimbursement from third-party payers, because their skills and knowledge have been validated through certification. Some pharmacist specialists have also reported increased salaries or one-time bonuses upon attaining BPS certification.

BPS certification has been formally recognized by the American Association of Colleges of Pharmacy, the American College of Clinical Pharmacy, the American Pharmaceutical Association, the American Society for Parenteral and Enteral Nutrition, the American Society of Health-System Pharmacists, the Ordre des Pharmaciens du Quebec, the Society of Infectious Diseases Pharmacists, and the Society of Hospital Pharmacists of Australia.

BPS-certified pharmacist specialists are recognized for their advanced level of knowledge, skills, and achievement by many government agencies and health care organizations. The following are examples of specific benefits that may be realized by BPS-certified pharmacist specialists:

- U.S. Nuclear Regulatory Commission: specialists may be licensed as Radiation Safety Officers and/or recognized as Authorized Users.
- U.S. Department of Defense: specialists may receive bonus pay.
- U.S. Department of Veterans Affairs: specialists may serve at higher pay steps.
- U.S. Public Health Service: specialists may receive bonus pay.
- New Mexico State Board of Pharmacy: specialists may apply for specified prescribing privileges.
- At least seven Colleges of Pharmacy may exempt BPS-certified specialists from some didactic courses in postbaccalaureate or nontraditional Pharm.D. programs. Other Colleges award advanced placement on an individual case basis and may recognize BPS certification in this process.

Many other national, regional, or local employers of BPS-certified pharmacists also recognize BPS certification in their hiring, salary, or privileging policies.

Bone Marrow Transplant Pharmacy Practice

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INTRODUCTION

The utilization of a bone marrow transplantation to treat hematologic malignancies, solid tumors, genetic disorders, metabolic diseases, immune deficiency disorders, and bone marrow failures has grown tremendously since the first successful transplant in 1968. If these diseases are not treated aggressively, they can be fatal. The seriousness of these diseases is reflected in the intense care provided to the patient during and after a bone marrow transplant. Whether the patient receives an autologous, syngeneic, or allogeneic bone marrow transplant, the patient needs to be followed very closely for the first several weeks to several years (depending on the type of bone marrow transplant and type of post-transplant complications) by the bone marrow transplant team. After an allogeneic bone marrow transplant, the patient needs to be seen in clinic 1 to 3 days per week for physical examinations, blood work, special microbiology testing, and medication adjustments. Once a bone marrow transplant patient is deemed to be stable, their outpatient visits will slowly decrease.

The medications used during a bone marrow transplant and post–bone marrow transplant carry extensive toxicity profiles and have numerous drug–drug/drug–food interactions, and the majority of medications are expensive. These characteristics in themselves justify the necessity of a pharmacist to be a key member of the bone marrow transplant team.

CLINICAL PHARMACY OPPORTUNITIES

The majority of bone marrow transplant centers (especially those performing allogeneic bone marrow transplants) in the United States have a pharmacist on the team. Currently, there are approximately 450 bone marrow transplant centers registered in 48 different countries with the National Marrow Donor Program.[1] In most cases, the pharmacist is employed by the Department of Pharmacy with partial or complete financial support from the Department of Medicine. With the stringent criteria developed for medical reimbursement by third-party payers (i.e., health maintenance organizations, preferred provider organizations, and medicaid/medicare), both the Departments of Pharmacy and Medicine have a strong interest in driving cost down. Since 11–37% of a bone marrow transplant cost is attributed to pharmaceuticals, the pharmacist plays a critical role in lowering the cost of a bone marrow transplant via close medication monitoring.[2] Similar to other clinical pharmacists, the bone marrow transplant pharmacist needs to monitor all drugs given to the patient for appropriate usage. However, the majority of medications used by a bone marrow transplant patient carry high levels of toxicities, narrow therapeutic windows, and life-threatening results if medication doses are forgotten or increased or decreased by the patient, thereby elevating the intensity of drug monitoring.

The bone marrow transplant team members primarily consists of a specially trained hematologist/oncologist, pharmacist, nurse practitioner/physician assistant, social worker, ± dietitian and/or total parenteral nutrition (TPN) personnel, and ± hematology/oncology medical fellow(s). The team members rely heavily on each other to ensure that appropriate, safe, and cost-effective care is given to each patient. The pharmacist–nurse practitioner/physician assistant relationship assists in combining physical assessment findings with drug outcomes. The pharmacist–social worker relationship is necessary for discharge planning to ensure medication affordability and appropriate home medication administration. The pharmacist–dietitian/TPN personnel relationship helps decrease drug–food interactions with mealtime plan changes and/or meal content changes and decrease cost by minimizing intravenous hyperalimentation usage. In some institutions, the pharmacist plays a lead role in dietary care, thereby negating the need for an additional dietary personnel. The pharmacist–hematology/oncology fellow relationship is primarily a teaching role for both parties. Finally, a sound pharmacist–physician relationship needs to be developed for the physicians to entrust patient care to a pharmacist. Once this bond has been established, a pharmacist's knowledge can be used for clinical advice on patient care, investigating innovative

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DOI: 10.1081/E-ECP 120006224

options for patient care, and developing research protocols to advance patient care. Therefore, in addition to a solid knowledge base in hematology-oncology, immunology, infectious diseases, fluid/electrolyte balance, and pain management, it is imperative for a bone marrow transplant pharmacist to possess excellent communication and people skills.

Because the patient's immune system is compromised for several months to several years secondary to the slow process of complete bone marrow recovery and/or long-term usage of immunosuppresives, the patient is vulnerable to numerous life-threatening infectious disease processes. In addition, the allogeneic bone marrow transplant patient always carries a certain risk (highest per-

Table 1 Pharmacist's responsibilities

Unstable patient	Stable patient
Adjust medication regimen(s) based on drug levels to enhance efficacy and/or prevent toxicity.[b]	Adjust medication regimen(s) based on drug levels to enhance efficacy and/or prevent toxicity.[a,b]
Monitor drug–drug and drug–food interactions to prevent toxicity.[c]	Monitor drug–drug and drug–food interactions to prevent toxicity.[a,c]
Educate the bone marrow transplant team about each medication's effect on the bone marrow.[d]	Educate the bone marrow transplant team about each medication's effect on the bone marrow.[a,d]
Offer advice on antibiotic choice(s) based on microbiology results, patient's immunologic state (i.e., neutropenic, type of underlying cancer), patient's infectious disease history (i.e., past infection(s), serology results), institution's microorganism–drug susceptibility record, and institution's microorganism resistance pattern.	
Adjust fluids and electrolytes based on daily laboratory values and medication changes.[e]	
Pain management. *Acute pain* secondary to mucositis needs persistent close monitoring and abrupt drug adjustments to attain near complete pain control within 4–6 hours.	Pain management. *Chronic pain* secondary to chronic GVHD needs close monitoring and drug adjustments to attain near complete pain control within 24–48 hours.
Monitor patients for *acute toxicities* secondary to conditioning regimen ± immunosuppressive agents. In addition, offer advice on preventive therapies for toxicities and treatment options for toxicities.	Monitor patients for *chronic toxicities* secondary to conditioning regimen ± immunosuppressive agents. In addition, offer advice on preventive therapies for toxicities and treatment options for toxicities.
Educate patient upon discharge on the importance of each medication by clearly writing the brand name and generic name of each medication, explaining the purpose of each medication, the time(s) of day each medication should be self-administered, the consequences of missing or doubling doses, and a contact name (preferably the pharmacist) and phone number for use if further questions arise at home.	Assure medication compliance by reviewing medication calendar. Once the patients are stable, they are more apt to develop their own regimens. These regimens may allow medications to be dosed too close together or too close to meal times, skip certain medications deemed unnecessary by the patient, and/or add certain medications (i.e., natural herbs, vitamins).
Conduct clinical research. Pharmacist-initiated research projects arise frequently from day-to-day unresolvable issues. Pharmaceutical industry-sponsored research projects are also available.[f]	Conduct outcome-based research. Because a pharmacist closely monitors the bone marrow transplant patients for a prolonged period of time, there is an abundance of data available for outcome-based research.

[a]Examples include, cyclosporine, tacrolimus, aminoglycosides, vancomycin.
[b]These tasks are performed at a lower intensity level than their counterparts.
[c]Examples include, choice of antihypertensive agent to be used while on cyclosporine or tacrolimus, timing medication ingestion around meal times.
[d]After identifying medications that are detrimental to the bone marrow, offer options for treatment that have no effect or minimal effect on the bone marrow.
[e]The pharmacist has the key role in preventing fluid and electrolyte abnormalities from occurring secondary to medications and aggressively correcting all fluid and electrolyte abnormalities.
[f]Pharmacists need to be aggressive in indentifying projects and seek funding for the projects.[3] Pharmacists should strive to be the primary investigator or coinvestigator on the projects.

centage if the donated bone marrow is from an unrelated individual without a 6/6 Human Lymphocyte Antigen match) for developing acute and/or chronic graft-versus-host disease (GVHD). If the patient develops GVHD, the immune system is even further compromised by not only the intense immunosuppressive agents needed for treatment, but also by the GVHD itself. Thus, an allogeneic bone marrow transplant patient may have numerous hospital readmissions for treatment of infectious disease processes, aggressive treatment, and close monitoring of moderate-to-severe GVHD or bone marrow failure (i.e., tumor relapse, bone marrow engraftment lost). The majority of patients are at highest risk for readmission during the first 100 days post-transplant. Bone marrow transplant recipients of mismatched or unrelated donors require more intense bone marrow immunosuppression for a longer period of time than their counterparts who receive matched or related bone marrow, thereby increasing their risk for hospital readmissions for a period greater than 100 days. Because the patient's medical needs can change drastically from day to day, the pharmacist needs to stay abreast of all new medication regimens required for patient care. It is imperative that the pharmacist has a good working relationship with the patient and patient's caregivers to ensure appropriate adherence to the evolving medication regimen.

Recently, there has been a surge of bone marrow transplant centers shifting inpatient care to the outpatient setting early in transplant (post bone marrow/peripheral blood stem cell infusion). The incentive for this trend has been to decrease the cost of bone marrow transplant and improve the patient's quality of life. Stringent, institution-specific criteria have been developed for patients to be outpatient bone marrow transplant candidates. The primary basis behind the criteria rely on the patient and a dedicated caregiver to be attentive to all their medical needs, including comprehension of appropriate medication administration guidelines. The patients are responsible for self-administration of scheduled and as needed oral, subcutaneous, and intravenous medications. By placing this level of responsibility on the patient and caregiver, the patient can be overcome with anxiety. A pharmacist plays a dominant role in alleviating any confusion or misunderstanding on medication self-administration. The bone marrow transplant pharmacist will need to thoroughly educate both the patient and caregiver on all the medications daily. Although the patient maybe medically stable in the outpatient setting, the initial amount of time the pharmacist needs to spend with the patient is equivalent to a complicated hospitalized bone marrow transplant patient.

There is a definite need for both an inpatient and outpatient bone marrow transplant pharmacist. Due to the patient's initial prolonged inpatient stay and high probability of multiple readmissions during the first several months post–bone marrow transplant, the distinction between an inpatient and outpatient bone marrow transplant pharmacist role becomes unclear. To help maintain continuity of care, usually one pharmacist (labeled as the inpatient pharmacist) will manage a patient's pharmaceutical needs both during the initial hospitalization and during the first several months of outpatient care. Once a patient's ambulatory visits decrease to at least once every 2 weeks, the outpatient pharmacist will attend to the patient's medication needs. If the institution predominantly performs autologous bone marrow transplants or if the number of bone marrow transplants (autologous combined with allogeneic) performed is low, then one pharmacist is sufficient to play both the inpatient and outpatient role.

The type and level of care provided by the pharmacist depends on the stability of the patient's health (Table 1). Generally, the patient is most unstable during the transplant and for the first several months post-transplant.

MODEL CLINICAL PRACTICES

The type of work a bone marrow transplant pharmacist performs on a daily basis depends on the goal of the employer. A pharmacist can be predominantly research based or clinically based.

Research-Based Practice

Most of the bone marrow transplant pharmacist positions with research emphasis are tenure-tracked or tenured with a teaching hospital. These pharmacists have minimal to no direct patient care duties assigned to them. Pharmacists are responsible for the following:

1. Developing research protocols
2. Applying for grants to fund the protocols
3. Screening and enrolling patients into study (when applicable)
4. Developing/running various assays
5. Publishing research results
6. Didactic, experiential university-based teaching

The majority of pharmacists will participate in pharmacy doctoral or postdoctoral programs or develop bone marrow transplant fellowships to attain reliable,

hardworking assistance in the laboratory. In turn, the students/fellows will be closely mentored by the pharmacist. This symbiotic relationship will allow both parties to augment research productivity, increase the number of publications, and attain larger funding sources.

Clinical-Based Practice

Most of the bone marrow transplant pharmacist positions with clinical emphasis are nontenure-tracked. The pharmacist's primary job responsibilities revolve around direct patient care. Pharmacists are responsible for the following:

1. Reviewing patient's laboratory bloodwork, microbiology results, and medication profiles on a daily basis
2. Attending and actively participating in patient medical rounds and patient clinic visits
3. Reviewing medications used in bone marrow transplant patients for inpatient and outpatient formulary usage
4. Helping to standardize care by developing protocols and procedures for bone marrow transplant medication utilization
5. Publishing material related to bone marrow transplant patient care

Although a clinical pharmacist's emphasis is on direct patient care, many of the pharmacists do perform clinical research, seek for grants or awards to fund their research projects, publish research results, participate in university-based teaching (didactic ± experiential), and assist in mentoring pharmacy residents specializing in hematology-oncology. A clinical pharmacist is expected to remain abreast of the bone marrow transplant literature, especially in the following areas: GVHD, veno-occlusive disease, infectious disease processes, and chemotherapy-radiation-related toxicities. In addition to the pharmacist's clinical knowledge, the bone marrow transplant team heavily relies on the pharmacist for their knowledge of the practical aspects of pharmacy (i.e., compatibility issues, ability to compound products, maximum/minimum concentrations of intravenous medications, understanding of the institution's medication order entry and medication delivery processes). The clinical bone marrow transplant pharmacist's main goals are to provide safe, therapeutic, and cost-effective care to each patient, and to maintain continuity of patient care upon initial hospital discharge.

HEALTH OUTCOME AND ECONOMIC BENEFITS

Currently, there is no published literature documenting health outcome or economic benefits provided by a pharmacist to a bone marrow transplant patient. There are several review articles analyzing the economics of bone marrow transplant, peripheral blood stem cell transplant, and outpatient-based transplant.[2,4–7] The articles refer to various detailed cost-effective and cost-minimization studies. Unfortunately, they do not breakdown the cost analysis studies to note the impact a pharmacist has on the total cost of a bone marrow transplant procedure. The input provided by a pharmacist to the bone marrow transplant team is substantial and necessary for a cancer center to remain competitive and fiscally responsible. There is a strong need for bone marrow transplant pharmacists to generate outcome data and collectively or individually publish the benefits of retaining a pharmacist on the bone marrow transplant team.

NECESSARY TOOLS/MATERIALS

Medline

Many of the complications encountered during a bone marrow transplant have few (if any) standardized treatment protocols developed. Therefore, pharmacists need easy accessibility to a medline service during and after patient rounds to provide valuable information to the bone marrow transplant team in a timely manner. Although physicians may also perform their own research on the topic of discussion, it is important for pharmacists to critique and review the literature separately. This will allow the pharmacist to

1. Evaluate various innovative treatment options.
2. Choose the best option that complies with the hospital policies and procedures for drug attainment, drug compounding, and drug administration.
3. Resolve drug availablity issues (i.e., orphan drug status, length of time to receive drug in hospital).
4. Present the options to the bone marrow transplant physician in a timely manner.

Hematopoiesis Chart

The bone marrow transplant pharmacist needs to have a sound understanding of the maturation of the hemato-

poietic stem cell to form the three lineages. It is important to understand the relevance of immunomodulators at each step of cell maturation. Because ex-vivo cytokines are very expensive and many of them carry high toxicity profiles, it is important for a pharmacist to know which stem cell maturation step(s) will be influenced by the cytokine(s).

Other

Currently, there are no published documents providing guidelines or consensus statements on how medications should be administered during and following a bone marrow transplant. There are numerous review articles available on bone marrow transplant preparative regimens, prevention and treatment of graft versus host disease, infectious disease topics related to bone marrow transplant, and pain management. The chemotherapy/radiotherapy used as the preparative regimen for a bone marrow transplant varies from center to center, depending on the hematologist's past experience with the various regimens, the patient's eligibility for drug study enrollment, the patient's past chemotherapy/radiotherapy history, and the patient's past medical history. The medications and medication doses used to prevent and treat GVHD and to treat other bone marrow transplant related complications is also dependent on the physician's preference, patient's eligibility for drug study enrollment, and patient's medical history.

PROFESSIONAL NETWORKING OPPORTUNITIES

There are numerous bone marrow transplant web sites available; however, they are oncology center initiated to increase patient referral base or patient initiated to provide personal advice to other bone marrow transplant patients. The networking opportunities available for bone marrow transplant pharmacists are primarily in the following medical conferences/meetings:

1. American Society of Hematology (ASH)
2. American Society of Clinical Oncology (ASCO)

Unfortunately, a pharmacy conference/meeting specializing or subspecializing in bone marrow transplant has not been identified. There is a rising interest in forming a bone marrow transplant pharmacy network group; perhaps modeled after the infectious disease pharmacy group (Society of Infectious Disease Pharmacy meet annually at their medical counterpart conference, Interscience Conference on Antimicrobial Agents and Chemotherapy).

ACCP Oncology prn mainly targets the hematology/oncology pharmacists and ACCP Transplant prn mainly targets the solid organ transplant pharmacists. Thus, bone marrow transplant pharmacist members of ACCP are not strongly committed to any particular ACCP prn group.

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Canadian Hospital Pharmacy Residency Board

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INTRODUCTION

The mission of the Canadian Hospital Pharmacy Residency Board is to establish and apply standards for accreditation of pharmacy practice residency programs and to promote excellence in hospital pharmacy residency programs and practice. The key objectives are as follows:

1. To gain external recognition and support for pharmacy residency programs.
2. To provide support to residency program participants in their role through education, skill development and practice tools.
3. To foster an environment that facilitates the growth and development of pharmacy residency programs.

ORGANIZATIONAL STRUCTURE AND GOVERNANCE

The Canadian Hospital Pharmacy Residency Board is organized under the auspices of Canadian Society of Hospital Pharmacists. The Board consists of seven members. The terms of reference of the Board specifies that at least one of the members be from a recognized Faculty of Pharmacy. The members of the Board are selected by the Board itself and approved by CSHP Council. A chairperson and vice-chair are elected from the seven member Board, with a term of two years for each of the executives. The members themselves serve for two years, a term which is renewable twice for a total of six years.

The Canadian Hospital Pharmacy Residency Board currently conducts its work under the auspices of the Canadian Society of Hospital Pharmacists. As such, the Board is provided administrative support from CSHP (at 1145 Hunt Club Road, Suite 350, Ottawa, Ontario, K1B 0Y3; telephone 613-736-9733).

HISTORY

The Canadian Hospital Pharmacy Residency Board was established in the early 1960s. The assessment of the residency training programs was done following review of written documentation submitted to the Board. The on-site accreditation process and survey did not begin until the early 1980s, however. At the present time, the Board accredits residency training programs in pharmacy practice. Currently, there are 30 programs in Canada with 104 positions for prospective residents. The Board is not currently involved in the accreditation of specialty programs or pharmacy technician training programs.

CURRENT INITIATIVES

The current major initiatives consist of:

1. Consistent with the four-year cycle for accreditation, to update the standards of the Board for 2002.
2. To promote the use of the CHPRB-sponsored preceptor guidelines.
3. To evaluate the need for innovative specialty practice standards and, in particular, those to be used in an ambulatory setting.
4. To conduct a needs assessment of residents who have been in the residency training program over the past three years to determine future directions of residency training in Canada.

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INTRODUCTION

The Canadian Pharmaceutical Association (CPhA) was founded in September 1907 as a national body for the profession of pharmacy in Canada. Its involvement in publishing began early in its history with the assumption of responsibility for the *Canadian Formulary* in 1929. The first edition of the *Compendium of Pharmaceuticals and Specialties (CPS)* was published in 1960 and continues today, along with a number of other well-respected health care publications including *Nonprescription Drug Reference for Health Professionals*, *Compendium of Nonprescription Products*, *Therapeutic Choices*, and *Herbs: Everyday Reference for Health Professionals*. The latter is published jointly with the Canadian Medical Association.

Throughout the late 1980s and early 1990s, CPhA scope of activities increased with staffing in the areas of professional development, research, and government and public affairs.

In 1995, CPhA began to change its structure from an organization representing provincial and national pharmacy organizations to an organization representing individual pharmacist members. This was followed in 1997 by a name change from Canadian Pharmaceutical Association to Canadian Pharmacists Association to better reflect the association's mandate.

ORGANIZATIONAL STRUCTURE AND GOVERNANCE

CPhA is an organization of approximately 9000 individual members. Members directly elect members of the Board of Directors to represent each province, pharmacy students, and the three practice specialties of hospital pharmacy, industrial pharmacy, and academia. The Board is responsible for managing the affairs of CPhA. The Board elects an Executive Committee comprised of president, president-elect, past president, and three vice presidents.

The executive director, who is a nonvoting member of the Executive Committee and Board, is responsible for the management and control of the affairs of the Association and general direction established by Board policy. A staff of approximately 50 reports to the executive director.

MISSION, VISION, AND KEY OBJECTIVES

The Canadian Pharmacists Association is the national voluntary organization of pharmacists committed to providing leadership for the profession of pharmacy.

The vision of CPhA is to establish the pharmacist as the health care professional whose practice, based on unique knowledge and skills, ensures optimal patient outcomes. CPhA will achieve its vision by serving its members through:

- Advocacy.
- Facilitation.
- Provision of knowledge.
- Participation in partnerships.
- Research and innovation.
- Education.
- Health promotion.

Strategic Plan

CPhA operates according to its strategic plan developed in 1999 and revised in 2001. The plan has five key result areas:

1. To represent the interests of a majority of pharmacists and to create cohesiveness within the profession on matters of practice, principle, and policy.

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DOI: 10.1081/E-ECP 120006202

2. To promote and facilitate the evolution of the pharmacy profession toward an expanded role in health care.
3. To foster public recognition of pharmacists as drug experts and as members of the health care team.
4. To secure appropriate reimbursement for pharmacists' professional services.
5. To effectively analyze and respond to the impact of advances in information technology on pharmacy practice.
6. To align resources to the key result areas.

CURRENT MAJOR INITIATIVES

Pharmacist Shortage

CPhA has taken the leadership position in addressing the shortage problem in the profession by initiating the development of a proposal for a labor market study to help pharmacy understand the current manpower shortage and its causes and develop tools to forecast future needs. Human Resources Development Canada (HRDC) commissioned an initial phase of the study, which is a literature search and key informant interviews to identify gaps in the available data. This study, "A Situational Analysis of Human Resource Issues in the Pharmacy Profession in Canada," is available on the CPhA web site.[1] The next step is development of a proposal for funding from HRDC for a comprehensive human resources study of the pharmacy profession in Canada to develop the foundation required to properly manage current and future pharmacy human resources.

Prescribing Authority

One of the key objectives of the strategic plan is a move to acquire prescribing authority for pharmacists. CPhA has developed a discussion paper to foster debate within the profession. The document has been distributed to solicit pharmacists' and other stakeholders' input.

Privacy Legislation

CPhA was pivotal in securing an amendment to the Personal Information Protection and Electronic Documents Act[2] which delayed its application to health care until January 2002. With the passage of the legislation, CPhA participated in a working group with six national health provider and consumer associations to examine the issue of privacy protection in Canada. The report of the Privacy Working Group focuses on the challenges of developing and implementing principles for privacy protection. It highlights the lack of consensus and the tension on this issue due to the disparate perspectives of the many stakeholders involved. CPhA continues to seek effective remedies to the shortcomings in the legislation, including presentations to federal officials.

Third-Party Payer Issues

It is recognized that pharmacists are spending an excessive amount of time dealing with claims reimbursement with third-party payers. This is having a significant impact on working conditions, and administrative burdens are proving an impediment to patient care. As a result, CPhA joined forced with the Canadian Association of Chain Drug Stores and the Ontario Pharmacists Association to sponsor a 2-day workshop to tackle these issues. Priorities for action include a standardized drug benefit card and PIN lists, patient awareness, benefit plan messages, and further collaboration with insurers and pharmacy software vendors.

Pharmacy Electronic Communications Standard (PECS)/National E-Claims Standard Initiative

Over the last decade, CPhA has been a leader in the development of pharmacy communication standards. CPhA's PECS Version 3.0 facilitates more than 98% of the electronic pharmacy claims in Canada. PECS Version 3.0 has undergone extensive revisions and now is being integrated into a National E-Claims Standard Initiative (NeCST)[3] designed to address the current need for a national electronic standard for health claims information.

E-Business and Enhanced Web Strategies

A major reengineering of the CPhA web site is underway. This revitalized site will offer Web services to benefit our members (e.g., electronic membership and order transactions, chat rooms, e-mentoring, e-broadcast).

In association with this initiative, an e-commerce advisory committee advises on e-commerce strategy and assists with visualizing and developing enhancements to CPhA's web site for member and nonmember pharmacists, other health care professionals, and consumers.

Advances in Publishing

CPhA, through its publishing program, provides pharmacists in every practice setting with accurate, current drug information and resource materials. However, on-line publishing of our drug information presents a new challenge. Work is underway on the *CPS* so that this publication can be easily accessible for print and electronic publishing. The *CPS* and our other publications are being repurposed for use on new e-media platforms.

MEETINGS

CPhA's annual meetings generally are held in May of each year in major locations in Canada.

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Cardiac Arrest/Emergency Pharmacy Services

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INTRODUCTION

Drug therapy plays a critical role in emergency medical care and, as a result, places the pharmacist in a position to have a significant impact on potentially life-saving therapeutic maneuvers. Pharmacists who practice in emergency medical care settings are often called upon to provide drug-related services and information without the luxury of time to retrieve information from external sources. This article reviews the role of pharmacy services in both the cardiac arrest setting and in the provision of other emergency medical services in which pharmacists play a central role.

CARDIAC ARREST

The spectrum of care required for patients in cardiac arrest ranges from providing basic life support (Cardiopulmonary resuscitation, or CPR) within or outside of an organized health care setting, to evaluating and treating complex cardiac arrhythmias in patients with multiple comorbidities receiving advanced cardiac life support. Pharmacists have been involved in the development of drug-related health services designed to support the care of such patients since the late 1960s.[1] As scientific and clinical outcome data has dramatically expanded since the 1960s and the efficacy of drug use in the cardiac arrest setting has been more critically evaluated, potential roles for the pharmacist have become more obvious. In addition, as hospital accrediting agencies begin to address quality improvement issues in the cardiac arrest setting, the evaluation and documentation of rational drug use will become a factor in setting standards of care.

CURRENT ROLES FOR PHARMACIST

The majority of information related to the activities of pharmacists participating in cardiac arrest teams in hospitals has been collected through questionnaires or surveys. Activities most frequently reported by pharmacists through such surveys are drug preparation, dosage and infusion rate calculation, drug use documentation, and the provision of drug information; very few pharmacists administer artificial respiration or chest compression.[2] Less frequently reported activities include setting up or operating infusion devices and administering medications.

According to data from the National Clinical Pharmacy Services study from 1992 to 1998, approximately 30% of 950–1600 hospitals surveyed had a pharmacist as an "active" member of the team attending most cardiac arrests when the CPR team pharmacist was in the hospital.[3–5] Despite the significant percentage of hospitals in which pharmacists are members of the cardiac arrest team, only 0.2%–0.3% of inpatients who experienced a cardiac arrest received resuscitation by a team that included a pharmacist. This disparity may be due to the fact that a CPR team pharmacist is not providing 24-hour, 7-day-per-week coverage, or that the CPR team pharmacist was assigned to provide service only in a specific area of the hospital. The national study also revealed that, of the hospitals with a pharmacist on the CPR team, approximately 65% routinely document pharmacists' involvement in patients' medical records. The average time commitment for pharmacists per arrest was 35 minutes. In the 1992 survey, this amount of time per encounter was more than the average amount of time for any other clinical service examined in the survey.

There is limited documentation of the value of pharmacists on cardiac arrest teams. What little data there are tend to be anecdotal in nature. As far back as 1972, Elenbaas responded to a review of the value of organized cardiac arrest teams in hospitals by noting the obvious absence of the inclusion of a pharmacist as a member of the team.[6] Given the extremely small number of actual patient arrests in which pharmacists participate, it would be difficult to accurately measure the actual or perceived value of pharmacist participation. Based on the small

number of reports in the literature, the provision of drug information seems to evoke the most comments regarding the value of pharmacist participation. Because the role of physicians and nurses in the cardiac arrest setting has been so well established compared with the role that pharmacists currently fill and because there are currently no standards established for pharmacists' activities in this setting, the value of the pharmacist remains to be measured.

A well-delineated support role for the pharmacist in the provision of care in the cardiac arrest setting clearly exists. The pharmacy department in concert with the hospital Pharmacy and Therapeutics Committee has a defined and traditional role in maintenance of the emergency drug boxes ("crash carts") located in various parts of the hospital. Assuring that emergency drug boxes are appropriately stocked and meet the needs of the institution, as mandated by the Pharmacy and Therapeutics Committee or other medical oversight committee has been a well-established support role for pharmacy services for many years. As Advanced Cardiac Life Support (ACLS) guidelines periodically change and new information related to pharmacotherapeutic efficacy of new and older drugs used in the cardiac arrest setting becomes available, the role of the pharmacist in updating the contents of the emergency drug box is critical to maintaining the standard of care for drug delivery in the cardiac arrest setting.

In addition to their role in drug delivery, the pharmacist's role of educator in the appropriate use of drug therapy in the cardiac arrest patient has been established in a number of hospitals across the United States. This educational role is important for several reasons. First, because cardiac arrests occur infrequently, especially in noncritical care areas of the hospital, the medical and nursing staff may not be as familiar with either the pharmacotherapeutic guidelines established by ACLS recommendations or the appropriate administration techniques for ACLS drug as are providers in critical care areas. Second, even in critical care units, implementing change in longstanding ACLS drug administration behaviors (modifying the role of lidocaine or sodium bicarbonate use) is often resisted by clinicians, but it is often essential to the provision of quality care. Third, despite the fact that changes in the official ACLS drug therapy guidelines occur only every 5–6 years, the results of landmark clinical trials often dictate changes in therapy prior to their incorporation into published guidelines. Pharmacists in many hospitals have taken active roles in teaching physicians, nurses, and affiliated health professionals the pharmacology and therapeutics of drugs used in the ACLS guidelines.

EDUCATION AND TRAINING

The education and training needs of pharmacists who serve as members of the cardiac arrest team vary from those that may be provided in some schools of pharmacy. All health care providers, as well as most laypersons, should be certified in Basic Life Support (BLS). In a study using questionnaires to determine attitudes toward and use of cardiopulmonary resuscitation training received in a school of pharmacy, 72% of responding graduates surveyed believed that a CPR-BLS program should be mandatory for graduation. Seventy percent of respondents believed that their training would be of value in their current practice, and 93% believed that such training would be of value in the future, despite the fact that only 5% had actually performed CPR since graduation.[7] Clearly, pharmacist members of a cardiac arrest team should possess BLS skills. In addition, since automated external defibrillators have been demonstrated to improve the chances of out-of-hospital cardiac arrest, training in the use of these devices is becoming an inherent part of BLS training both within hospitals and in routine BLS out-of-hospital training.[8,9] In addition to the prerequisite BLS training, cardiac arrest team pharmacist should be certified in ACLS, the procedure in which most drug therapy is instituted in the cardiac arrest setting. Even if the role of the pharmacist as a team member is limited to drug preparation or documentation, it is essential that the pharmacist understand the rationale, efficacy, and potential side effects associated with the use of the drug therapy being implemented. As in all other clinical pharmacy practices, the cardiac arrest team pharmacist should be trained to monitor for both the efficacy and side effects of the agents being used.

The need for the cardiac arrest team pharmacist to be certified in ACLS is further reinforced by the standards developed by the Joint Commission on Accreditation of Health Care Organizations (JCAHO) related to in hospital cardiac arrests.[10] Of the several standards adopted by the commission, several relate to activities in which the pharmacist may have a significant role. These standards include the development of "appropriate policies, procedures, processes or protocols governing the provision of resuscitative services, appropriate data collection related to the process and outcomes of resuscitation," and "ongoing review of outcomes, in the aggregate, to identify opportunities for improvement of resuscitative efforts." According to the Bethesda Conference on Cardiopulmonary Resuscitation, the majority of U.S. hospitals are deficient in one or more of the areas in which these new JCAHO standards have been established and will require significant restructuring of their resuscitative efforts.[11] It

is clear that a real opportunity exists for the pharmacist to influence those efforts related both to the improvement of drug use policies, and to the creation of quality improvement and feedback processes that can identify and improve hospital resuscitative efforts. Despite the assumption that hospitals function as self-contained emergency medical services (EMS) systems with respect to their management of cardiac arrest based on their abundance of health care providers in a defined environment, the Bethesda Conference report stated, "the process of improving resuscitation in the hospital remains in its infancy." Such an assessment presents a unique opportunity for pharmacy to establish itself as a necessary component of a process that has become a part of required standards of hospital care.

EMERGENCY MEDICAL SERVICES

Pharmacists have provided clinical services in emergency medicine-related areas of hospitals since the late 1960s.[12] Documentation of clinical pharmacy services relate primarily to the provision of services in hospital emergency departments. Services vary from those provided fundamentally as support to the emergency department staff, to those provided directly to patients in specific disease management programs.[13,14] In a report of follow-up observations on 3787 pharmacotherapy consultations provided in an emergency department in a university hospital, 33% involved patients with pulmonary disease, 22% involved toxicology cases, 17% involved patients with seizure disorders, 11% involved cardiac cases, 7% were pharmacokinetic consultations, and 8% were miscellaneous consultations.[15] Consultations averaged 100 minutes each, and serum drug concentration determinations primarily involved theophylline, phenytoin, phenobarbital, and acetaminophen. An early questionnaire of the value of clinical pharmacy services in a medical center emergency department setting reported that clinical pharmacy services added benefit to both patient care and to educational programs in the department.[16] Eighty-seven percent of the responding physicians reported the pharmacist capable of providing primary care to specific patients once a physician-based diagnosis was established. Ninety-five percent of responders believed that clinical pharmacy services could be transferred to other emergency departments, and 83% were willing to have their patients charged for clinical services provided by the pharmacist. A more recent evaluation of the utility of clinical pharmacy services in the emergency department revealed that provision of a 24-hour consultative service by clinical pharmacy residents provided 3.1 consultations per 14-hour call period. Ninety percent of these consultations were completely followed by the recipient physicians.[17] Clinical pharmacy services involving a pediatric subspecialty emergency practice has been described in which a pharmacist is a member of a pediatric trauma team consisting of a pediatric surgeon, neurosurgeon, emergency physician, intensivist, radiology technician, and an intensive care unit nurse.[18]

Opportunities for clinical pharmacy service in the emergency department may expand because of the considerable effects resulting from changes in health insurance provision in the United States focused on reducing the number of hospital admissions. Perhaps the most prominent example of clinical pharmacy services in the emergency department setting is related to the management of asthma. The number of asthma-related deaths in the United States is increasing, especially among children. One potential cause for this increase may be inappropriate early discharge of patients from emergency departments. Pharmacists have participated in interdisciplinary efforts to maximize the urgent care of asthma patients in a number of environments, including the emergency department. In a university-affiliated urban teaching hospital, the number of emergency department visits for a group of asthma patients was significantly reduced after institution of a comprehensive program of asthma management.[19]

Finally, a number of nontraditional practice sites have been described in which pharmacist have participated in natural disaster relief or as part of a humanitarian effort relief team. These nontraditional practices have included a pharmacy consultative service for wilderness emergency drug planning, pharmacy involvement in emergency preparedness/response, the provision of pharmaceutical services at a medical site after Hurricane Andrew in Florida, and the experience of several pharmacists providing service in Bosnia-Herzegovina.[20–23]

In conclusion, there are numerous current emergency practice opportunities in which pharmacists play a significant role. Although the number of pharmacists who provide clinical services in these settings is relatively small, the critical nature of drug use in such setting suggests that the potential for direct pharmacotherapeutic intervention is large. Well-designed outcome evaluation of such service is sorely needed.

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PROFESSIONAL DEVELOPMENT

Cardiology, Clinical Pharmacy Practice in

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INTRODUCTION

The roots of the clinical pharmacy movement are firmly imbedded in cardiology as a discipline. From the beginning, clinical pharmacists emphasized and specialized in cardiology pharmacotherapy. This is not surprising given several factors: the overall prevalence of heart disease in the United States, the prominence of cardiology as a discipline within medicine, and the fact that the cornerstone of the treatment of heart disease is drug therapy. Indeed, cardiac drugs tend to be complex, replete with drug interactions and narrow therapeutic margins and the need for close therapeutic monitoring, so that contributions by pharmacists to the care of patients with heart disease seem to be natural. The exact history of cardiology clinical pharmacy remains ill-defined, but programs with intensive training in cardiology therapeutics in the mid-1970s were the University of Missouri at Kansas City and the University of Texas at San Antonio. Of note, E. Grey Dimond, MD, a founding member of the American College of Cardiology, also initiated the clinical pharmacy program at Truman Medical Center and the University of Missouri at Kansas City School of Medicine. Strong training programs (specialized residencies and/or fellowships) subsequently developed in the early 1980s at the University of Illinois at Chicago, the University of Tennessee, and the University of Connecticut. Graduates of these programs in turn seeded many academic health centers and colleges of pharmacy throughout the United States. Today, many cardiology clinical pharmacists can trace their ancestry to a few of these programs.

Cardiology within pharmacy is not a stand-alone specialty. Rather, it is viewed as a subspecialty of sorts within the umbrella specialty of clinical pharmacy (or pharmacotherapy). In 2000, the Board of Pharmaceutical Specialties designated a process whereby a board-certified pharmacotherapy specialist may apply for "added qualifications" in cardiology pharmacotherapy practice. The applicant must submit a portfolio that documents training, clinical practice, educational efforts, and scholarly activities (among other details) specifically within cardiology. For this process to be approved by the Board of Pharmaceutical Specialties, a petition[1] was submitted (and subsequently approved) outlining the rationale, need, and demographics of the subspecialty, along with appropriate supporting information. This petition was prepared by the Cardiology Practice and Research Network (PRN) of the American College of Clinical Pharmacy (ACCP); within it are a number of facts that help to define the discipline:

1. In 2000, there were about 30 fellowships or specialized residencies in cardiology clinical pharmacy in the United States.
2. About 13% of all board-certified pharmacotherapy specialists list cardiology as the main emphasis of their practice.
3. The Cardiology PRN of ACCP has about 400 members, one of the largest subspecialties within this organization.
4. About 1100 members list cardiology practice as their primary emphasis on membership surveys of ACCP (750) and the American Society of Health-System Pharmacists (350).
5. From a survey of board-certified pharmacotherapy specialists performed for the BPS petition for added qualifications in cardiology, the following was listed as the respondent's practice area: cardiac intensive care (40%), stepdown/telemetry unit (26%), anticoagulation clinic (18%), lipid clinic (18%), managed care (7%), and other primary care clinic (35%). Of those responding, 24% had fellowship training, 13% had a specialized residency, and 19% had completed a certificate program.

Although the discipline of clinical pharmacy (or pharmacotherapy) within organized medicine is relatively young, specialized practice in cardiology is one of its more mature areas. It is not a stand-alone specialty because one uses the principles and skills of the specialty pharmacotherapy (as it is presently defined) simply applied to an area of knowledge (i.e., cardiology therapeutics). There are numerous citations documenting the role of and out-

comes (clinical and economic) associated with clinical pharmacy practice in cardiology settings. These are summarized in the following sections. One will find that the role of pharmacists providing services to targeted areas (e.g., lipid clinic, anticoagulation clinic, smoking cessation) in ambulatory settings is much more frequently studied than the role of the pharmacist practicing in an acute care, inpatient setting where the clinical functions are more broad.

ACUTE CARE CARDIOLOGY PHARMACY PRACTICE

Twenty-five percent of Americans discharged from hospitals have a primary diagnosis of cardiovascular (CV) disease.[2] The pharmacist practicing in an acute care setting helps manage common cardiac disease states, including the spectrum of acute coronary syndromes (ACS), hypertensive emergencies and urgencies, acute heart failure, and cardiac arrhythmias, along with comorbid conditions. Decisions regarding optimal medication use in such patients are complex. Beginning with the initial choice of medication to treat a patient acutely, and through selection of appropriate chronic therapy and proper titration and monitoring, the acute care pharmacist is a vital component in the system of health care provision.

As part of the health care team, the acute care pharmacist works with attending physicians, physicians-in-training nurses, and other health care professionals to provide patient care. Daily activities are often centered around medical rounds, where the team reviews each inpatient's progress over the last day. Here, drug therapy decisions are made within the constructs of a team approach. Information shared during rounds includes results of lab tests, physical exams, diagnostic and therapeutic procedures, and symptomatology. Using this information, a pharmacist assists in evaluating patient response to medications, including assessing dose, route, and monitoring of each drug that the patient is receiving. When prospectively adding a medication to the patient's orders, the pharmacist recommends appropriate agents based on the clinical indication, dosing (initial and "target"), and both efficacy and safety monitoring parameters. In providing such information, the pharmacist becomes a primary source of education regarding optimal medication use for all the members of the health care team. Other tasks the pharmacists might perform include obtaining medication histories from patients admitted to the hospital, patient medication education, and discharge counseling for patients discharged from the hospital on a new medication regimen.

An important role for the pharmacist is prevention of adverse drug events (ADEs), which significantly contribute to health care costs in numerous ways, including increases in lengths of stay, medication, and laboratory costs. Medications used in acute cardiac settings tend to have narrow therapeutic windows with substantial risk for toxicity and require close monitoring to optimize therapy (e.g., antithrombotics, antiarrythmic agents, intravenous inotropes, nitroprusside). Drug–drug interactions (also quite common with cardiac regimens), inappropriate dosing, and inappropriate drug selection are just a few examples of common ADEs where pharmacy intervention could have a tremendous impact. An important study by Leape et al. noted that the inclusion of a clinical pharmacist on a multidisciplinary team rounding in an intensive care setting reduced ADEs by 66%, through order clarification, provision of drug information, and recommendations of alternative therapy.[3]

A unique responsibility of a cardiology specialty pharmacist is the management of drug therapy of ACS, particularly those involving unstable angina and cardiac catheterization-associated procedures. Low-molecular-weight heparins and glycoprotein IIb/IIIa receptor antagonists are newer treatment modalities, but are considerably more expensive than older medications used for ACS. Newer thrombolytics used in treatment of acute myocardial infarction are easier to administer (in one or two bolus doses versus an infusion), yet are more expensive. Therefore, there is a need to develop cost-effective treatment strategies that encompass these newer agents. These strategies must take into account critical literature evaluation (i.e., are there superior outcomes between studies involving the newer agents?) and knowledge of patient characteristics (i.e., determining if the patient has an appropriate indication for use of a new therapy, identifying appropriate dosage adjustments in the face of renal insufficiency) when formulating guidelines. The cardiology specialty pharmacist may play a significant role in developing such guidelines for the institution, selecting individual patients for therapy, and selecting which therapy to use in particular ACS scenarios.

It is common to find a pharmacist as a member of the hospital cardiopulmonary resuscitation (CPR) team, which responds to emergent situations that may require immediate patient care. These scenarios usually involve a patient who suddenly becomes nonresponsive, ceases spontaneous respirations, and/or experiences a life-threatening cardiac arrhythmia. The CPR team responds to such patients by implementing advanced cardiac life support (ACLS), which involves quick provision of an airway and electrical (defibrillation) and/or pharmacologic interventions to sustain cardiac function. The pharmacist's role on such a team involves the preparation of intravenous infusions needed in an emergent situation, dose calculations, and consultation regarding appropriate medication use.

Participation by a pharmacist on a CPR team was associated with significantly lower hospital mortality rates in a study by Bond and colleagues.[4]

OUTPATIENT CARDIOLOGY SPECIALTY PRACTICE

In the outpatient setting, cardiology pharmacists frequently provide services in a wide array of clinic types, including general cardiology clinics, primary care/family medicine clinics, and disease management clinics. The impact of a cardiology pharmacist in these settings has been clearly documented in the medical literature. Generally, a pharmacist's knowledge of CV disease state pathophysiology, presentation, and course, coupled with extensive knowledge of drug therapy options and monitoring are invaluable insofar as enhancing comprehensive patient care. The following is a description of types of specialty care that a pharmacist might provide.

Hypertension

Some of the earliest published reports on the effects of provision of pharmaceutical care provided insight into the effects of a pharmacy program in the care of patients with hypertension. In an early study by McKenney and colleagues, the effects of clinical pharmacy services in a group of hypertensive patients were described.[5] Those patients who received pharmacy services in addition to standard care by their physician demonstrated an improvement in self-knowledge of their disease state, improved compliance, and better blood pressure control. Subsequent investigations have demonstrated a positive effect of pharmacy services on cost and quality of life in patients treated for hypertension.[6,7]

In this largely asymptomatic yet morbid disease, early identification and treatment are the mainstays for excellent patient care. The proper management of a hypertensive patient begins with selecting an appropriate goal blood pressure, recognizing other risk factors for CV disease, noting concomitant disease states, and selecting appropriate drug therapy for the patient. When selecting such therapy it is important to bear in mind compelling indications (as defined in the Sixth Report for the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure,[8] which is the consensus guidelines for the treatment of hypertension), contraindications or cautions for using certain classes of medications, patient compliance, and cost. As a drug expert, pharmacists are in an ideal position to enhance care through the selection and monitoring of antihypertensive therapy. In addition, a pharmacist can provide patient education regarding the importance of compliance, adverse effects, and goals of therapy, thereby increasing the likelihood of successful control of patients' disease states.

Dyslipidemia

Dyslipidemia is a major risk factor for several CV diseases, including myocardial infarction, stable and unstable angina, and stroke. Control of cholesterol levels is important in reducing risk of both primary and secondary CV events. High cholesterol levels may be treated by altering diet and through pharmacologic intervention. Outpatient dyslipidemia clinic models that include intervention by a clinical pharmacist have demonstrated larger reductions in total cholesterol level, greater likelihood for achieving National Cholesterol Education Program[9] low-density lipoprotein goals, and better medication compliance.[10–12]

The decision to start cholesterol-lowering therapy can be complex and should involve patient assessment for concurrent risk factors (hypertension, diabetes), concomitant medications, diet, and social history (alcohol and cigarette use). The pharmacist can recommend and counsel regarding nonpharmacologic interventions such as reduction in body weight, dietary alterations, exercise, and cessation of cigarette smoking. It is also important to ensure that comorbid disease states (diabetes, hypertension) are adequately treated and monitored. If the decision is made to start a cholesterol-lowering agent, the pharmacist must ensure that the appropriate agent is selected because each agent may have a distinct effect on each lipoprotein component (low density, high density, triglycerides) of the lipid profile. In addition, prospective identification and avoidance of drug interactions when using cholesterol-lowering therapy is a salient pharmacist responsibility. For example, HMG CoA reductase inhibitors (some of the most commonly used cholesterol-reducing medications) are agents that inhibit a major metabolizing enzyme in the liver and may be a source of clinically significant drug interactions, including the occurrence of myositis, rhabdomyolysis, or renal dysfunction. Recommendation of pertinent monitoring parameters and patient education are additional contributions that the clinical pharmacist can make when caring for the dyslipidemic patient.

Chronic Heart Failure

There are many drug therapy-specific tasks unique to the care of a heart failure patient. A thorough review of the medication profile of a patient with heart failure should include ensuring the presence of appropriate medications

(ACE inhibitors, beta blockers) for reducing mortality related to this devastating disease. Cardiology pharmacists can optimize therapy by identifying and achieving goal doses (those doses achieved in clinical trials of heart failure) for each of these medications, depending on patient tolerability. Of equal importance is a check for medications that may potentially exacerbate heart failure or cause toxicity when given in conjunction with existing heart failure therapy.

Numerous trials document that many patients do not always receive drugs shown to decrease mortality in heart failure (e.g., ACE inhibitors) or do not receive the proper ("goal") doses (see studies by Smith et al.[13] and Roe et al.[14]). Clearly, cardiology pharmacists have an impact on outcomes related to the use of these medications by ensuring appropriate dosing parameters. Such responsibilities may include recognition of an appropriate patient for ACE inhibitor or beta blocker therapy, proper uptitration of each agent, management of adverse effects related to therapy, and identification of true ACE or beta blocker intolerance.

Gattis and colleagues demonstrated the valuable contributions made by a clinical pharmacist in the care of patients with heart failure.[15] In this study, pharmacists made therapy recommendations (including ensuring attainment of goal doses of heart failure medications, avoidance of contraindicated medications), provided patient education regarding medical therapy, and monitored for adverse drug events. By providing intensive pharmacy services, the investigators were able to demonstrate a reduction in all cause mortality, attainment of higher ACE inhibitor dose, and greater use of alternate vasodilators in those patients intolerant to ACE inhibitors.

Antithrombosis Specialty Pharmacy Practice

Antithrombotic therapy is used in myriad CV diseases such as atrial fibrillation, heart failure, valve replacement, peripheral vascular disease, and stroke. This presents an ideal setting for a pharmacist-managed antithrombosis clinic. Today, many institutions have antithrombosis clinics managed by clinical pharmacists; this trend continues to grow.

In such a clinic, a pharmacist is responsible for the careful, periodic monitoring of prothrombin time (or international normalized ratio [INR]) to ensure safe and efficacious therapy with oral anticoagulants such as warfarin. In addition, the pharmacist emphasizes patient eduation regarding adverse effects, vitamin K-containing diets, and potentially interacting drugs. The patient's drug profile should be reviewed at every visit (for prescription and over-the-counter medication) to prevent possible drug interactions. Guidance is also provided to other health care providers regarding appropriate dosage changes and monitoring parameters.

Numerous studies have described clinic models and outcomes related to pharmacist-managed antithrombosis clinics. Chiquette and colleagues demonstrated fewer incidences of supratherapeutic levels of anticoagulation, more consistent maintenance of appropriate levels of anticoagulation, lower rates of bleeding complications, and thromboembolic events in a group of patients managed in a pharmacist-managed clinic versus those managed by usual medical care.[16] These investigators also showed lower rates of hospital admissions and emergency department visits due to warfarin therapy in those patients managed in the clinic. Similar superior care was noted in investigations published by Wilt and colleagues who also demonstrated a 20-fold increase in events (warfarin-related hospitalization, hemorrhagic or thrombotic events) in patients cared for in a family practice setting versus a pharmacist-managed clinic.[17] Both of these investigations translated these reduced event rates into significant cost savings; Chiquette estimated annual health care costs would be reduced by more than $130,000 per 100 patients, whereas Wilt attributed a $4000 cost avoidance per person-year of follow-up for those patients managed by a pharmacist.

Other antithrombotic therapies that are managed by pharmacists include the oral antiplatelet agents ticlopidine and clopidigrel, which are used for therapy for ischemic stroke and postcoronary stent placement. As with warfarin, therapy with these medications requires specific monitoring (especially of blood counts) and patient education. Another potential role for an antithrombosis pharmacist is management of patients on low-molecular-weight heparin (e.g., enoxaparin). As the use of these agents has expanded to the outpatient setting, particularly as a transition to oral anticoagulant therapy, the need exists for a skilled clinical pharmacist to maintain effective and safe treatment with the agents. Dedden and colleauges published a report on a pharmacist-managed program to treat proximal deep vein thrombosis.[18] Patients were treated at home with enoxaparin and warfarin until the patient's INR was therapeutic; all therapeutic monitoring was done by pharmacists. In treating 55 patients, a total of 294 patient hospital days were avoided, which could be translated into significant cost savings.

Other Clinic Types

Given the many clinical conditions related to or caused by cardiac conditions combined with the numerous medications used to treat such conditions, it is clear that the po-

tential for pharmacist collaboration in the care of cardiology patients is endless. Other clinic types described in the literature include pharmacist-managed smoking cessation clinics[19–22] amiodarone monitoring clinics,[23] and cardiac medication assistance programs[24] (for those who cannot afford these medications).

NETWORKING OPPORTUNITIES

Many cardiology clinical pharmacists collaborate closely with their physician colleagues in patient care and scholarly matters. Presentations of the results of major clinical trials that will influence the daily practice of clinicians compel many to attend major medical cardiology meetings, such as the annual meetings of the American Heart Association or the American College of Cardiology, and follow cardiology specialty journals such as *Circulation*, *Journal of the American College of Cardiology*, *American Journal of Cardiology*, and *American Heart Journal*, among others. However, the primary forum for networking of cardiology clinical pharmacists is through the Cardiology PRN of the ACCP. This group meets at the annual meeting of ACCP, and maintains a useful and ac-

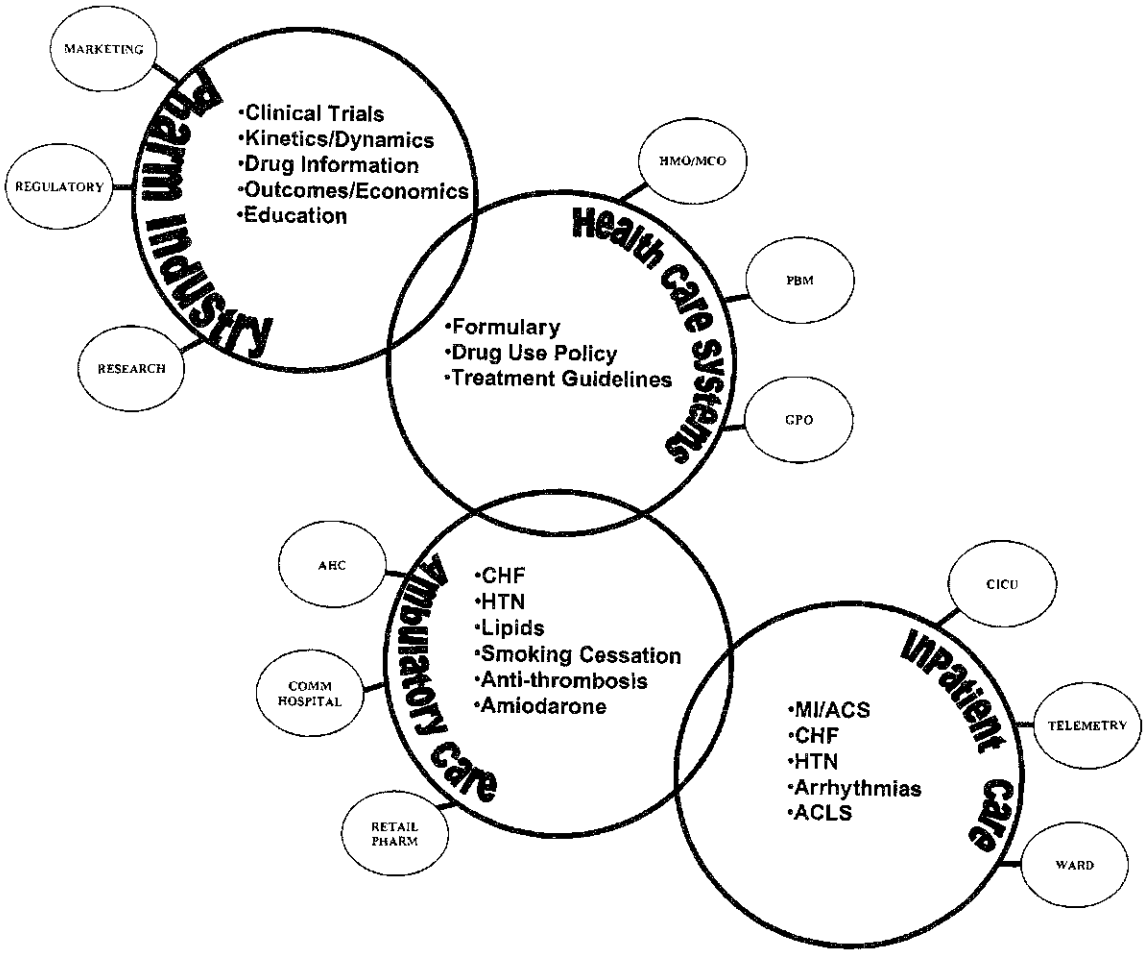

Fig. 1 Representation of the spectrum of cardiology clinical pharmacy practice. Clinical pharmacists may use their skills and knowledge of the drug treatment of heart disease in a variety of sites (large circles) such as the pharmaceutical industry, health care systems, ambulatory care, or inpatient settings. Specific duties are listed inside the large circles; they may include the direct care of patients (inpatient and ambulatory practice) or more global responsibilities for drug use (health care systems and industry), and overlap to some degree. The smaller circles represent more specific practice sites for each of the respective areas. Abbreviations: HMO, health maintenance organization; MCO, managed care organization; GPO, group purchasing organization; AHC, academic health center; Comm, community; Pharm, pharmacy or pharmaceutical; CICU, cardiac intensive care unit; CHF, congestive heart failure; HTN, hypertension; MI/ACS, myocardial infarction/acute coronary syndromes; ACLS, advanced cardiac life support (i.e., cardiac arrest team).

tive listserv for discussion on therapeutic problems or issues in clinical pharmacy practice.

PROFESSIONAL OPPORTUNITIES

There are numerous opportunities for cardiology clinical pharmacists, and these opportunities appear to be expanding (Fig. 1). Traditionally, positions with a predominantly clinical practice focus were concentrated in academic medical centers, often those affiliated with a college of pharmacy. Here, clinicians would practice—either collaboratively (particularly in an inpatient setting) within a health care team on cardiology units or independently (particularly in an ambulatory setting)—to manage specialized clinics. Typically, this type of clinician has teaching duties and some scholarly duties, in addition to clinical responsibilities. These roles have expanded to some degree into community hospitals as the clinical pharmacy movement grew. Further, because of the shift to managed health care, some clinical pharmacists with skills in cardiology may take responsibility for the drug use in a health care system, managing formularies and developing systemwide treatment guidelines and drug-use policies. Here, cardiology clinical pharmacists use their skills and knowledge to effect drug use in *populations* of patients with heart disease rather than select individuals.

For positions with a research focus, cardiology clinical pharmacists (usually with research fellowship training) have opportunities as clinical science faculty at research-intensive universities (colleges of pharmacy and/or medicine) or in the pharmaceutical industry. In industry positions, cardiology clinical pharmacists may coordinate clinical trials (phase III and IV) or work in drug disposition and pharmacokinetics. These types of positions remain, but other opportunities have arisen more recently. For instance, opportunities in the pharmaceutical industry for "medical service managers" or medical liaisons have expanded. These individuals may coordinate some smaller, single-site research projects (e.g., phase IV), have educational responsibilities to physicians and pharmacists, and also have a minor sales component within their duties (or combinations of all of the above, depending on the specific company). The industry is seeking sophisticated health care professionals who can represent the company and their products on a sophisticated level; thus, the cardiology clinical pharmacist seems well suited for such positions.

Last, there has been an expansion of cardiology clinical pharmacy into ambulatory settings. Due in part to prospective and fixed payment systems and the growing sophistication of pharmacists in therapeutic decision making, cardiology clinical pharmacists can find opportunities in managing disease state-specific clinics such as the ones previously reviewed (e.g., antithrombosis, smoking cessation, heart failure lipid management). Indeed, it has become very common (if not standard of care) for health care systems to employ cardiology pharmacists to manage outpatient antithrombosis treatment (e.g., warfarin, low-molecular-weight heparin). Usually, this is accomplished by establishing approved treatment protocols and collaborative drug therapy agreements with physician colleagues. It should be noted that a growing number of states have passed legislation to allow collaborative drug management by pharmacists (i.e., prescriptive authority under approved protocols and/or agreements with physicians).

The next frontier is cardiology clinical practice in community pharmacy settings. It is hoped that the progress made in ambulatory practice can be extrapolated into these environments. This possibility has been fueled by demonstration projects where pharmacists receive financial payments for cognitive services. Noteworthy is that some of these initial disease state management efforts (e.g., management of hypertension, lipid disorders, and thrombosis) require practice skills and specialized knowledge in cardiovascular pharmacotherapy.

APPENDIX

Clinical Pharmacy Guidelines, Consensus Statements, and Resources for Cardiology Specialty Pharmacy Practice

General

American Heart Association web site: www.americanheart.org.

Acute coronary syndromes

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Smith EE III; Steward DE; Theroux P. ACC/AHA 2002 Guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). 2002. Available at: http://www.acc.org/clinical/guidelines/unstable/unstable.pdf.

Stable angina

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Hypertension

- The Sixth Report for the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med **1997**, *157*, 2413–2446.

Dyslipidemia

- Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), JAMA **2001**, *285*, 2486–2497.

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Atrial fibrillation

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Heart failure

- Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and mangement of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for Evaluation and Management of Heart Failure. 2001. American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/failure/hf_index.htm.

Advanced cardiac life support

- The American Heart Association in Collaboration with the International Liaison Committee on Resuscitation (ILCOR). Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation **2000**, *102* (suppl I), I-1–I-384.

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Clinical Evaluation of Drugs

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INTRODUCTION

The process of developing a new drug, from the identification of a potential drug candidate to postmarketing surveillance, is extremely complex. The drug development process requires input from various members of a multidisciplinary team and the conduct of numerous studies. The time from drug discovery to marketing takes an average of 13 years. Once a chemical is identified as a new drug candidate, extensive preclinical analyses must be completed before the drug can be tested in humans. The pharmacology, toxicology, and preclinical pharmacokinetics must be characterized. The formulations of the drug product that were used in the preclinical studies may be different from the formulation of the final drug product, which may require that additional formulation work and pharmacokinetic analyses be performed. If the characteristics of the new drug candidate are acceptable for all of the preclinical assessments, it may then be tested in humans. The new drug candidate, at this point, enters the clinical research stage of drug development.

Clinical research represents a vital stage in the development process a stage that is no less daunting than the preclinical research stage. The data obtained from the first-time-in-human, Phase 1 pharmacokinetic studies, and initial safety evaluations in healthy volunteers can make or break the entire developmental program for a drug candidate. The sponsoring company, of course, hopes that the data collected in these initial studies will show minimal safety concerns over an adequate dose range. The pharmacokinetic data can then be used to help design future studies in which efficacy and long-term safety are assessed and additional pharmacokinetic and pharmacodynamic data are collected.

Although the basic designs of the initial single and multiple dose-escalating studies are generally straightforward (but the starting dose is often intensely debated), it is imperative that these studies and future studies be designed to address specific questions. The questions vary depending on numerous specific considerations, including the targeted disease characteristics (e.g., acute or chronic); desired safety, efficacy, and pharmacokinetic evaluations; and assessment of clinical pharmacology (e.g., dosage formulations or dose frequency). Basic study procedures must also be considered. Thus, the design, conduct, data reporting and analysis, and production of the final study reports can be completed only through the coordinated efforts of a multidisciplinary drug development team.

For every clinical study, input is required from multiple personnel with various areas of expertise. Members of a drug development team include physicians, scientists, pharmacists, project managers, statisticians, computer programers, study monitors, regulatory experts, and for some studies, a representative of the formulations group. While some team members may be able to perform multiple tasks, no one team member has the expertise or the time to do everything required to conduct a clinical study. In addition, some members may have overlapping abilities, but other members with particular expertise may be called upon. For example, pharmacokineticists are the experts in pharmacokinetics, but they may also be knowledgeable in pharmaceutics, biostatistics, and clinical care. However, scientists (PhDs) are trained primarily in basic research, while physicians (MDs) are trained in clinical medicine. Since a single drug development program is derived from both of these distinct disciplines, considerable overlap, cooperation, and coordination are necessary to take a drug successfully and efficiently from discovery to market.

Clinical drug development is generally divided into four phases: Phase 1 through Phase 4. For each study conducted within a particular phase, specific information is collected according to the requirements for individual drugs being developed. Collection of safety, efficacy, and pharmacokinetic data is the focus of most clinical trials. Although these topics appear to be distinct disciplines,

they are intertwined and represent different ways of evaluating the intrinsic properties of a drug. While the safety, efficacy, and pharmacokinetics of a drug may be assessed in most studies, the team must establish the type and extent of information to be collected, which will vary based upon the specific objectives and designs of the studies.

A critical function of the drug development team is the development of the study protocol. The study protocol must clearly describe the study design and methodology that will be used to achieve the study objectives. Input from nonmedical and nonscientific members of the team, such as marketing and information technology experts, also is helpful in establishing development strategies and in designing and conducting of clinical studies. Finally, project planning efforts can synchronize team efforts, help contain the soaring costs of pharmaceutical research, and coordinate international development efforts.

The drug development team's primary goal is to gain approval to market the drug, which requires that a marketing application be submitted to a regulatory agency (e.g., a New Drug Application [NDA] is submitted to the Food and Drug Administration [FDA] in the United States and to the Health Products and Food Branch [HPFB] in Canada, while a Marketing Authorization Application [MAA] is submitted to European regulatory agencies). During the conduct of the studies and the compilation and analyses of the data, the team must consider and evaluate many issues, such as how to collect, categorize, and report adverse events. All of these decisions will affect the marketing application that is submitted and may ultimately define how the drug is to be administered.

Many of the decisions to be made by the team, and particularly by the investigators, pose ethical dilemmas. Legislation has been enacted to protect human research subjects. Recently, the most pressing ethical dilemma facing the clinical research scientist concerned biotechnology and genetic engineering research.

Frequent changes in the regulations and guidelines of various regulatory agencies, differences in interpretations of these rules, and special reporting mechanisms for adverse events represent only a few of the challenges facing a drug development team. Due to continuous advances in scientific information, understanding of disease processes, and gene therapy, change continues to be the rule in modern drug development. However, through the efficient application of sound scientific principles in an ethical manner and with a coordinated team effort, effective new therapies can continue to be developed and marketed.

ROLES OF THE DRUG DEVELOPMENT TEAM MEMBERS

Physicians

The physician's contribution to drug development and the physician's role on a drug development team have changed over the last few decades (1). Before the 1960s, medical departments of pharmaceutical companies were primarily composed of physicians who were routinely involved in responding to drug information requests rather than developing new drugs. The Kefauver–Harris Amendment, enacted in 1962, required pharmaceutical companies to demonstrate before marketing that a drug was efficacious, which necessitated that physicians increase their presence on drug development teams. Along with the advent of additional governmental regulations, the increase in complexity of medical knowledge has mandated that physicians become an integral member of any drug development team. In fact, because of the different roles of the physician within an organization, companies may now have various departments (e.g., a clinical research department and a clinical safety department) within the medical department.

Although physicians are trained in patient care, physicians who are typically employed by pharmaceutical companies have more training in scientific methodology than those in the past. The physician on the team is the one qualified to follow the progress of each patient enrolled in a clinical trial and to interpret the results. Some physicians continue to spend time treating patients at a university hospital or a specific clinic where their specialty can be utilized and practiced, which allows these physicians to maintain sharp diagnostic skills. Also, some may perform basic research in academic settings to develop or maintain their knowledge and skills in basic research.

However, much of today's clinical research is actually conducted by investigators who are not employed by the company sponsoring the development of the drug. The physician on the drug development team must help in the selection of appropriate investigators to conduct the clinical studies. Pharmaceutical physicians may rely on colleagues who are experts in their respective fields and who have appropriate patient populations and facilities for the targeted research project. The physician is also the expert who deals with emergency situations that may arise during the course of a clinical research project, such as an overdose or severe adverse experience (SAE) that might be experienced with the drug. Similarly, the physician assists investigators who are responsible for evaluating the severity of adverse experiences (AEs) and determining

the causal relationship of the AEs to the drug under development.

The physician's involvement in clinical research does not end with the completion of the clinical study. Medical reports, clinical study reports, and sections of NDAs must be written. Interactions with regulatory agencies that require the physician's input may occur frequently. Physicians in clinical research may also be called upon to promote new drugs in a scientific environment by organizing symposia and workshops and by reviewing journal advertisements and promotional material for medical validity and accuracy.

The role of the physician in a clinical drug development program has expanded and has been refined in the last 40 years. Physicians increasingly contribute clinical and scientific expertise and administrative skills. Many physicians on drug development teams today spend most of their time designing and implementing studies and interpreting and reporting data rather than being in direct contact with patients. An experienced clinician is an important member of any drug development team.

Scientists

While a drug development team may have only one primary physician, it may have multiple scientists. Pharmacokineticists, pharmacologists, toxicologists, and pharmaceutical scientists are all involved in the clinical development of drugs. The contributions of scientists to a drug development project are derived from their experience in both scientific methodology and basic research (1).

Although physicians are trained in patient care, scientists are trained in problem-solving skills related to scientific research. To obtain a doctoral degree, a scientist must conduct research and write a dissertation that covers a topic of sufficient scope and depth. During this process, the scientist learns how to solve problems from different perspectives. The scientist also collects extensive data and performs data analyses, thereby gaining valuable insight into the considerations necessary to determine the feasibility of collecting data in a clinical trial. Also, some scientists, such as pharmacokineticists with a pharmacy background, may receive some clinical experience during their training as a scientist.

Scientists help design major portions of study protocols and clinical case report forms (CRFs). The study protocol is the overall plan that the study follows, and it must contain certain types of information, including the following: 1) background data on the targeted disease; 2) the empirical and structural formula of the drug being studied; 3) preliminary pharmacology and toxicology of the drug (specific study objectives and designs); 4) the methods and materials to be used in the study; 5) information regarding drug packaging, labeling, dosage forms, and decoding procedures; 6) overdose management; 7) patient discontinuation procedures; 8) explanation of informed consent and provisions regarding institutional review board approval; and 9) any relevant references and appendices. The CRFs are the forms on which individual patient data are recorded during a clinical trial. From these data, clinical and statistical analyses are performed. All the information that is stipulated in the study protocol must be collected on the CRFs.

In conjunction with nonscientific personnel, scientists are responsible for ensuring that the CRFs will capture the appropriate information for each study subject according to the objectives, tests, and evaluations stipulated in the protocol. Careful attention must be given to the administration of special tests or collection of samples so that the timing of the assessments or sample collections do not conflict.

Experience in basic research enables the scientist to function as an important link between the basic research labs within the company and the drug development team. Departments specializing in drug metabolism, microbiology, pharmacology, and toxicology need feedback from early human safety and pharmacokinetic studies so they can continue to plan and conduct appropriate long-term animal studies. Thus, communication between the clinical scientist and the basic scientist is important throughout the progress of the drug development program.

Because clinical research has become increasingly more scientific, experts in the methodology of science are necessary for a complete research program. The drug development team's scientists may account for much of the scientific expertise, but the roles of the research team overlap to form a scientifically sound, medically astute cohesive group. In addition to scientific expertise, use of the scientist's administrative talents, such as organizational skills and familiarity with personnel practices, enables effective drug development. Thus, scientists with these skills are often employed in management positions in many organizations.

Pharmacists

The pharmacist's role on the drug development team has greatly expanded the professional opportunities of individuals with backgrounds in pharmacy. Pharmacists can provide valuable therapeutic insight into medical research. Training of pharmacists as clinical scientists with

both clinical skills and scientific research skills continues to be an emphasis at many pharmacy schools. Several programs have been devised for the education and development of the pharmacist as clinical scientist (2). Pharmacists have a broad knowledge in both clinical medicine and pharmaceutics, and therefore are able to bridge the gap between the clinic and the laboratory.

Pharmacists' training focuses on drug therapies in disease states, whereas physicians' training focuses on the diagnosis of disease states. Studies regarding drug interaction, positive control, or drug comparison involve drugs that have been studied and marketed. Pharmacists can help in the design of such trials because of their knowledge of marketed drugs.

Additional roles of pharmacists appear in the areas of drug information and education and training. Pharmacists have the appropriate expertise in drug therapy to answer inquiries from physicians (and other health professionals) concerning both marketed and investigational drug products. Similarly, the clinic/laboratory bridge that the pharmacist builds makes this team member especially well suited to educate and train new employees in drug development. By offering both general and special skills, the research pharmacist blends clinical medicine with pharmaceutical science and is well qualified as an educator and drug information specialist.

Nonscientific Personnel

Drug development includes many tasks that may not require the specialized expertise of a physician or a scientist. Administrative skills, creativity, and excellent communication abilities, which are qualities not necessarily emphasized within traditional medical and scientific educational curricula, may be required for many of these tasks.

The administrative skills necessary for drug development include incorporating seemingly disparate but vitally linked concepts into a single overall plan. Integration planning may mean organizing study files into a logical sequence or helping to assemble the various parts of an NDA. In the first example, files must be set up in a way that can facilitate internal quality assurance audits and FDA inspections. In the second example, knowledge of the FDA's regulations and good abstracting capabilities are required.

Creativity is a quality that cannot be developed through formal training. Creativity requires bold conjecture and it expresses itself in newer, better ways to accomplish the same goals. An example of creativity in clinical drug research might involve the development of a variable report that could support all of the different research documents that are generated by drug research teams. With such a variable report, common information need not be recreated each time another document is generated.

Excellent communication skills may be the most important quality for individuals working in drug development, even for those with strong medical backgrounds. Clinical research requires extensive interactions with personnel within the organization and with outside vendors or clinical sites. The information flow must be both efficient and accurate. For example, marketing departments must communicate frequently with medical departments so that marketing studies, advertising, and package inserts can be planned and evaluated. Individuals who lack strong science backgrounds but who have excellent communication skills often act as liaisons in these situations.

One aspect of clinical research that requires extensive contribution by the drug development team personnel is study monitoring. Study monitors oversee the planning, initiation, conduct, and data processing of clinical studies (3). While monitoring studies, monitors must communicate frequently with investigators and help ensure the data are being collected properly, FDA regulations are being followed, and any administrative problems are resolved as quickly as possible. Although monitors traditionally have had a nonscientific background, many monitors today have training in the basic sciences, and some even have advanced degrees, which allows them to better understand the scientific aspects of the project. Effective study monitors have a wide range of talents.

The many facets of a clinical research program afford individuals with varying types of training, education, and experience, the opportunity to contribute to the drug development process. Although some tasks clearly require the clinical or scientific expertise of a physician or a scientist, other tasks are better suited to those individuals with less specialized and more general capabilities.

STAGES IN CLINICAL DRUG DEVELOPMENT

Before clinical drug development can begin, many years of preclinical development occur, millions of dollars are spent, and countless decisions are made. Basic research teams consisting of chemists, pharmacologists, biologists, and biochemists first identify promising therapeutic categories and classes of compounds. One or more compounds are selected for secondary pharmacology evaluations and for both acute and subchronic toxicology testing in animal models. A compound that is

pharmacologically active and safe in at least two nonhuman species may then be selected for study in humans. Before the drug can be tested in humans, an Investigational New Drug (IND) application, which contains supporting preclinical information and the proposed clinical study designs, must be filed with an appropriate regulatory agency.

Clinical drug development follows a sequential process. By convention, development of a new drug in humans is divided into four phases: preapproval segments (Phases 1 through 3) and a postapproval segment (Phase 4) (1–4). The definitions of the three preapproval phases have relatively clear separations. However, the different phases refer to different types of studies rather than a specific time course of studies. For example, bioequivalence studies and drug–drug interaction studies are both Phase 1 studies, but they may be conducted after Phase 3 studies have been initiated. The generalized sequence of studies may be tailored to each new drug during development.

Phase 1

After the appropriate regulatory agency has approved a potential drug for testing in humans, Phase 1 of the clinical program begins. The primary goal of Phase 1 studies is to demonstrate safety in humans and to collect sufficient pharmacokinetic and pharmacological information to permit the determination of the dose strength and regimen for Phase 2 studies.

Phase 1 studies are closely monitored, are typically conducted in healthy adult subjects, and are designed to meet the primary goal (i.e., to obtain information on the safety, pharmacokinetics, and pharmacologic effects of the drug). In addition, the metabolic profile, adverse events associated with increasing dosages, and evidence of efficacy may be obtained. Because most compounds are available for initial studies as an oral formulation, the initial pharmacokinetic profile usually includes information about absorption. Additional studies, such as drug–drug interactions, assessment of bioequivalence of various formulations, or other studies that involve normal subjects, are included in Phase 1.

Generally, the first study in humans is a rising, single-dose tolerance study. The initial dose may be based on animal pharmacology or toxicology data, such as 10% of the no-effect dose. Doses are increased gradually according to a predetermined scheme, often some modification of the Fibonacci dose escalation scheme (5), until an adverse event is observed that satisfies the predetermined criteria of a maximum tolerated dose (MTD). Although the primary objective is the determination of acute safety in humans, the studies are designed to collect meaningful pharmacokinetic information. Efficacy information or surrogate efficacy measurements also may be collected. However, because a multitude of clinical measurements and tests must be performed to assess safety, measurements of efficacy parameters must not compromise the collection of safety and pharmacokinetic data.

Appropriate biological samples for pharmacokinetic assessment, typically blood and urine, should be collected at discrete time intervals based upon extrapolations from the pharmacokinetics of the drug in animals. Depending on the assay sensitivity, the half-life and other pharmacokinetic parameters in healthy volunteers should be able to be evaluated, particularly at the higher doses. The degree of exposure of the drug is an important factor in understanding the toxicologic results of the study. Pharmacokinetic linearity (dose linearity) or nonlinearity will be an important factor in the design of future studies.

Once the initial dose has been determined, a placebo-controlled, double-blind, escalating single-dose study is initiated. Generally, healthy male volunteers are recruited, although patients sometimes are used (e.g., when testing a potential anticancer drug that may be too toxic to administer to healthy volunteers). These studies may include two or three cohorts, with six or eight subjects receiving the active drug and two subjects receiving placebo. The groups may receive alternating dose levels, which allow assessment of dose linearity, intrasubject variability of pharmacokinetics, and dose-response (i.e., adverse events) relationship within individual subjects.

Participants in the first study are usually hospitalized or enrolled in a clinic so that clinical measurements can be performed under controlled conditions and any medical emergency can be handled in the most expeditious manner. This study is usually placebo-controlled and double-blinded so that the drug effects, such as drug-induced ataxia, can be distinguished from the nondrug effects, such as ataxia secondary to viral infection. The first study in humans is usually not considered successfully completed until an MTD has been reached. An MTD must be reached because the relationship between a clinical event (e.g., emesis) and a particular dose level observed under controlled conditions can provide information that will be extremely useful when designing future trials. Also, the dose range and route of administration should be established during Phase 1 studies.

A multiple-dose safety study typically is initiated once the first study in humans is completed. The primary goal of the second study is to define an MTD with multiple

dosing before to initiating well-controlled efficacy testing. The study design of the multiple-dose safety study should simulate actual clinical conditions in as many ways as possible; however, scientific and statistical validity must be maintained. The inclusion of a placebo group is essential to allow the determination of drug-related versus nondrug-related events. The dosing schedule, which includes dosages, frequency, dose escalations, and dose tapering, should simulate the regimen to be followed in efficacy testing.

Typically, dosing in the second study lasts for 2 weeks. The length of the study may be increased depending on the pharmacokinetics of the drug so that both drug and metabolite concentrations reach steady state. Also, if the drug is to be used to treat a chronic condition, a 4-week study duration may be appropriate. To obtain information for six dose levels with six subjects receiving active drug and two receiving placebo for each of two cohorts, a minimum enrollment of 24 subjects should be anticipated. Similar to the first study in humans, these subjects would be hospitalized for the duration of the study.

Also similar to the first study, pharmacokinetic data must be obtained. These data will be used to help determine dosage in future efficacy trials. The new pharmacokinetic information that can be gathered includes the following: 1) determination regarding whether the pharmacokinetic parameters obtained in the previous acute safety study accurately predicted the multiple dose pharmacokinetic behavior of the drug; 2) verification of pharmacokinetic linearity (i.e., dose proportionality of C_{max} and AUC) observed in the acute study; 3) determination regarding whether the drug is subject to autoinduction of clearance upon multidosing; and 4) determination of the existence and accumulation of metabolites that could not be detected in the previous single-dose study. A number of experimental approaches can be used to gather this information, and all require frequent collection of blood and urine samples. The challenge to the clinical pharmacokineticist is to design an appropriate blood sample collection schedule that will maximize the pharmacokinetic information, yet can be gathered without biasing the primary objective—determination of clinical safety parameters.

Phase 2

After the initial introduction of a new drug into humans, Phase 2 studies are conducted. The focus of these Phase 2 studies is on efficacy, while the pharmacokinetic information obtained in Phase 1 studies is used to optimize the dosage regimen. Phase 2 studies are not as closely monitored as Phase 1 studies and are conducted in patients. These studies are designed to obtain information on the efficacy and pharmacologic effects of the drug, in addition to the pharmacokinetics. Additional pharmacokinetic and pharmacologic information collected in Phase 2 studies may help to optimize the dose strength and regimen and may provide additional information on the drug's safety profile (e.g., determine potential drug–drug interactions).

Efficacy trials should not to be initiated until the MTD has been defined. In addition, the availability of pharmacokinetic information in healthy volunteers is key to the design of successful efficacy trials. The clinical pharmacokineticist assists in the design and execution of these trials and analyzes the plasma drug concentration data upon completion of the efficacy studies.

During the planning stage of an efficacy trial, the focus is on the dosage regimen and its relationship to efficacy measurements. Plasma drug concentrations for various dosages can be simulated based upon the data collected in the first two studies in humans. The disease or physiological states of the test patients (e.g., organ dysfunction as a function of age), concurrent medications (e.g., enzyme inducers or inhibitors), and the safety data obtained earlier must be considered when choosing an optimal dosage regimen for the study. In addition, if the targeted site of the drug is in a tissue compartment, theoretical drug levels in this compartment can be simulated, which may help scientists determine the appropriate times for efficacy measurements.

On completion of the efficacy trial, a therapeutic window for plasma drug concentrations can be defined by reviewing the correlation between plasma drug concentrations and key safety and efficacy parameters. The goal is to improve efficacy and safety of the drug by individualizing the dosage based upon previous plasma drug concentration profiles in the same patient.

Phase 3

If the earlier clinical studies establish a drug's therapeutic, clinical pharmacologic, and toxicologic properties and if it is still considered to be a promising drug—Phase 3 clinical trials will be initiated. Phase 3 studies enroll many more patients and may be conducted both in a hospital or controlled setting and in general practice settings. The goals of Phase 3 studies are to confirm the therapeutic effect, establish dosage range and interval, and assess long-term safety and toxicity. Less common side effects and AEs that develop latently may be identified. In addition, studies targeted to evaluate and quantify specific effects of the drug, such as drowsiness or impaired coordination, are conducted during this phase.

Phase 3 studies are also used to identify the most appropriate population or subpopulation for the study drug and to establish a place for the drug in its therapeutic class. A drug may be developed in a therapeutic class that already has effective alternatives, but the investigative compound may have a better safety profile than its established competitors. A Phase 3 clinical study can be designed to assess relative safety profiles.

Closer inspection of drug interactions is warranted in Phase 3 clinical trials. In many disease states, the use of polytherapy is quite common, and the risk of drug–drug interactions is high, both from pharmacokinetic and pharmacodynamic perspectives. The likelihood of drug interactions and semiquantitative estimates of magnitude may be predicted from in vitro data (6). The potential for interactions needs to be evaluated from two perspectives: the potential that the new drug may affect the pharmacokinetics of other drugs, and the potential that other drugs may affect the pharmacokinetics of the new drug. The former generally depends on the ability of the new drug to affect various enzyme and carrier-mediated clearance processes. Most notably, this concerns the cytochrome P450 (CYP) isoforms but could also involve conjugative enzymes and transporters, such as p-glycoprotein. Drugs may be an effective inhibitor without being a substrate of a CYP isoform, as is the case for quinidine's inhibition of CYP2D6.

The potential for significant drug–drug interactions caused by other drugs requires knowledge of the components of clearance for the new drug and the likelihood that known inhibitors will be coadministered. For drugs with multiple pathways and a broad therapeutic index, the need for formal interaction studies may be limited. Population pharmacokinetic analyses of data obtained from Phase 3 studies may be used to help discover and quantify drug interactions due to classes of drugs often associated with inhibition (e.g., macrolides, systemic antifungals, calcium channel antagonists, fluoxetine, paroxetine) or induction (e.g., anticonvulsants, rifampin).

Most early clinical trials are conducted at university medical centers with physicians who specialize in a certain area of medicine. When study drugs are eventually marketed, however, general practitioners will be prescribing them as well. Therefore, it is important that family physicians are exposed to study drugs during this phase because they represent the segment of clinicians who will be writing most of the prescriptions. Similarly, to maximize the commercial return on drug development, a multi-indication strategy may be pursued (sometimes designated as Phase 5 if conducted postapproval). In addition, testing of the drug in foreign countries is appropriate during Phase 3; however, other countries may operate under different regulatory obligations than in the United States.

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Phase 4

Whereas Phase 1, 2, and 3 studies are conducted prospectively using subjects or patients whose entrance into the study depends on strict inclusion and exclusion criteria, Phase 4 studies employ mainly observational, rather than exclusionary, study designs. Postmarketing surveillance and any additional studies requested by the regulatory agency as conditional approval of the NDA are conducted during Phase 4.

Data collection in premarketing clinical trials is an extensive, scientific exercise. Detailed blood work, special laboratory tests, and careful physiologic monitoring are typical in these studies. Postmarketing studies, however, are often targeted for much larger patient populations (5000–10,000 or more), which limits extensive data collection from each patient and emphasizes collection of safety information. These studies are complemented by reports of AEs from patients not enrolled in a study. The large numbers of patients in Phase 4 studies make it easier for researchers to determine rare AEs and can help identify patient populations that are at particular risk for certain AEs. For example, demographic trends toward side effects involving geographic locus, gender, or race may be determined from postmarketing surveillance data.

PROTOCOL CONSIDERATIONS

The task of designing a clinical study cannot be undertaken until the study objective of that trial has been rigorously defined. The objective should explicitly state what is being investigated and vague language should be avoided (7). Once an unbiased and specific objective has been developed, scientists can build the study design around it and then develop and write the protocol (8).

One of the main considerations when designing an investigational study concerns the type and number of comparative groups that will be involved. A control group of subjects may be evaluated in addition to the group taking the investigational drug. Sometimes more than one control group is used in a study. The control groups take either placebo or active medication and are compared with the group taking the investigational drug. This design is used to rule out the possibility of a placebo effect or to assess the efficacy and safety of the investigational drug relative to other drugs currently marketed.

Regulatory agencies frequently require the pivotal Phase 3 studies, which will be used to support an NDA, to be placebo-controlled studies. Placebo medication should be as similar as possible to the drug being investigated (e.g., same color, taste, and shape). No statistically significant difference in response between this group and the subjects taking the investigational drug is evidence against that drug having any real effectiveness.

Similar to the placebo considerations, active medication taken by the control group also should be as similar as possible to the drug being investigated (e.g., same color, taste, and shape). If the formulations cannot be made with similar appearances (e.g., tablet, suspension, etc.), a placebo of each formulation could be made so subjects would take one active formulation and the placebo of the other formulation to maintain the blind. No statistically significant difference in response in this group relative to the subjects taking the investigational drug is evidence that active medication has no advantage therapeutically over the existing therapy. However, a higher incidence of AEs in the control group and an equal rate of efficacy relative to the subjects taking the investigational drug are evidence of the new drug's advantage over the existing therapy.

In addition to determining the types and number of control groups that should be included in a study, the drug development team must decide between a parallel and a crossover design. For example, in a placebo-controlled clinical trial, a parallel design is one in which each study group takes the same medication (i.e., either placebo or active drug) throughout the study. With a crossover design, each study group eventually receives both placebo and active drug (e.g., one group may take placebo for a 6-week period and then cross over to receive active drug for the following 6-week period).

An advantage of the crossover design is that it allows each group to be its own control, thereby allowing a demonstration of efficacy to occur during the treatment with the drug. A disadvantage of the crossover design is that residual effects from one treatment period may carry over into the other treatment period. Absolute determination of efficacy and safety of the different treatments is difficult and sometimes impossible. One way to avoid the problem of residual effects on crossover studies is to have washout periods between the different treatment phases. During the washout period, the patient is either given a placebo or no treatment for several days or weeks so that any possible metabolite or effect of the drug is "washed out" of the patient before the next treatment phase begins.

An advantage of the parallel design is that it avoids the problems associated with possible residual effects of one treatment period influencing the other treatment period(s) because each treatment group is only exposed to one drug. Compared with a crossover study, more patients may be required for a parallel study so that statistical significance can be established between the study groups. In a parallel study, recruiting the required larger numbers of patients who fit the study criteria takes longer, but the duration of that study is usually shorter than the duration of a crossover study.

Crossover designs span greater periods of time because each group must sequentially take an active and a control medication over a period that is long enough to allow a treatment effect to emerge. When washout periods are added, the time required to conduct these studies becomes longer still, and more study subjects may drop out. These difficulties are often outweighed by the fact that statistical significance can be achieved with fewer patients in crossover studies.

Once the study design has been chosen, there are many other issues to consider when developing and writing clinical protocols. Among the topics to be considered are criteria for patient eligibility, efficacy and safety parameters, timing of the events, packaging and dispensing of the clinical trial material, and the informed consent form. Also, to be determined is how the study will be blinded. For most well-controlled studies, subjects are assigned to the various groups by using a randomization process so that biased selection is eliminated, the overall collection of the subjects' variables is comparable in each group, and statistical power is guaranteed (9). In these double-blind studies, neither the subject nor the investigating scientists know to which group the subject has been assigned. Thus, extensive input from the drug development team is required when designing studies and writing protocols.

DRUG DEVELOPMENT CONSIDERATIONS

Most drugs are tested in humans to treat a specific disease entity or some adverse clinical condition. Because the pathogenesis of diseases and the exact mechanisms of action of drugs are often poorly understood, the process of evaluating a drug's efficacy can be complicated. Upon treatment, a patient's adverse clinical condition may improve; however, for many diseases this occurrence can only be evaluated indirectly by clinical assessments (e.g., via blood pressure measurements in the treatment of hypertension). However, a drug's characteristics can also be measured directly. For example, measurement of blood concentrations of the drug enabling calculation of pharmacokinetic parameters is a direct evaluation of the drug.

Similar to efficacy assessments, evaluation of the safety of a drug may also involve indirect measurements. One of the primary methods of obtaining safety information in a

clinical trial is through a patient's reporting of AEs. Although the exact biochemical mechanisms responsible for many AEs cannot be evaluated directly, the indirect evaluation of the drug's adverse effect can be seen clinically. Because clinical assessments are indirect measures, AE reporting leads to several complex questions. The degree of drug-relatedness or causality, the effect of concomitant medication, the severity of the AE, the complications of the disease state, and the effects of other clinical conditions or diseases are usually difficult to determine, particularly early in the drug development program. Also, all reports of AEs in a clinical drug research program are recorded, tabulated, and cross-referenced to form a safety database, regardless of whether the AE is determined to be drug related. The information contained in this database is used to generate the package insert.

Although the clinical effect of a drug is perhaps the primary concern of drug development, an understanding of the drug's biochemical and physicochemical properties and mechanism of action is also desired. These direct measures are of equal concern in drug development as are the indirect evaluations of a drug's clinical effects. The primary tool used to study the intrinsic physicochemical properties of a drug is pharmacokinetics, which is a branch of biopharmaceutics. Pharmacokinetics describes the relationship between the processes of drug absorption, distribution, metabolism (biotransformation), and excretion (collectively abbreviated ADME) and the time course of therapeutic or adverse effects of drugs (10). Efficacy is determined by the drug concentration at the site of action, which generally is correlated with the drug concentration in the blood. The ultimate goal of pharmacokinetics is to characterize the sources of variability in the concentration–time profile, which may be correlated with variability in efficacy and adverse events.

Pharmacokinetics can be used to guide dosage regimen selection and thereby optimize pharmacologic effects and minimize toxicologic effects when a drug is administered to an individual patient. Thus, although the basic pharmacokinetic properties of a drug are identified during the earliest stage of clinical drug development, the many factors affecting the pharmacokinetics in the patient population must be identified throughout the drug development process to enable proper dose selection for individuals. Thus, both indirect and direct measures are used to evaluate a drug.

MARKETING INPUT

A successful pharmaceutical company has an appropriate blend of both research and marketing to enable a symbiotic, rather than antagonistic, relationship. Because an effective scientific and clinical research team often designs and executes experiments and clinical trials that involve costly overhead expenses, it is essential for marketing decisions to be geared toward company profitability being made allow the company profitable so these expenses can be met. Therefore, both medical and marketing input are necessary if a pharmaceutical company is to be successful.

By gathering data on all facets of the needs in the marketplace from clinicians and by maintaining a profile awareness of new products under development by competitors, marketing personnel are in an excellent position to advise their colleagues in the research arena who are responsible for the drug development program. Also, a marketing expert can help identify the problems other companies are having in selling their product and thereby avoid the same difficulties. For instance, sales problems may be related to ineffective advertising or faulty packaging; therefore, they do not concern clinical research. However, problems in sales can also be related to a drug's undesirable effects. An effective drug that does not lead to the AEs associated with an already approved drug would have a marketing advantage. Someone in marketing research may suggest conducting clinical studies that would evaluate the relative incidence of the AE with the hope that the data could be used to support effective advertising.

Thus, research and marketing are mutually benefical in a successful pharmaceutical company. Marketing groups help clinical research teams by supplying them with information about competing products, the needs of the marketplace, and suggestions for new formulations. Clinical research teams provide the data to support therapeutic and marketing claims and act as chief advisors to marketing personnel concerning drug research studies and promotional claims.

EFFECTIVE GLOBAL PLANNING

Because drugs are frequently marketed worldwide and the clinical development of drugs may involve studies that are conducted internationally effective global planning can present its own difficulties. Obviously, medical practice, regulatory guidelines, and the cultural environment may be different in various countries, but also the manner in which research is conceived can differ vastly between countries. Medical researchers in some countries may be more conservative than researchers in other countries, which could potentially lead to the underdosing of drugs.

These differences in research approaches actually stem from differences in ethical standards.

Another reason that international planning may be difficult in drug research concerns the way in which various countries view early clinical trials and drug safety. Some countries view volunteer subjects and patients differently from a regulatory perspective, making it easier to recruit and enroll subjects for Phase 1 studies than it is to recruit and enroll patients for Phase 2 or Phase 3 studies. In the United States, both patients and volunteers are viewed in the same way, and studies with patients and volunteers cannot be initiated until the FDA has authorized an IND.

In addition to regulatory guidelines, the regulatory process is still another aspect of clinical drug development that can differ widely between countries. In England, sponsoring research firms do not interact very much with the British drug regulatory agency the Committee on Safety of Medicines. This lack of direct interaction stems from the desire to keep commercial influence away from the objective evaluation of a pharmaceutical company's study data. This lack of communication results in British companies treating government guidelines for conducting clinical research as a routine checklist rather than an aid in forming the most appropriate development strategy.

In the United States, federal guidelines (Code of Federal Regulations, CFR) have been established by the FDA to help sponsoring research firms conduct good, consistent clinical studies. However, some of the items in these guidelines may not be appropriate for all clinical studies, and some items that may be appropriate to include in a clinical study may not have been incorporated into the federal guidelines. These variations occur because each drug and disease state is unique, and complete guidelines cannot be established for all cases. For these reasons, several meetings are held between clinical research teams and the FDA before an NDA submission to ensure that all appropriate methodology and experimentation is being incorporated into the overall drug development project.

Beginning in the early 1990s, the FDA participated in a collaborative effort to harmonize the technical procedures for development and regulatory approval of human pharmaceuticals internationally. Forces that led the agency in this direction included increased trade, the multinational nature of the pharmaceutical industry, trade agreements such as the North American Free Trade Agreement and the General Agreement on Tariffs and Trade by the World Trade Organization, European activism, and pressures on the industry to control costs (11). These pressures included intense competition and health care reimbursement controls. This harmonization effort is the work of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH has focused on achieving harmonization of technical requirements in three major regions of the world: the United States, the European Union, and Japan. Some of the earliest ICH guidelines addressed the format and content of the Investigator's Brochure (12), stability testing (13), and genotoxicity testing (14). The FDA also works with the World Health Organization and other international organizations to set standards for health care products (11).

Clinical drug research is a complicated, multidisciplinary task that may be conducted internationally. In fact, many pharmaceutical companies are multinational, with locations in several countries. Planning and coordination become even more complex for such global drug development programs. Despite the differences among countries in medical practice, regulation, and culture, international drug development and marketing are vital parts of many organizations. The successful multinational pharmaceutical company will plan its clinical research strategy according to any differences among nations before to implementing its international development plans.

ETHICAL CONSIDERATIONS

No topic in clinical drug development is more controversial and emotionally charged than the myriad ethical dilemmas that face physicians and scientists involved in clinical research. Given that clinical research has generally proved to have moral consequences through its direct and indirect influence on alleviating suffering, steps must be taken to ensure that abuses do not occur during the course of drug development. Therefore, guidelines for the protection of human subjects have been developed, proposed, and accepted worldwide (15).

Because of the atrocities committed by Nazi medical researchers in the 1930s, the Nuremberg Code (16) was written, and highlighted the importance of obtaining all research subjects' voluntary consent to their participation in clinical studies. The Declaration of Helsinki (17), which was published by the World Medical Association in 1964 and has been updated several times since, takes the informed consent issue one step further by giving only qualified medical scientists and physicians the right to conduct clinical research. However, similar concerns go back at least to the 1830s, when Dr. William Beaumont developed a contract with a patient, and in the late 1800s, when a leprosy worker experimented on a patient without her consent (18).

Legislation that ensures the protection of human research subjects in the United States includes the 1979 publication of the Belmont Report on the Ethical Principles and Guidelines for the Protection of Human Subjects of Research (19). This report concerns the fine line between biomedical research and the routine practice of medicine and explores the criteria that determine the risk-benefit ratio in the consideration of conducting clinical research. It also addresses basic guidelines for the proper selection of human research subjects and further defines the elements of informed consent.

Other important legislation in the United States includes the FDA's Guidance for Institutional Review Boards (IRBs) (20) for further guarantees of protection for human research subjects. IRBs are independent committees that review proposed clinical research projects before the commencement of the research. These committees decide whether the risk to research subjects outweighs the potential benefit of the research; they can suggest modifications in the research proposal or disapprove the project altogether. IRBs must consist of both men and women of varying professions. At least one member must have his or her primary concern in a nonscientific area (e.g., a lawyer or clergyperson), and at least one member must not be affiliated with the institution at which the research will be conducted.

Closely related to the rights of human research subjects are the rights of routine patients involved in nonresearch medical matters. In 1973, the American Hospital Association published the Patient's Bill of Rights (21), which requires that the acting physician give his patients complete information concerning their diagnosis, treatment, and prognosis; that the patient be given respectful care; that the patient be given the opportunity to refuse treatment; and that the patient's records, condition, and medical care be treated confidentially.

Another ethical issue facing clinical research scientists concerns study design, in particular, the placebo-controlled clinical trial. The reason placebo-controlled clinical trials are conducted is quite compelling from a scientific standpoint: to ensure that the evidence supporting the efficacy of an experimental drug is actually due to the properties of the drug and not to the psychologic properties of the study subjects. In other words, if a placebo effect from the experimental drug occurs rather than a true therapeutic effect, then a comparison of the drug group with the placebo group will show statistically similar response rates. It is a way to help separate actual drug responses from placebo responses, especially in studies investigating psychiatric compounds, but also in other therapeutic areas with a clearer "physiologic" or "biochemical" basis.

One defense for conducting placebo-controlled clinical trials is that the subjects chosen for the placebo group are randomly chosen, so that no malicious withholding occurs. Also, many study protocols have provisions of study extension that guarantee subjects in placebo groups have the opportunity to take the drug as an extension of the study after they complete the original part, or they are offered the chance to receive alternative therapy. Study subjects may be given monetary compensation for their participation in studies, in addition to free, thorough physical exams, lab work, and physician visits.

Interestingly, experimental drugs have unknown side effects that can cause serious biochemical and physiologic problems, whereas placebo medication does not. This fact makes possible the contrary argument and objection, on purely ethical grounds, to giving study subjects experimental and hence unproven drugs. Of course, informed consent and careful monitoring by trained medical personnel help to alleviate the ethical problems associated with giving subjects an active, investigational drug. The most important aspect of all studies is that the patient be completely informed of all study procedures and agree to willingly participate in the study.

The most recent pressing ethical dilemma facing the clinical research scientist surrounds the increasing amount of research that is being conducted in biotechnical and genetic engineering. Ethical issues will continue to play important parts in the medical and legal worlds. Whereas pure science is value-neutral, its application is always open to debate. Undesirable extremes are likely to exist at both ends of the spectrum.

CONCLUSIONS

To conduct a clinical study for the evaluation of a new drug, a vast array of personnel is required. Physicians are largely used because of their knowledge of clinical medicine and patient care, whereas scientists are used because of their knowledge of the methodology and the science. Pharmacists serve a bridging function due to their unique training in therapeutics and the pharmaceutical sciences. Nonscientific personnel are indispensable because of their ability to coordinate the many facets of a drug development project.

The clinical evaluation of drugs involves many different levels of scrutiny before a drug product can be marketed. These levels include Phase 1 for safety testing, Phase 2 for evaluating efficacy and determining the correct therapeutic dose, Phase 3 for large-scale studies and determination of drug interactions, and Phase 4 for

postmarketing surveillance. Phase 1 studies are typically conducted in healthy volunteers, and Phase 2 through 4 studies are conducted in patients.

Study design plays a critical role in the clinical evaluation of drugs. A clinical study cannot be conducted without specifically outlined objectives and a definitive plan, which are vital components around which the study protocol is constructed. The use of placebo or active drug control groups in the study, and whether the design should be open, parallel, or crossover, must be determined. In most studies, patients are assigned to study groups randomly.

The developmental objectives facing the clinical research team include indirect evaluations of a drug's safety and efficacy, such as effects on vital signs or behavior, and direct evaluations of a drug's intrinsic properties, such as its pharmacokinetics and mode of action. Also, the marketing–medical liaison is important if research is to support future sales plans and advertising is to reflect study results. Finally, effective global planning is necessary because drugs are more frequently developed and marketed worldwide, and therefore involve differing patient populations and different government regulations. ICH guidelines have helped to standardize regulations worldwide.

The ethical dilemmas facing clinical research scientists affect much of the legislation that currently regulates the conduct of clinical trials. The goal of drug development research is to develop effective pharmacotherapy for mankind's ailments, and regulatory agencies have enacted legislation to prevent unethical research.

Although traditional medicines continue to be discovered and developed, the fields of biotechnology and gene therapy continue to advance. In addition, new methods to collect and evaluate clinical data on a real-time basis will help to speed the development process.

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Clinical Laboratory Improvement Amendments of 1988

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INTRODUCTION

Today, any facility that examines or tests material derived from the human body for patient care purposes is subject to federal regulation under the Clinical Laboratory Improvement Amendments of 1988 (CLIA 1988).[1,2] Historically, CLIA 1988 was passed in response to perceived and documented problems in cytology testing, but the law also expanded federal regulation to large numbers of previously unregulated laboratories, such as physician offices and health screening sites. Except for laboratories performing only the simplest of tests, CLIA provides a comprehensive regulatory framework including personnel, quality control and quality assurance standards. This is significant for pharmacists since advances in laboratory technology have created new opportunities for pharmacists to conduct testing services.[3,4] Although these services are not within the traditional pharmacist role, they are consistent with the scope of pharmacy practice under the definition of pharmaceutical care.[5,6] Since the role of the pharmacist is continually expanding, pharmacists should be familiar with the history and general regulatory framework of CLIA 1988.

HISTORY

Current federal regulation of clinical laboratories is found within the Clinical Laboratory Improvement Amendments of 1988 (CLIA 1988) and implementing regulations.[1,2] The law is quite comprehensive, but this wasn't always so. Prior to 1965, there was very little federal involvement in laboratory regulation.[7,8] In fact, only a few states regulated or licensed medical laboratories. Those states that did regulate laboratories did so mostly in conjunction with hospital licensing requirements.

After 1965, federal government involvement in clinical laboratory regulation increased, somewhat indirectly, through conditions of participation in Medicare and Medicaid.[7] The laboratory conditions of participation for Medicare and Medicaid were basically designed to ensure that the government and its beneficiaries received the services paid for and that such services met specified minimum standards. In general, the conditions of participation only affected hospital and larger independent laboratories participating in the Medicare and Medicaid programs.

In 1967, Congress took a direct role in expanding the federal regulation of clinical laboratories by passing the Clinical Laboratory Improvement Act of 1967.[7,9] Under CLIA 1967, private laboratories receiving specimens in interstate commerce had to be licensed. While this expanded the number of regulated laboratories, it was by no means comprehensive. Federal and state laboratories were exempt. In addition, any laboratory receiving fewer than 100 interstate specimens per year was exempt from licensure if it registered and applied for the exemption. Therefore, most physician office laboratories were exempt.

In addition to expanding the number of regulated laboratories, CLIA 1967 also increased federal quality standards. The new law required that regulated laboratories successfully participate in proficiency testing. Proficiency testing is the periodic testing of unknown samples by a laboratory under normal laboratory procedures and workload. The purpose of proficiency testing is to identify poorly performing laboratories.

While imperfect in scope, CLIA 1967 continued to govern the regulation of clinical laboratories for the next 20 years. In 1987, the *Wall Street Journal* published two articles suggesting that, at least for Pap smears, the quality of laboratory testing was not as good as expected.[10,11] In response to the articles, committee hearings were held in both the U.S. House of Representatives and the U.S. Senate. In addition, the Department of Health and Human Services began revising regulations implemented under CLIA 1967. On October 31, 1988, Congress enacted the Clinical Laboratory Improvement Amendments of 1988 (CLIA 1988).

DOI: 10.1081/E-ECP 120006196

CLIA 1988 significantly increased the scope of federal laboratory regulation both in terms of the number of laboratories regulated and quality standards.[5] Under CLIA 1988, any facility that examines or tests material derived from the human body for patient care purposes is subject to federal regulation. Furthermore, the law provides for personnel, patient test management, quality control and quality assurance standards, as well as proficiency testing to identify poorly performing laboratories.

The legislation came under immediate criticism.[7] Initial criticism called the need for more comprehensive regulation into question. The *Wall Street Journal* articles that precipitated the legislation focused on "errors" that resulted in missed or delayed diagnosis of carcinoma of the uterine cervix. The problems described did exist to some degree but the articles were considered by many to be sensationalistic and misrepresentative. Furthermore, neither the *Wall Street Journal* article nor congressional testimony revealed that the CLIA 1967 regulations already applied to cytology and that all cited instances of unacceptable laboratory practice had been subject to enforcement under existing regulations.

Continuing criticism focused on the extent of the regulation.[12–14] Many laboratory professionals expressed concern that certain portions of the CLIA regulations were overly prescriptive and burdensome. While laboratory management welcomed the decreased stringency in personnel requirements as providing greater flexibility in staffing, laboratory professionals expressed concern that personnel changes were a dangerous weakening of standards.

Physicians operating office laboratories were also concerned. Much of the concern focused on the intrusiveness of quality standards, especially proficiency testing.[14] A chief criticism of proficiency testing was that the proficiency testing process is highly artificial with many operational, technical, and clerical variables that are absent from routine patient testing. Physicians argued that in an office setting significant inaccuracies were likely to be detected by the physician. Requiring physicians to comply with burdensome regulations might cause many physicians to eliminate office-based laboratory services. They argued quicker and more accessible results were more important for immediate patient care than highly accurate results after the patient has gone home.

In contrast to the concerns about overregulation were concerns about underregulation of persons engaged in relatively simple laboratory activities such as health screenings.[14] Under the CLIA 1988 regulations, persons collecting human specimens for patient care purposes using specified, relatively simple equipment and tests are required to register but are exempt from most quality standards. The exception raised concerns with regard to accuracy and interpretation of results in these settings.

RELATIONSHIP TO PHARMACY

Although relatively few pharmacies engaged in laboratory activities when CLIA 1988 was passed, the issues and concerns raised with the passage of CLIA 1988 are extremely important to pharmacists.[15] There is an increasing need for timely, accurate laboratory values in modern pharmacy practice. Objective laboratory measures help in determining dosages, evaluating medication efficacy, assessing for adverse drug reactions or toxicity, and monitoring adherence to therapy. Furthermore, in-pharmacy laboratory testing allows for the provision of screening services, a valuable public service in the detection of unrecognized disease.

Pharmacists share in the concerns about underregulated laboratories, especially with regard to accuracy and interpretation of results.[15] Since the results of pharmacist-conducted laboratory tests are used in making clinical decisions, the values must be accurate. Additionally, pharmacists must be knowledgeable about interpretations of laboratory results, the variables that can affect them, and their clinical implications. Finally, these concerns require that equipment be maintained and operated in full accordance with the manufacturer's instructions.

REGULATORY FRAMEWORK

Given the importance of laboratory data to pharmacy practice, pharmacists should be familiar with the regulatory framework of CLIA 1988. A major aim of expanding the reach of CLIA 1988 to virtually all clinical laboratories was to ensure that laboratory tests varied only by differences in methodology, equipment used, and training required for test performance.[16,17] In other words, the type of regulatory standards applied to a pharmacy, physician's office, or some other previously unregulated site would be determined only by the tests performed. This regulatory framework is known as a "complexity model."

Under the complexity model there are three categories of tests on which regulatory standards are based: waived tests, tests of moderate complexity (including a provider-performed microscopy subcategory), and tests of high complexity. The complexity of tests performed within the laboratory determine which personnel, proficiency test-

ing, patient management, and quality control and quality assurance standards will apply to the laboratory.

Waived Tests

Facilities that perform only simple procedures with an insignificant risk of an erroneous result may apply for waived status (Table 1).[18] A test may obtain waived status if it employs simple and accurate methodologies, the likelihood of erroneous results is negligible, and testing poses no reasonable risk of harm if performed incorrectly. Tests cleared by the FDA for home use are automatically waived.[19] A complete list of waived tests can be found at www.hcfa.gov/medicaid/clia/waivetbl.htm.

A laboratory performing only waived tests must register with Health Care Finance Administration (HCFA) and obtain a certificate of waiver. However, laboratories operating under a certificate of waiver are only required to permit inspections and follow manufacturers' instructions in performing tests. While proficiency testing, quality control, and personnel standards are not required, persons performing waived tests should adhere to basic tenets of quality control and quality assurance.[16]

Moderate- and High-Complexity Tests

Tests that are not specifically waived are categorized as either moderate- or high-complexity tests.[20] Categorization into high or moderate complexity depends on the knowledge and experience needed to perform the test, complexity of reagent materials and preparations used, characteristics of operational steps, characteristics of and availability of calibration, quality control, and proficiency testing materials; troubleshooting and maintenance required; and the degree of interpretation and judgement required in the testing process.

Using these criteria, virtually hundreds of tests have been classified as moderately complex, while fewer, highly

Table 1 Tests granted waived status under CLIA used in drug monitoring

Test name	Manufacturer	Use
Glucose monitoring devices cleared by the FDA for home use	Various	Monitoring of blood glucose levels
Bayer DCA 2000	Bayer	Measures the percent concentration of hemoglobin A1c in blood for monitoring long-term diabetic control
Metrika DRx HbA1c	Metrika, Inc.	
LXN Fructosamine Test System LXN Duet Glucose Control Monitoring System LXN IN CHARGE Diabetes Control System	LXN Corp.	Measures glucose/fructosamine to evaluate diabetic control over a 2–3 week period
ChemTrack AccuMeter	ChemTrak	Cholesterol monitoring
Advance Care	Johnson & Johnson	
Accu-Check Instant Plus Cholesterol	Boehringer Mannheim Corp.	
ENA.C.T Total Cholesterol Test	ActiMed Laboratories	
Lifestream Technologies Cholesterol Monitor	Lifestream Technologies	
MTM Bioscanner 1000 (for OTC use)	Polymer Technology Systems, Inc.	
PTS Bioscanner Test Strips Cholesterol	Polymer Technology Systems, Inc.	
Cholestech LDX	Cholestech	Measures total cholesterol, HDL cholesterol, triglycerides, and glucose levels
PTS Bioscanner (for OTC use)—for HDL	Polymer Technology Systems, Inc.	Measures HDL cholesterol in whole blood
PTS Bioscanner 2000 for Triglycerides	Polymer Technology Systems, Inc.	Measures triglycerides in whole blood
ITC Protime Microcoagulation System	International Technidyne Corp.	Evaluation of heparin, coumarin, or warfarin effect
CoaguChek PST	Boehringer Mannheim Corp.	
AvoSure Pro	Avocet Medical, Inc.	
Roche Diagnostics CoaguChek S Systems Test	Roche Diagnostics Corp.	

specialized tests (for example, cytogenetics, histopathology, histocompatibility, cytology, and other highly specialized tests) have been classified as high complexity.[16] The categorization of tests enables a laboratory to determine easily what level of regulation it will follow.[21,22] The intent is that testing environments not eligible for a certificate of waiver, and which do not conduct highly specialized testing, will be certified to perform moderate-complexity testing. The personnel, proficiency testing, patient test management, and quality control and assurance standards for moderate- and high-complexity tests are outlined below.

Personnel

Personnel standards are a significant differentiating element in the regulation of moderate- and high-complexity testing laboratories.[23] Both types of laboratories require a laboratory director, a technical consultant, a clinical consultant, and testing personnel. However, the education, training, and experience required for these positions differ. In addition, high-complexity laboratories are required to maintain technical supervisor and general supervisor positions.

Proficiency Testing

Each laboratory performing tests of moderate and high complexity must enroll in an approved proficiency testing program for each specialty or subspecialty for which it seeks certification.[24] In general, proficiency testing requires five challenges per testing and three testing events per year. Failure to attain an overall testing event score of at least 80% is unsatisfactory performance. Proficiency testing samples must be tested with the laboratory's regular patient workload, using routine testing methods, and by personnel who routinely perform testing.

Patient Test Management

Laboratories performing moderate-complexity or high-complexity testing must also employ and maintain a system that provides for proper patient preparation and proper specimen collection, identification, preservation, and processing.[25] This system must assure optimum patient specimen integrity and positive identification throughout the pretesting, testing, and posttesting processes and must meet the standards as they apply to the testing performed.

Quality Control

After December 31, 2000, laboratories performing either moderate- or high-complexity tests may, in general, meet quality control standards by following manufacturer's instructions when using a device cleared by the FDA as meeting CLIA requirements for quality control.[26] For other tests of moderate and high complexity, the regulations state specific quality control standards.

Quality Assurance

Finally, laboratories performing moderate-complexity or high-complexity testing must establish and follow written policies and procedures for a comprehensive quality assurance program that is designed to monitor and evaluate the ongoing and overall quality of the total testing process.[27] The laboratory's quality assurance program must evaluate the effectiveness of its policies and procedures; identify and correct problems; assure the accurate, reliable, and prompt reporting of tests results; and assure the adequacy and competency of the staff.

CONCLUSION

Currently, most pharmacy-based testing falls within the waived category and is exempt from extensive quality standards. However, given the importance of timely and accurate laboratory data in the provision of pharmaceutical care, it is likely that pharmacy-based laboratory testing will expand in breadth and scope.[28] Therefore, pharmacists need to be aware of the quality issues raised and addressed by CLIA 1988.

Although the detail is beyond the scope of this monograph, pharmacists should also be aware of other laws and regulations impacting pharmacy-based laboratory testing. Many states have their own laws regulating laboratory quality and professional competency.[15] In addition, there are Occupational Safety and Health Administration (OSHA) standards pertaining to laboratory operations.[29,30] Before engaging in laboratory testing pharmacists should be thoroughly familiar with all laboratory regulations.

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Clinical Pharmacist as Principal Investigator (ACCP)

American College of Clinical Pharmacy
Kansas City, Missouri, U.S.A.

INTRODUCTION

Research is critical to advancing the practice of pharmacy. Indeed, the last three decades contain many examples where seminal research papers authored by clinical pharmacists have advanced pharmacy care and improved patient outcomes. Whereas many clinical pharmacists have established strong research programs, there must be continued efforts to increase the number of highly competent pharmacist researchers by reducing barriers into a research career and improving the quality of research training programs. The American College of Clinical Pharmacy (ACCP) continues to receive inquiries regarding the requisites for a pharmacist to serve as the principal investigator (PI) for industry-sponsored research. This article summarizes Food and Drug Administration (FDA) policies regarding the pharmacist's ability to serve as PI on clinical drug research; presents a brief view on this issue from the perspective of the pharmaceutical industry; describes FDA regulations governing clinical research, and the PI's responsibilities in meeting those regulations; and provides advice to clinical pharmacists who desire to serve as PIs on clinical drug research sponsored by the pharmaceutical industry.

HISTORY OF CLINICAL PHARMACIST AS PRINCIPAL INVESTIGATOR

The ACCP's role as an advocate for the clinical pharmacist as PI began in 1983. At that time, there was generally a great deal of reluctance within the pharmaceutical industry to allow pharmacists to function as PIs. Some clinical pharmacists were successfully participating as PIs in industry-sponsored and FDA-regulated clinical research, whereas others were being told by some industry sponsors that they interpreted FDA regulations to allow only physicians to be PIs. To clarify this matter then-ACCP president Peter H. Vlasses, Pharm.D., wrote then-FDA Commissioner Arthur Hull Hayes, MD, regarding FDA regulations on the issue. Stuart L. Nightingale, MD, then-FDA Associate Commissioner for Health Affairs, responded by writing, "It has long been FDA policy to accept Doctors of Pharmacy as primary investigators of studies of investigational drugs within their areas of expertise." The FDA response noted that a person "licensed to diagnose and treat disease be officially associated with the study" as a coinvestigator (Fig. 1).[1] Subsequently, many clinical pharmacists used the correspondence to educate industry research sponsors and gain the ability to serve as PIs.

Some companies continued to have internal policies that required a physician to be the PI. Others interpreted the FDA letter to apply only to pharmacokinetic studies and not to clinical trials. To clarify the latter point, Dr. Vlasses again corresponded with the FDA. Dr. Nightingale responded, stating, "Doctors of Pharmacy may serve as clinical investigators for both clinical pharmacology studies and clinical trials of a drug provided they do so in conjunction with a person licensed to diagnose and treat disease," again emphasizing that a physician must be a subinvestigator to assess the patient and make medical decisions.[2] In 1990, correspondence from the FDA to the American Association of Colleges of Pharmacy reiterated that "pharmacists can serve as principal investigators in any clinical trial" (Fig. 2).

Fifteen years later, many clinical pharmacists have served and continue to serve as PIs in human trials. Nonetheless, it is important to emphasize that one's academic degree alone—whether MD or Pharm.D.—does not qualify the individual to serve as PI. The person's overall training and experience, complemented by their research environment, are integral to their designation as PI. As noted by Dr. Nightingale, the FDA may "reject any investigator as unsuitable as part of [the] review process" if their overall portfolio is insufficient to demonstrate that they possess the knowledge, skills, and

From *Pharmacotherapy* 2000, 20(5):599–608, with permission of the American College of Clinical Pharmacy.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006414

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 10 1983

Peter H. Vlasses, Pharm.D.
Associate Director, Clinical Pharmacology Unit
Thomas Jefferson University Hospital
11th and Walnut Streets
Philadelphia, PA 19107

Dear Dr. Vlasses:

Your letter of February 24,_1983 to Dr. Hayes has been referred to me for response. In that letter you posed the question whether Doctors of Pharmacy (Pharm.D.s)may serve as investigators in clinical pharmacological studies of investigational drugs. You noted that you have received varying interpretations of our regulations on this point from different manufacturers who sponsor clinical pharmacological studies.

It has long been FDA policy to accept Doctors of Pharmacy as primary investigators of studies of investigational drugs within their areas of expertise. Because such studies may require the diagnosis of disease and the recognition and treatment of- adverse reactions or other medical incidents occurring during the course of the study, we have required that a person licensed to diagnose and treat disease be officially associated with the study to be performed. This is ordinarily done by naming such an individual in item 6(f) of the Form FD-1572 as being responsible to the principal investigator of record. Alternatively, both the Doctor of Pharmacy and the licensed individual may sign the Form FD-1572 as co-investigators, having equal responsibility in the performance of the study in question.

I trust that this clarifies FDA policy on the matter.

Sincerely yours,

Stuart L. Nightingale, M.D.
Associate Commissioner for
Health Affairs

Fig. 1 1983 Response letter from the FDA addressing participation of clinical pharmacists as PIs.

experience needed to assume the significant responsibilities of PI.[2]

CURRENT INDUSTRY PERSPECTIVE

To better understand current industry policies regarding pharmacists as PIs, a short, informal survey was administered by telephone to a small number of pharmaceutical companies. Information was obtained from five companies and suggests that most companies do not have specific policies that exclude pharmacists from functioning as PIs. However, the general consensus was that pharmacists were used primarily for pharmacokinetic studies and not for other types of clinical trials. In most instances, the program manager or study team leader

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Original dated: April 3, 1990

American Association of Colleges of Pharmacy
Attention: Carl E. Trinca, Ph.D.
1426 Prince Street
Alexandria, Virginia 22314

Dear Dr. Trinca:

Your Letter of November 28, 1989, asked two questions about the qualifications for clinical investigators. Please excuse my delayed response.

You asked whether FDA would consider pharmacists, especially Pharm.D.'s with adequate training and experience eligible to be principal investigators in 1) pharmacokinetic studies and 2) clinical efficacy studies. This question has been addressed on a number occasions, beginning in 1980 with Dr. Marion Finkel, then director of the office of Scientific Evaluation (now called the Offices of Drug Evaluation I and II), and most recently in a memorandum (enclosed) from the Directors of the Offices of Drug Evaluation. In 1980 and at present, the conclusion is the same: pharmacists can serve as principal investigators in any clinical trial. Section 505(I) of the Food, Drug and Cosmetic Act requires that FDA assure that the investigational drug will be provided only to "experts qualified by training and experience to investigate" a new drug. Whether or not FDA will permit a particular pharmacist to be an investigator in a clinical study will be determined on a case by case basis, and may depend on the type of study (pharmacokinetic study, clinical efficacy study) proposed in the IND.

You also asked whether board certification is likely to become an important indicator of whether a person is qualified to be a principal investigator. Certainly, as boards become more widespread, and it becomes more and more probable that well-trained investigators will have then, lack of Boards will become more and more conspicuous. Nonetheless, the totality of the proposed investigator's experience will be considered and it is improbable that Boards will become necessary.

I hope this is helpful to you. If I can be of further assistance, please contact me.

Sincerely yours,

Carl Peck, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

ENCLOSURE

Fig. 2 1989 and 1990 Response letters from the FDA reiterating that clinical pharmacists can serve as PIs in clinical trials.

C

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 4, 1989

FROM: Director, Office of Drug Evaluation I, HFD-100
Director, Office of Drug Evaluation II, HFD-500

SUBJECT: Non-M.D.'s as Clinical Investigators and Monitors

TO: Division Directors

At the June 1, 1989 Division Director's Policy Meeting, one of the topics was FDA policy on qualifications of principal investigators. It was agreed that FDA policy should continue to be as stated in the July 16, 1980 memorandum from Dr. Finkel, but that the memo should be updated to reflect the wording of the IND Rewrite as follows:

Clinical Investigators

Qualified individuals who are not M.D.'s can participate in clinical trials either as principal investigators or sub-investigators provided that an M.D. or D.O., (or D.O.S. depending upon the study) is either a sub-investigator or is listed in the IND as an individual who will be responsible for drug administration and evaluation of patient safety.

Clinical Monitors

Qualified individuals who are not M.D.'s can serve as monitors of clinical trials provided that an M.D., D.O., or D.O.S. is involved in the review and evaluation of the ensuing clinical data and the adverse reactions.

Please remind division staff of the above policy.

Robert Temple, M.D.

James Bilstad, M.D.

Fig. 2 1989 and 1990 Response letters from the FDA reiterating that clinical pharmacists can serve as PIs in clinical trials (*Continued*).

makes the decision regarding which investigators to approach as PIs based on their overall qualifications. If a pharmacist can demonstrate their expertise in a therapeutic area (as outlined later), and their ability to enroll the required number of qualified subjects into the clinical trial within an established time period, it would appear that most pharmaceutical companies will allow a pharmacist to serve as the PI for a study.

If the contact at a particular company states that a pharmacist may not serve as a PI, it may be worth inquiring about this policy. It could be that the decision maker is unaware of FDA's policy regarding pharmacists as PIs. Such information could influence the decision of the study manager, especially if there is no company policy that precludes pharmacists from functioning as PIs.

Given the importance of investigator experience and qualifications to their designation as PI, the remainder of this article centers on the capabilities and responsibilities (including FDA regulations) needed to serve in this capacity.

FDA POLICIES, REGULATIONS, AND GUIDELINES FOR INVESTIGATORS

FDA's Role and Responsibilities

Investigations of new chemical entities and dosage forms in the United States are regulated by the FDA. A qualified PI must have a comprehensive understanding of FDA policies and regulations regarding the conduct of clinical trials and the use of an investigational new drug. The PI must also demonstrate their ability to consistently abide by these policies and regulations. The Center for Drug Evaluation and Research (CDER) monitors the clinical development of drugs, whereas the Center for Biologics Evaluation and Research (CBER) supervises the clinical development of biologics, including most biotechnology products. Regulations are designed so clinical trials can proceed with new compounds, but with adequate safeguards to protect the health and safety of study subjects in particular and the well-being of the American people in general. Society benefits from the availability of new medicines in a timely, cost-efficient manner, but there must be protection from unanticipated adverse reactions or impure compounds. Information about CDER and CBER can be obtained from their respective web sites: www.fda.gov/cder and www.fda.gov/cber. An excellent review of the new drug development process is found in the *CDER Handbook*, available from CDER's web site.

The document, "Guidance for industry: E6—Good Clinical Practice: Consolidated Guidance," was developed by the Expert Working Group (Efficacy) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance encompasses the ethical tenets of the Declaration of Helsinki, as well as good clinical practices within the European Union, Japan, Australia, Canada, the Nordic countries, and the World Health Organization. It also represents the FDA's current thinking on good clinical practices. This Good Clinical Practice (GCP) guidance establishes standards for all aspects of the conduct of clinical studies; seeks to provide assurance that the data and results of these studies are credible and accurate; and assures that the rights, integrity, and confidentiality of trial subjects are protected.

Investigators are defined in the GCP guidance as the persons responsible for the conduct of a clinical trial at a given site. If that trial is conducted by a team of individuals, the PI is the responsible team leader. Subinvestigators are individual team members designated and supervised by the PI to perform critical trial-related procedures and/or make important study-related decisions. In the same document, a clinical trial or study is defined as any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or pharmacodynamic effects of an investigational product.

FDA Regulations and Policies for Investigators

The FDA's overwhelming principle of clinical investigation is that the rights, safety, and well-being of trial subjects should prevail over the interests of science and society. The medical care given to, and medical decisions made on behalf of, study subjects must always be the responsibility of a qualified physician (or when appropriate, a qualified dentist). However, responsibility for medical care is not the same thing as responsibility for conduct of the clinical trial.

All investigational new drug research must have an FDA-approved study protocol. In the case of research supported by the pharmaceutical industry, the sponsor (company) designs the trial to generate safety and efficacy data needed to support appropriate labeling claims for the new product. Frequently, sponsors consult with expert scientists to assure that the study has scientific and clinical merit. Investigators are frequently asked for suggestions to improve the protocol, but the decisions on study design rest with the sponsor and FDA. The sponsor identifies and recruits investigators, who then have the right to agree or decline to participate in the study. The PI must submit their credentials on an FDA Form 1572 for approval by the sponsor and FDA.

Before a trial is initiated, the FDA requires the protocol to be approved by an institutional review board (IRB) or independent ethics committee. The IRB must address the investigator's qualifications to conduct the proposed trial. It does so by reviewing a current curriculum vitae and other relevant documentation. Pharmacists seeking approval by an IRB must demonstrate experience in the conduct of clinical trials similar to the one for which approval is being sought. The investigator provides information to the IRB, but does not participate in the committee's deliberations.

The FDA requires each PI to comply with GCP and other applicable regulatory requirements, permit monitoring and audits by the sponsor and the FDA, and maintain a

list of qualified persons to whom the investigator has delegated significant trial-related duties. A qualified PI must show familiarity with the compound to be studied and demonstrate adequate resources to conduct the trial. This includes being able to recruit in a timely manner an adequate number of subjects that meet protocol-defined entry criteria, have an adequate number of qualified staff, and have necessary facilities available for the anticipated duration of the trial. The PI is responsible for assuring that all staff assisting in the trial are well informed about the protocol, the investigational drug, and their duties with regard to the trial.

RESPONSIBILITIES OF INVESTIGATOR

General Responsibilities

A PI is responsible for the conduct of a scientific investigation in accordance with study methodology, a signed investigator agreement or contract with the sponsor (if applicable), and any federal or state rules and regulations regarding performance of a study using human subjects. The underlying premise is to protect the rights, safety, and welfare of subjects under the investigator's care and to control the distribution and use of drugs under study.

As mentioned, prior to initiation of the trial, the investigator needs IRB approval, an approved subject informed consent form, and approved subject recruitment procedures. The investigator must provide the IRB with current copies of the Investigator's Brochure for each investigational drug before beginning the trial, and must provide updated copies if the Investigator's Brochure is revised during the conduct of the study. The PI is accountable for obtaining written informed consent from all subjects. In life-threatening situations necessitating the use of the study drug, the IRB may approve other methods of obtaining informed consent. Regardless, an investigator may only obtain consent after a subject or their legally authorized representative has had sufficient opportunity to consider the risks and benefits of participation without coercion or unreasonable influence.

During the clinical study, a qualified physician or dentist, as appropriate, who is at least a subinvestigator must be responsible for all trial-related medical (or dental) decisions. The PI and the institution must ensure that adequate medical care is provided to subjects for any adverse events related to the trial. Intercurrent illnesses that are detected during the course of the study must be noted and the subject informed. If agreeable to the study subject, the PI is also responsible for informing their primary physician about their participation in the trial. The investigator should make every effort to determine the reason for subject withdrawal from the trial, while being respectful of the subject's rights to withdraw without explanation.

During the performance of the study, the investigator must maintain adequate documentation of study activities and must promptly report any deviations from the protocol to both the IRB and study sponsor. Any changes to the protocol, all adverse drug reactions that are both serious and unexpected, and any new information that may affect adversely the safety of the subjects or their willingness to participate in the clinical trial must be promptly reported to the IRB. Substantive changes to the protocol must receive IRB approval. Investigators must also submit progress reports to the IRB at least annually; sponsors will usually request more frequent progress reports.

Investigator Record Keeping

The PI is responsible for maintaining records associated with the clinical study. These include case histories designed to record all observations or other pertinent data on each enrolled subject, independent of whether the subject received active treatment. Data for each trial subject is normally recorded on a case report form provided by the sponsor. The sponsor may also require study data to be recorded in a source document (patient chart). It is the responsibility of the PI to assure that the forms are filled out with the correct information and according to guidelines established by the sponsor.

Study drugs, whether investigational or commercially available, must be controlled and accounted for, and may only be administered to study subjects who have provided informed consent and who are under the supervised care of a trial investigator. Accordingly, a drug accountability log must be kept up to date and accurate. The log should record the disposition of the drug, including dates, quantity, and use by subjects. Study drugs must be secured in a locked storage area until destroyed, properly disposed of, or returned to the study sponsor.

Case histories, drug accountability logs, and all correspondence associated with the study must be secured and kept for 2 years after the marketing application is approved by the FDA. If no such application is filed, or if the application is not approved by FDA, these records must be retained for 2 years after the investigation is discontinued and the FDA is notified. It is advisable that records from clinical trials supported by grants from academic, government, or voluntary health organizations also be maintained for this same time period, unless

otherwise specified by the agency. If the study is part of an international clinical trial, or if specified by the sponsor, the PI may be required to keep a patient list with study drug assignments for 15 years after the conclusion of the trial.

In the case of premature termination or suspension of the trial, the investigator must promptly inform trial subjects, assure appropriate follow up and treatment if required, and inform the IRB and regulatory authorities as appropriate. Similarly, when a trial is completed under normal conditions, the investigator must file final reports with the sponsor and inform the institution, the IRB, and regulatory authorities (as appropriate) that the trial is completed.

Finally, all records must be available on request from the FDA or study sponsor within a reasonable time. The authorized representative from the sponsor or FDA must be allowed to copy documents with patient identifiers omitted and must be provided sufficient time to verify records associated with the conduct of the study. Investigators are not required to provide the names of subjects unless the records of a specific individual require more intensive examination related to an adverse event, or there is suspicion that the records are falsified. Frequent or deliberate falsification of records may lead to disqualification of a PI to conduct future clinical studies, as well as potential criminal or civil prosecution.

ADVICE TO PHARMACIST INVESTIGATORS

Before agreeing to participate in a sponsored clinical study, the PI should answer a number of questions about the logistics of conducting the protocol at their site and

Study Logistics: Assessment and Plan

I. Administrative Plan

a. Institutional approvals

- Determine if contract and investigator agreement regarding responsibilities, intellectual property, confidentiality, indemnification, data ownership, and publication rights are acceptable to your institution.
- Is approval needed from other institutional regulatory committees? This might include radiation safety or biohazards committees.
- If the investigator is receiving funding for the study, how will these monies be handled within the institution? How much time is needed by the institution to set up the payment infrastructure?
- Does the institution have an overhead charge for government, voluntary organizations, or corporate studies? Will the PI have access to these excess monies after the study is complete?

b. IRB Logistics

- How often does the IRB meet?
- What are the requirements for submission of an IRB study packet?
- Take time to talk with the IRB personnel to understand the complete review process before submission. This will save time and prevent anxiety.

II. Operational Plan

a. Physical Resources

- Where will the study be conducted?
- Does the study require an ambulatory care clinic, a clinical research center, or will patients need to be hospitalized? Use of these facilities will need to be negotiated with the institution.
- What types of tests are necessary? Laboratory testing, radiography, nuclear medicine, physical therapy, or other services should be contacted about the proper method of sending samples, ordering tests, and paying for services. Some institutions may offer research discounts for tests.
- How will the test data be collected? If study data are recorded in patient's charts or institution computers, will the investigator have access to these charts after the patient is discharged or the study is complete? Verification of records may occur several years after a study is complete: therefore, access to records must be confirmed prior to starting the study.

b. Human Resources

- Determine need for coinvestigator(s) and outline their roles.
- Determine need for study coordinator and responsibilities.
- Assign responsibilities and establish deadlines and milestones for all personnel closely related to the study (e.g., study coordinator, coinvestigators, research fellows).
- Visit with the nursing staff of the faculty to avoid unnecessary delays in starting the protocol.

Fig. 3 Recommended guidelines for assessment and planning of study logistics before conducting a study protocol.

should create a sound plan for study implementation. To do so, the PI must understand the structure that governs research support and funding within their institution to avoid technical or financial problems during or after the study. Addressing the issues and questions identified in Fig. 3 before starting the protocol will help in conducting a timely and successful study.

Once the PI agrees to participate in a clinical study, its successful initiation requires that the PI have the following: 1) regulatory approval from the sponsor and FDA [if the study requires an Investigational New Drug application (IND)] through submission of FDA Form 1572; 2) legal approval by the investigator's institution of their contract and agreement with the study sponsor that details the scope of work, data ownership, intellectual property, publication rights, indemnification, and confidentiality; 3) budget approval from the institution's grants and contracts office; and 4) IRB approval of the study protocol and informed consent procedure. Investigators are encouraged to complete this process within 45 days to be competitive with other research service providers. Two major pitfalls of which investigators must be aware involve budgetary planning and ownership of data. Poor planning in either regard can jeopardize the PI's ability to complete the project and disseminate new scholarly information (data ownership and publication).

Budget

An essential component to any clinical trial is a well-planned budget that accounts for all resources and project costs. In many instances, the investigator will be competing with other sites for the research contract. Therefore, the budget must cover costs, provide a reasonable incentive to the investigative team, and be competitive in the marketplace. All direct and indirect costs must be identified and negotiated among the PI, their institution, and the sponsor before initiating the study. In doing so, the PI will assure that the study can be completed and that useful information will be provided to all parties. The most commonly made error on the part of the PI is to underestimate study costs because of failure to identify all resources required to complete the study or to underestimate their true costs. As a result, the study may not be completed and/or the investigator's research program will not benefit from residual funds remaining in the contract budget after study completion. These monies can usually be used to sustain the infrastructure of the clinical facility or laboratory.

To avoid these problems, it is recommended that the PI consult with internal support staff knowledgeable in budget design and institutional overhead. Most academic centers have a clinical trials office that can help construct a comprehensive budget and provide accurate estimates on all institutional costs. If such an office does not exist, one can contact the campus grants and contract office or a peer group with experience in conducting clinical studies in the investigator's setting. Many times, the sponsor will generate a proposed budget for a trial based on usual and customary costs. These budgets are typically very complete, although they can be modified through negotiation with the sponsor if the increased costs can be justified.

The investigator must remember that most clinical trial budgets derived in academic settings must conform to the Health Care Finance Administration's corporate compliance regulations. The regulations state that federal health care payers are responsible for covering only those resources that are medically necessary for the care of a patient. Taxpayer dollars (e.g., Medicare) cannot be used to subsidize purely research activities, or for experimental or unproven medical therapies.

Research-related costs are derived from the investigator's hospital or clinic, laboratory testing or analysis, or through contractual arrangements with other laboratories. In addition, there may be patient recruitment costs such as advertising, patient expense reimbursement (parking and transportation), and participation honoraria. Research resources usually include equipment, supplies, and salary support for the PI and associated personnel. Salary support for the PI and other study personnel generally has the greatest flexibility and provides an opportunity to generate residual funds to support the PI's overall research program.

From a financial perspective, the PI's primary objective when entering into a research contract is to complete the study successfully at or below the requested budget. The residual funds that result are often placed into a development fund on behalf of the PI and can be used at the investigator's discretion to support other research projects. Although this objective is perfectly reasonable, study expenditures and allocation of funds must be thoroughly documented throughout the course of the investigation. Accurate records are often requested by the sponsor, and occasionally by outside auditing agencies, and are essential to maintaining a productive clinical research program.

Publication Rights

A clear understanding of study responsibilities and publication rights should be negotiated among the PI, their collaborators, the study sponsor, and the investigator's institution prior to initiating the trial. It is best to involve all parties as early as possible and to negotiate all aspects before agreeing to the study contract. In this

regard, most academic institutions have a liaison within their research office for business and industry contracts that can assist the investigator to organize and expedite this process. It should be the mission of the PI and liaison to ensure the investigator's freedom to publish the research findings. This includes the right to publish negative results. In doing so, the investigator has ownership of the data, materials, and documentation, but the sponsor receives copies and is given the right to use the materials for certain purposes. In general, sponsoring companies are aware of the research mission of academic institutions and are flexible in the negotiation process.

Any terms and conditions that restrict the publication rights of the investigator are usually reserved for the protection of the sponsor's patent rights that may arise from the contracted work. In this situation, the sponsor is granted a specified period of time (e.g., 30 days) to review the proposed publication before its submission and is provided the right to withhold publication for a specified time period (preferably no more than 90 days), pending submission of a patent application. It is always important to identify in the contract that the investigator and supporting institution will not allow any publication restriction in such a way as to impede the academic progress of a graduate student or research fellow if these individuals were integrally involved with the study. If any publication restrictions are accepted on behalf of the PI and students, they should be agreed to in contractual form before initiating the trial.

Finally, in single-center trials, the order in which authors are listed on the publication is usually the responsibility of the investigators involved with the study. Therefore, choose collaborators wisely. In multicenter trials, the publication rights of individual investigators and the expeditious publication of results become more complex. In this case, the investigator must accept the risk of sacrificing both ownership and timely publication of research findings despite a priori agreements with the study sponsor. Many sponsors choose authors for multicenter studies based on the reputation of those authors in the area of study or based on the number of subjects that their site enrolled in the trial. Thus, younger investigators, or investigators from smaller study sites, may find themselves excluded from the publication process.

QUALIFICATIONS OF A SUCCESSFUL PRINCIPAL INVESTIGATOR

It is important to emphasize that even though pharmacists may serve as PIs for industry-sponsored clinical research, the mere fact that a person is a pharmacist does not automatically qualify them to serve in this capacity. An investigator must establish their qualifications and credentials before they can reasonably expect an industry sponsor to trust them to serve as PI.

Experience

A PI typically evolves from a subinvestigator. Although we may consider our research trainees ready to assume a career as an independent scientist on completion of their program, 2–3 years of postdoctoral research training may not realistically provide them with sufficient experience. For example, a qualified PI should have relevant clinical experience in the proposed study population, usually gained from several years of experience in patient care. However, this patient care experience alone does not automatically qualify someone as an investigator. Understanding and demonstrating competence in clinical research practices, demonstrated compliance with research regulations and data management, and the ability to create and manage an investigational plan through task delegation must also be considered.

Local Resources

The PI must demonstrate that they have acceptable and adequate resources available to manage the trial, including access to or control over clinical space such as beds and clinics, if needed. The facilities must have appropriate staff and other resources to conduct the research and to protect the subjects. Specialized testing equipment needed for the experiments must be available, either in the form of general testing purchased from the health system or in the PI's own laboratory.

Command of Research Process

The PI must be knowledgeable about the multiple processes needed to manage a clinical study, including the medical records system, investigational drug pharmacy, clinical laboratory, other clinical departments necessary to support the project, the institutional review and approval processes, budget and financial management, and contract initiation.

Human Resources

The PI must generally demonstrate the existence of a qualified research and clinic staff, as appropriate. Very few studies can be managed by a single individual, and PIs have many other responsibilities. Thus, a successful PI must be able to delegate responsibility and hold other people accountable.

Access to Patients

An industry sponsor is very keen on knowing that the PI can enroll and complete the number of patients required or requested in a contractual agreement. The sponsor's research and business plans are entirely dependent on productive and enthusiastic PIs and study coordinators. Some pharmacists may be limited in identifying and enrolling study subjects by having insufficient direct professional responsibility for patient management, or by having access to patients only through physicians. To overcome this potential limitation, the PI should demonstrate the ability to recruit qualified patients through advertising or similar means.

Audits

Proof of competence is an increasing demand. Principal investigators must be able to show they have the ability to perform in compliance with research regulations through outside audits of process and product. The ability to demonstrate this competence through a portfolio of projects, meeting contractual obligations, and generating good data will serve as an effective reference for obtaining recognition as a PI.

Local Leadership and Environment

The leadership of local pharmacy organizations (e.g., colleges of pharmacy, departments of pharmacy, academic medical centers) must be supportive and encouraging, must remove barriers to successful research, and must encourage multidisciplinary collaboration permitting pharmacists to reach their potential. These local leaders can play a great role in promoting their new members into a career in clinical research and providing an environment conducive to this endeavor.

CONCLUSION

Clearly, an individual's academic degree alone does not imply that they possess adequate skills and experience to serve as a PI. The FDA and pharmaceutical industry are aware that pharmacists can be excellent investigators. However, as is the case with any PI, the pharmacist must have a proven track record that demonstrates successful clinical trial management. As outlined previously, serving as PI is an arduous task. There are many responsibilities that require the investigator to adhere to local institution, industry, regulatory, and human assurance guidelines and policies. Adherence to these guidelines requires extensive documentation. In addition, the investigator must enroll patients, execute the protocol, and meticulously collect and report patient data. Given these responsibilities, it is understandable why the industry sponsor needs to select PIs carefully. It is the opinion of the ACCP that the pharmaceutical industry should support policies and practices that use clinical pharmacists as PIs, as long as the pharmacist is an experienced clinical researcher with documented credentials, has the adequate institutional infrastructure and support, and has access to the required patient population.

ACKNOWLEDGMENTS

This document was prepared by the 1999 Research Affairs Committee: Myryam Bayat, Pharm.D.; Lisa Davis, Pharm.D, FCCP; Darren Knoell, Pharm.D.; Joan Korth-Bradley, Ph.D., Pharm.D., FCCP; Mark Munger, Pharm.D., FCCP; Mark Shaefer, Pharm.D., FCCP; Peter Vlasses, Pharm.D., FCCP; Daniel Wermeling, Pharm.D.; Chair: Michael Ujhelyi, Pharm.D., FCCP. Endorsed by the ACCP Board of Regents on January 17, 2000.

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Clinical Pharmacist, Evaluation of a (ACCP)

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INTRODUCTION

As the focus of the standard of pharmacy practice moves from dispensing products to optimizing patient outcomes, so must the standards for evaluating pharmacists' performance. The goal of pharmacy practice is to deliver pharmaceutical care to patients. Opportunities are expanding for clinical pharmacists to have direct responsibility for patient well-being by ensuring optimum outcomes of therapy in various health care environments. In 1989 the Clinical Practice Affairs Committee of the American College of Clinical Pharmacy (ACCP) developed practice guidelines for pharmacotherapy specialists.[1] To complement the guidelines, the committee developed a template for evaluating clinical pharmacists, a tool for assessing the extent to which clinical pharmacists' performance meets predefined practice standards. The template can be adapted to meet site-specific requirements.

TEMPLATE DEVELOPMENT

The core materials for the development of this template (Appendix) were the ACCP practice guidelines for pharmacotherapy specialists,[1] the eight steps of the drug use process,[2] and the American Society of Hospital Pharmacists' technical assistance bulletin on assessment of departmental directions for clinical practice in pharmacy.[3] Initially, the standards, criteria for meeting the standards, and methods of assessment were developed for each drug use process step. These reflected important activities in drug distribution and outcomes for patient care. Subsequently, standards, criteria, and assessment methods for evaluating clinical activities outside of the drug use process were added.

The initial draft of the template was evaluated at four hospitals under the direction of clinical pharmacy administrators. The evaluators noted several advantages of the template; for example, it could lead to quality clinical pharmacy services universally, help to justify the development of clinical pharmacy programs, and improve efficiency by minimizing the need for different evaluation tools for every institution or practice site. In addition, the standards could be incorporated into policy and procedure manuals, if desired.

However, the first draft had several disadvantages, including its complexity, the time required to complete it, its general rather than specific focus, the assigned percentages for performance standards, and the lack of space for documenting findings or adding written comments. Opinions varied concerning appropriate predefined standards. Some believed that all standards should be met 100% of the time, whereas others believed such expectations were unrealistic. The latter group argued that standards must reflect pharmacists' level of education and training, as well as individual institutions' expectations and resources. In addition, certain sections appeared to be redundant. The evaluators recommended that sections on dispensing and administrative activities be deleted, and that the template evaluate either clinical pharmacists or clinical pharmacy services, but not both. Also, certain assumptions regarding pharmacists' activities were simply not true for every clinical pharmacist; for example, attending medical rounds and performing physical assessments.

Based on this feedback, a revised template that evaluates only clinical pharmacists was developed and tested at seven institutions. The revised version did not define standards, allowing it to be adapted to each institution's standards and to the expected performance of the clinical pharmacist. Response to the revised template was excellent; additional recommendations for revision as well as instructions for personalizing the tool were incorporated into the final template.

ASSESSMENT METHODS

Assessment methods describe how the evaluator will collect data to evaluate performance for each criterion. Examples from the template are review of selected monitoring forms, chart notations, or orders; review of adverse drug reaction or incidence reports; review of in-

From *Pharmacotherapy* 1993, 13(6):661–667, with permission of the American College of Clinical Pharmacy.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006413

service evaluations or formal evaluation of presentations; and comparison of monitoring forms with patient charts. Other methods that could be used are physician evaluations, formulary decisions, evaluations of patient profiles, acceptance of clinical pharmacotherapy suggestions, evaluation of patient response, peer review, documentation in patients' charts, patient consultation logs, drug use evaluation records, and patient satisfaction surveys.

Appendix. Template for the Evaluation of a Clinical Pharmacist[a]

The template for evaluating a clinical pharmacist is for use by clinical pharmacy managers. It should be revised to meet specific institutional requirements for clinical pharmacy practice prior to implementation. Specific numbers and types of patient interventions should be included and reviewed to reflect accurately the individual clinical pharmacist's practice responsibilities.

This template represents only part of the evaluation process. A letter or form should be submitted by an attending physician that addresses specific contributions to individual patient care by the practicing clinical pharmacist. Other health professionals (i.e., nurses, physician assistants, etc.) who interact daily with the individual clinical pharmacist should participate in the annual evaluation process.

Date _____ Clinical Pharmacist _____ Supervisor _____

Instructions for Using the Template

The template for the evaluation of a clinical pharmacist was designed to be flexible and adaptable to a particular institution, clinical pharmacy service, and clinical pharmacist. The administrator (evaluator) and clinical pharmacist for whom it will be used should work together to modify and individualize the tool as necessary. Such communication is vital to its effective use. The pharmacist being evaluated must be an active participant in the process.

Step 1.

Review the performance appraisal requirements of the institution or practice site. Guidelines or other requirements for employee evaluations should be incorporated into the instrument.

Step 2.

Review the criteria within each section of the template and delete or add criteria as necessary to reflect activities performed at the practice site. The template can be tailored to an individual pharmacist's activities or to the patient care activities of the entire clinical staff.

Step 3.

Determine the standards (thresholds) for each criterion. These can reflect universal standards established for the institution's clinical program or expectations of an individual clinical pharmacist. The standards establish departmental expectations regarding the extent to which the individual performs each criterion. The expectations should be objective and expressed clearly. Some sites may decide not to use standards; however, they should be cautioned that objective evaluation may be difficult without standards.

Step 4.

Review the assessment methods for each criterion and tailor them to the practice site, the evaluator, and the pharmacist being evaluated. No matter who completes the performance assessment, the methods used must be discussed, documented, and understood by the evaluator and the person being evaluated. Methods such as chart review and direct observation are time consuming but yield useful information.

Step 5.

Use the individualized evaluation tool to identify areas for improvement and opportunities for professional growth. These can be noted in the "comments" section of the template.

I. Perception of the Need for a Drug

Criteria	Assessment Method	Standard	Meets Criteria	Comments
Interviews patient to obtain a complete list of prescription and OTC drug use, response, and toxicity.	Reliability testing between pharmacist and supervisor			
Actively participates in medical rounds to obtain pertinent information required to determine necessity of drug therapy.	Joint rounds with supervisor and evaluation by physicians			
Determines accurate problem list.	Comparison of monitoring form and medical chart			
Consults physicians about drugs without indications.	Review of selected patient-monitoring forms and medical charts			
Obtains pertinent information required to determine the necessity of drug therapy.	Discussion of selected patients and therapy with manager			

II. Selection of a Specific Drug

Criteria	Assessment Method	Standard	Meets Criteria	Comments
Assures the drug of choice for a particular patient condition is ordered.	Review of 25 patient-monitoring forms, chart notations, or orders			
Assures there are no contraindications for selected drug products (e.g., allergy, history of severe adverse reaction).	Review of selected monitoring forms and medical charts			
Selects drug products that are effective, are cost-beneficial, and promote patient compliance.	Review of selected monitoring forms and medical charts			
Participates in patient care rounds to provide input into drug selection.	Review of documentation on activity reports or productivity reports			
Actively participates in writing or evaluating drug therapy protocols.	Review of accuracy of standing protocols for drug therapy			
Suggests appropriate therapeutic alternatives for nonformulary drugs.	Order review with therapeutic and cost saving outcome evaluation			
Suggests nondrug therapy when appropriate.	Review of selected monitoring forms or medical charts			

C

III. Evaluation and Review of Drug Regimen

Criteria	Assessment Method	Standard	Meets Criteria	Comments
Determines drug therapy compliance with protocols, guidelines, or recommendations.	Review of selected patient-monitoring forms, chart notations, or orders			
Recommends drug discontinuation or dosage alteration when indicated.	Review of selected monitoring forms and medical charts			
Identifies potentially significant drug-drug, -food, -laboratory, and -disease interactions.	Review of selected monitoring forms and medical charts			
Communicates clinically relevant interactions with therapeutic alternatives to health care practitioners.	Review of selected monitoring forms and medical charts			
Obtains and uses clinical laboratory data to evaluate appropriateness of drug product selection and/or dosing regimen.	Review of selected monitoring forms, medical charts, and orders			
Adjusts drug therapy according to changes in concomitant therapy or the patient's condition.	Review of selected monitoring forms or selected patient charts for documentation			
Provides pharmacokinetic consultation for agents requiring such monitoring.	Review of selected patient-monitoring forms or selected patient charts for documentation			
Provides and evaluates drug therapy orders for appropriateness of dosage, route, interval, schedule, and duration throughout patient's hospital course.	Review of selected monitoring forms, medical charts, and orders			

IV. Monitoring Effects of Drug Therapy

Criteria	Assessment Method	Standard	Meets Criteria	Comments
Independently evaluates patient response to drug therapy.	Review of selected patient-monitoring forms, chart notations, or orders			
Participates in patient care rounds to provide input into the monitoring of drug therapy.	Review of documentation on activity reports or productivity reports			
Assures compliance with adverse drug reaction-reporting programs or medication error-reporting programs.	Review of adverse drug reaction or incident reports			
Records recommendations, interventions, or other appropriate activity in the medical record or appropriate activity report.	Review of selected medical charts or activity reports			

V. Education

Criteria	Assessment Method	Standard	Meets Criteria	Comments
Provides drug education and counsels patients on appropriate drug use and storage.	Review of selected patient-monitoring forms or chart notations			
Provides written information for appropriate drug products.	Review of selected patient-monitoring forms or chart notations			
Provides educational presentations to pharmacy staff, students, and other health care professionals.	Review of inservice presentations, evaluations, and/or scores on post-test evaluations			

VI. Evaluation of Drug Usage and Therapy

Criteria	Assessment Method	Standard	Meets Criteria	Comments
Employs drug usage evaluation information to alter therapy effectively.	Review of developed guidelines or drug therapy protocols			
Participates in drug use evaluation programs.	Review of selected patient-monitoring forms or chart notations			
Participates in research activities.	Review of selected protocols			

VII. Information Retrieval

Criteria	Assessment Method	Standard	Meets Criteria	Comments
Provides complete and accurate information.	Supervisor review; recipient evaluation			
Effectively communicates information in a timely manner to requester.	Supervisor review; recipient evaluation			

C

VIII. Committee Involvement

Criteria	Assessment Method	Standard	Meets Criteria	Comments
Contributes to department, hospital, or pharmacy committees.	Evaluation of meeting minutes; assessment of committee members			
Actively participates as a member or chairperson of hospital committees.	Evaluation of meeting minutes			

IX. Miscellaneous Activities

Criteria	Assessment Method	Standard	Meets Criteria	Comments
Participates in local, state, national, or international pharmacy organizations.	Organization membership, committee membership			

Comments_____

[a]This template may be photocopied and used for evaluating clinical pharmacists.

SUMMARY

Pharmacists are expected to deliver pharmaceutical care, that is, to accept responsibility for patients' well-being by ensuring optimum outcomes of drug therapy. Therefore, their performance must be evaluated based on this expectation. The template should be a useful tool for assessing the extent to which clinical pharmacists' performance meets predefined practice standards. Its adaptability will allow it to meet site-and pharmacist-specific requirements for performance appraisal. The evaluator and clinical pharmacist should work together to establish a priori percentage standards.

ACKNOWLEDGMENTS

The committee gratefully acknowledges the following institutions and persons who assisted in the review process: Patricia Hudgens, Medical University of South Carolina, Charleston, SC; Donald Kendzierski, University of Illinois at Chicago, Chicago, IL; Marsha A. Raebel, Scott and White Hospital, Temple, TX; Barbara Zarowitz, Henry Ford Hospital, Detroit, MI; Christine Rudd, Duke University Medical Center, Durham, NC; Beth Noer and Glen Schumock, University of Illinois at Chicago, Chicago, IL; Mary Anne Koda-Kimble, University of California, San Francisco, CA; Terri Graves Davidson, Emory University, Atlanta, GA; Louis Pagliaro, University of Alberta, Edmonton, Alberta, Canada; and Katherine Michael, Medical University of South Carolina, Charleston, SC.

This document was written by the following subcommittee of the 1989–1990, 1990–1991, and 1991–1992 ACCP Clinical Practice Affairs Committees: Mary Beth O'Connell, Pharm.D., FCCP, FASHP, Co-Chair 1991–1992; Christine Rudd, Pharm.D., FCCP, FASHP, Chair 1991–1992; Glen Schumock, Pharm.D.; Karen E. Bertch, Pharm.D.; Carl A. Hemstrom, Pharm.D.; and Marsha A. Raebel, PharmD, FCCP, BCPS, Board liaison. Other members of the 1989–1990 ACCP Clinical Practice Affairs Committee were Barry L. Carter, Pharm.D., FCCP, BCPS, Chair, 1989–1991; Michael W. Jann, Pharm.D.; W. Francis Lam, Pharm.D.; Milap C. Nahata, Pharm.D., FCCP; Douglas Anthony Powers, Pharm.D.; Anthony E. Ranno, Pharm.D.; and Nathan J. Schultz, Pharm.D.. Members of the 1990–1991 ACCP Clinical Practice Affairs Committee not mentioned above were Ryon Adams, Pharm.D.; Richard Berchou, Pharm.D.; G. Dennis Clifton, Pharm.D.; Joseph F. Dasta, MS, FCCP; Terri Graves Davidson, Pharm.D.; Donald Kendzierski, Pharm.D.; Edward Krenzelok, Pharm.D.; Bruce Kreter, Pharm.D.; Veronica Moriarty, Pharm.D.; Louis Pagliaro, Pharm.D.; Richard Ptachcinski, Pharm.D., FCCP; and Dominic Solimando Jr., Pharm.D. Members of the ACCP 1991–1992 Clinical Practice Affairs Committee not mentioned above were Daniel Buffington, Pharm.D.; Lea Ann Hansen, Pharm.D.; Kim Kelly, Pharm.D., FCCP; Gary Matzke, Pharm.D., FCP, FCCP; Katherine A. Michael, Pharm.D.; Beth Noer, Pharm.D.; Andrew T. Pennell, Pharm.D.; Dana Reid, Pharm.D.; and Joseph Tami, Pharm.D.. Staff editor: Toni Sumpter, Pharm.D. Approved by the Board of Regents on July 20, 1993.

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Clinical Pharmacokinetics Specialty Practice

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INTRODUCTION

Clinical pharmacokinetics involves applying pharmacokinetic principles to determining optimal dosage regimens of specific drugs for specific patients to maximize pharmacotherapeutic effects and minimize toxic effects.[1] The birth of clinical pharmacokinetics as a discipline was spurred on by an increasing awareness of concentration–response relationships and knowledge of pharmacokinetic characteristics of various drugs, the advent of computerization, and advancements in analytical technology.[2] Therapeutic drug monitoring is an important aspect of clinical pharmacokinetics that has helped many pharmacists enter the clinical arena. Clinical pharmacokinetics emerged as a specialty pharmacy practice in the late 1960s and early 1970s to provide clinical pharmacokinetic consultation or dosing service.

Initially, many pharmacokinetics services were centralized programs with only specialists in pharmacokinetics providing these services.[3] The more recent advent of pharmaceutical care, however, has led to more integrated approaches such that clinical pharmacokinetic monitoring is becoming a fundamental responsibility of *all* pharmacists providing pharmaceutical care.[1,3] As such, most pharmacokinetics services are no longer centralized or stand-alone programs. However, various practice and research opportunities still exist for pharmacists with specialized education, training, or experience in clinical pharmacokinetics. These opportunities are outlined following a review of the specialty pharmacy practice since the 1980s.

CLINICAL PHARMACY EXPERIENCES AND OPPORTUNITIES

In 1994, Howard et al.[4] published the results of a survey mailed to Veterans Administration (VA) medical centers in the United States ($n = 160$, with 93% return rate) to assess the provision of pharmacokinetics services. Survey results indicated that 104 (70%) of the respondents provided pharmacokinetics services. Of the remaining 30% who did not, almost two-thirds planned to begin one in the future. Ninety-eight (94%) of the existing pharmacokinetics services were considered to be formally recognized in that they were approved by the Pharmacy and Therapeutics Committee, offered consultation on request, or had a contact person for serum drug concentration evaluations. Aminoglycosides, vancomycin, and theophylline were the most frequently monitored drugs. Selected characteristics (i.e., bed capacity, geographic region, pharmacy chief's highest degree, pharmacy residency, and teaching affiliation) were used to evaluate whether differences existed between VA medical centers with or without each characteristic. Medical centers with a pharmacy residency program were more likely to have a pharmacokinetics service compared with those without a residency program ($p<0.02$). Differences among geographic regions also were significant ($p<0.01$), with the following percentage of respondents having pharmacokinetics services: 51 (eastern); 77 (central); 82 (southern); 81 (western); 0 (unknown).[4]

In 1996, Murphy et al.[3] published the results of their national survey of hospital-based pharmacokinetics services. Altogether, 252 questionnaires were mailed to all respondents of the 1994 American Society of Health-System Pharmacists (ASHP) national survey of hospital-based pharmaceutical services[5] who indicated that their institution provided pharmacokinetics services. The response rate was 42.1% ($n=106$); however, only 98 surveys had complete data thus yielding a net response rate of 40.2%.[3] Aminoglycosides were the main focus ($60.8 \pm 27.7\%$ of total) of pharmacokinetic consultations, followed by vancomycin ($21.1 \pm 18.3\%$), theophylline ($4.6 \pm 7.4\%$), other ($3.6 \pm 16.0\%$), warfarin ($3.1 \pm 11.1\%$), digoxin ($2.2 \pm 6.1\%$), phenytoin ($1.2 \pm 3.0\%$), lithium

(0.9 ± 5.2%), carbamazepine (0.6 ± 3.4%), valproic acid (0.5 ± 3.0%), procainamide or N-acetylprocainamide (0.2 ± 0.9%), phenobarbital (0.2 ± 0.8%), caffeine (0.1 ± 0.7%), quinidine (0.1 ± 0.6%), cyclosporine (0.1 ± 0.4%), ethosuximide (0.02 ± 0.1%), and methotrexate (0.02 ± 0.1). Pharmacokinetics services were paid primarily through the pharmacy budget (74.5 ± 43.6%), although 15.8 ± 36.5% billed the patient for the consultation via a pharmacy number. A disappointingly high number [i.e., 60 (61.2%)] of institutions providing pharmacokinetic consultations did not counsel patients receiving the service, although 12 (12.2%) provided educational materials to patients and 30 (30.6%) provided patients with individual instruction by the pharmacist or other health care professional. The survey showed that pharmacists, mostly staff pharmacists, spent on average of 19 hours per week providing pharmacokinetics services.[3]

Responses of 20 survey statements on attitudes toward pharmacokinetics services were all on the agreement side of neutral, with the exception of "Pharmacokinetic software is so sophisticated that very little judgment is needed for pharmacokinetic evaluation" (2.4 ± 1.6 on a scale of 1 = strongly disagree and 7 = strongly agree, n = 92). Notably, the statements whose average responses were >6 included: "Pharmacokinetic reviews and/or consultations should be integrated into the duties of every hospital pharmacist" (6.3 ± 1.3, n = 94); "Provision of pharmacokinetic services is an important component of hospital pharmacy practice" (6.2 ± 0.9, n = 94); and "Our pharmacokinetic services are very successful in terms of acceptance and use by prescribers" (6.1 ± 1.0, n = 93). However, only about 6% of respondents indicated a potential for increased pharmacokinetic consultations or reviews in the future. The authors surmised that as the profession embraces the concept of pharmaceutical care, pharmacokinetic consultations are being integrated into the pharmaceutical care process, with the pharmacokinetics specialist in larger institutions acting as a consultant to the nonspecialists. Because the survey revealed that only a minority of pharmacokinetics service providers interact directly with patients or their advocates (12 ± 22% of patients), the authors also encouraged greater direct involvement of pharmacists with patients.[3]

In 1998, Raehl et al.[6] published the results of the 1995 National Clinical Pharmacy Services study that determined the extent of hospital-based clinical pharmacy services in 1109 U.S. acute care, general, medical–surgical, and pediatric hospitals with 50 or more licensed beds. Pharmacokinetic consultations (i.e., pharmacist review of the serum drug concentration data and patient medical record with appropriate verbal or written follow up) were provided in 778 (70%) of hospitals surveyed, compared with only 54% in 1992. According to the 1995 survey, provision of pharmacokinetic consultations no longer varied by hospital ownership or geographic location as they did in 1992. Those hospitals with greater involvement in pharmacokinetic consultations included large hospitals, pharmacy teaching hospitals, hospitals in which the pharmacy director had a PharmD degree, and hospitals with decentralized pharmacists. Pharmacokinetic consultation was among the three services (the other two being adverse drug reaction management and drug history) that were more common in hospitals with a pharmaceutical care program than in those without one. In addition, pharmacokinetic consultations and drug therapy protocol management were the clinical services that experienced the most consistent and greatest growth since the first national survey in 1989. In hospitals providing pharmacokinetic consultations, 80.4 ± 30.3% of inpatients on aminoglycoside therapy for greater than 48 hours had a measured serum aminoglycoside concentration. In the hospitals offering pharmacokinetic consultations, 74% routinely provided documentation in patient medical records.[6]

Detailed teaching affiliation data were available for 1102 of the 1109 surveyed hospitals in the 1995 national clinical pharmacy services study.[6,7] Hospitals affiliated with both PharmD and BS degree-granting Colleges of Pharmacy provided pharmacokinetic consultation as a core clinical service (defined as being offered in 50% or more of hospitals). However, the percentage was significantly greater for PharmD-affiliated hospitals [85% (PharmD), 66% (BS Pharmacy), 63% (nonpharmacy teaching), and 57% (nonteaching), $p < 0.001$].[7]

In 1999, Ringold et al.[8] published the results of the 1998 ASHP national survey of pharmacy practice in acute care settings, which pertained to prescribing and transcribing practices. Of 1058 general and children's medical–surgical hospitals surveyed in the United States, 548 (51.8%) responded. Of the 536 hospitals or health systems for which information was available, 432 (80.6%) provided pharmacokinetic consultations. On average, 435.5 ± 943.2 consultations were provided per year (n = 362 hospitals or health systems). Of 411 total respondents, 71.2% indicated a >80% adoption rate for pharmacokinetic recommendations.[8]

In 2000, Raehl et al.[9] published the results of the 1998 National Clinical Pharmacy Services study that determined the extent of hospital-based clinical pharmacy services in 950 U.S. acute care, general, medical–surgical, and pediatric hospitals with 50 or more licensed beds. Eighty percent of hospitals offered pharmacokinetic consultations compared with 70% in 1995, 54% in 1992, and

only 40% in 1989. Again, pharmacokinetic consultations and drug therapy protocol management were the clinical services that experienced the most consistent and greatest growth since the first national survey in 1989. According to the 1998 survey, those hospitals with greater involvement in pharmacokinetic consultations included pharmacy teaching hospitals, hospitals in which the pharmacy director had a PharmD degree, hospitals with decentralized pharmacists, and those in the Pacific region. In hospitals providing pharmacokinetic consultations, 68.9 ± 37.8% of inpatients on aminoglycoside therapy for greater than 48 hours had a measured serum aminoglycoside concentration. In the hospitals offering pharmacokinetic consultations, 79% routinely provided documentation in patient medical records.[9]

Clinicians in general agree that pharmacokinetic software cannot replace clinical judgment. Nevertheless, judicious use of software programs can facilitate optimization of patients' drug therapy. The USC*PACK PC program (University of Southern California Laboratory of Applied Pharmacokinetics, Los Angeles, CA, USA) is a software package developed by investigators at the University of Southern California. Within the package, individual drug programs enable the clinicians to fit a patient's dosing history and drug concentrations to a population model. This Bayseian approach has been shown to provide good prediction of concentrations and dosage regimens. Seminar courses regarding the scope and use of the USC*PACK PC programs are scheduled each year. DataKinetics (ASHP, Bethesda, MD, USA) is another dosing program based on one-compartment modeling. Most of the commonly monitored drugs are included in the program. With animation and drawing features, STELLA (High Performance Systems, Lyme, NH, USA) is a useful program for teaching. Programs primarily for analysis of pharmacokinetic data include PCNonlin (Scientific Consulting, Inc., Cary, NC, USA), RSTRIP (MicroMath, Salt Lake City, UT, USA), and NONMEM (University of California, San Francisco, CA, USA). Modeling of pharmacodynamic data is available with P-PHARM (Simed, Creteil, France) and MKMODEL (Biosoft, Ferguson, MO, USA), an National Institutes of Health and Prevention (NIH)-supported PROPHET program. A list of pharmacokinetic programs and other resources is also available on the world wide web at http://www.boomer.org/pkin/.[a]

Clinical pharmacokinetics specialists have opportunities as directors and/or consultants of clinical pharmacokinetics services[3–9] to assume the following responsibilities, as delineated in the "ASHP Statement on the Pharmacist's Role in Clinical Pharmacokinetic Monitoring": 1) design and conduct of clinical pharmacokinetic/dynamic research, explore concentration–response relationships for specific drugs, and evaluate and expand clinical pharmacokinetic monitoring as an integral part of pharmaceutical care; 2) develop and apply computer programs and point-of-care information systems; and 3) serve as an expert consultant to pharmacists with a general background in clinical pharmacokinetic monitoring.[1]

Aside from being directors and consultants of clinical pharmacokinetics services, clinical pharmacokinetic specialists also have professional practice opportunities as preceptors of pharmacokinetic residency and/or fellowship programs. The American College of Clinical Pharmacy's (ACCP's) *2000 Directory of Residencies and Fellowships* lists two residency preceptors (with a total of three positions) whose programs have "pharmacokinetics" as their primary specialty.[10] At least one of these residencies is accredited by ASHP.[10] Using the search engine "Yahoo" and the search terms "Clinical Pharmacokinetic Service" and "Pharmacokinetic Practice," two more residencies in pharmacokinetics were identified.[11,12] All these residencies are designed to prepare the resident for a career in clinical practice or teaching with a focus on pharmacokinetics. The same directory lists 7 fellowship preceptors (with a total of 11 fellow positions) whose programs have "pharmacokinetics" as their primary specialty.[10] Of these 7 fellowship programs, 4 are ACCP recognized. These fellowship programs seek to provide fellows with clinical pharmacokinetic/dynamic research experience that involves, but is not limited to, study design, research methodology, study conduct, analytical methodology, data analysis, and scientific writing and research.[10]

Compared with the 1990s, the current numbers of specialized clinical pharmacokinetics pharmacy practices and fellowships are small. This likely reflects the general trend of integration of clinical pharmacokinetics into the concept of pharmaceutical care provided by pharmacists. In addition, concentration measurement is only an intermediate endpoint for optimal patient care. However, outside the traditional realm of therapeutic drug monitoring, there are other opportunities for pharmacists with indepth knowledge of clinical pharmacokinetics. This includes drug evaluation and regulatory review at the Food and Drug Administration (FDA), clinical research or drug development at pharmaceutical companies, the potential role of pharmacokinetic and monitoring for the increasing trend of home/community-based parenteral antibiotic therapy, and the relatively untested disciplines of toxicokinetics and clinical toxicology. Toxicokinetic studies are

[a]See the section on Professional Networking Opportunities later in this article.

not confined to preclinical drug development, and clinical toxicology presents a challenging opportunity for evaluating the adverse effects of drugs and poisons, as well as characterizing altered pharmacokinetics and response in overdose situations. Even within the current redefined practice of therapeutic drug monitoring, opportunities still exist. One good example is *optimizing* the use of once-daily aminoglycoside dosing.

DESCRIPTION OF MODEL CLINICAL PRACTICES

Following is a description of a model clinical practice in the specialty area of pharmacokinetics practice. This is an actual practice setting at the University of Kentucky Medical Center.

The mandate of the Clinical Pharmacokinetics Service at the University of Kentucky Medical Center is to ensure safe and efficacious dosage regimens through the application of pharmacokinetic/dynamic principles and the determination of serum drug concentrations.[13] The *Clinical Pharmacokinetics Service Policy and Procedure Manual* outlines standard dosing and monitoring guidelines (for aminoglycosides, carbamazepine, digoxin, fosphenytoin, lidocaine, lithium, phenobarbital, phenytoin, procainamide, quinidine, theophylline, valproic acid, and vancomycin) when providing clinical pharmacokinetic monitoring.[14] In addition, the Clinical Pharmacokinetics Service provides warfarin monitoring for patients on services or teams that do not have an assigned clinical pharmacist.[13]

At the University of Kentucky Medical Center, the primary pharmacist or pharmacy resident who attends rounds or precepts pharmacy students on a primary medical team is responsible for clinical pharmacokinetic monitoring of all patients on that team. The Clinical Pharmacokinetics Service oversees the pharmacokinetic monitoring process for all patients [i.e., those on teams with assigned pharmacists (''covered'')], as well as those who are on teams that do not have an assigned primary pharmacist or resident (''noncovered''). The Clinical Pharmacokinetics Service consists of a faculty member who serves as the director and of pharmacy practice residents and senior pharmacy students during their clinical pharmacokinetic rotations.[13]

Patients with serum drug concentrations on ''noncovered'' services are identified by two daily printouts provided by the Therapeutic Drug Monitoring (TDM) Laboratory (in the hospital's clinical laboratory, which analyzes all serum drug concentrations). Drug profiles also are reviewed at least thrice weekly for all patients on ''noncovered'' services to identify any patients who are prescribed ''monitorable'' drugs for which no serum drug concentrations have been ordered. Any physician also may request a pharmacist to provide a clinical pharmacokinetic evaluation by verbal or written communication.[13]

The TDM Laboratory notifies the primary pharmacist of any ''supratherapeutic'' drug concentrations, between 0800 and 1700 during the week; after 1700 and on weekends and holidays, the pharmacy resident on-call is notified. The TDM Laboratory also notifies the Clinical Pharmacokinetics Service of any supratherapeutic levels for any ''noncovered'' service. All other TDM issues are directed to the Director of the Clinical Pharmacokinetics Service.[13]

For every patient with a serum drug concentration ordered, the primary pharmacist writes a ''Clinical Pharmacokinetics'' note in the progress notes section of the patient's chart within 24 hours for normal or ''subtherapeutic'' concentrations. For ''supratherapeutic'' drug concentrations, the medical team is notified immediately if clinically warranted and a chart note written within 12 hours after the concentration was reported. The chart note contains all relevant patient information and pharmacokinetic parameters necessary to provide dosing and monitoring recommendations.[13]

At the University of Kentucky Medical Center, an average of approximately 800 serum drug concentrations are assessed every month, of which about 300 are directly evaluated through the Clinical Pharmacokinetics Service. On average, the Clinical Pharmacokinetics Service provides direct consultations for 100 to 125 patients monthly.[13]

Several other examples of clinical pharmacokinetics services are described in the literature. Briefly, Shevchuk and Poulin[15] described a pharmacist training program at Regina General Hospital, a 485-bed acute care facility in Saskatchewan, Canada, for an aminoglycoside monitoring service and a quality assurance program involving pharmacist certification. Ament and McGuire[16] described a pharmacokinetic dosing service at Latrobe Area Hospital, a 300-bed teaching-community hospital in Pennsylvania, wherein the pharmacist initiates and adjusts aminoglycoside and vancomycin regimens, and schedules serum drug concentration measurements and renal function lab tests without contacting a physician for verbal approval. Williams[17] also described a pharmacokinetic consult service at York Hospital, a 565-bed community teaching hospital in Pennyslvania, that expanded to include other clinical activities.

DOCUMENTATION OF THE BENEFITS OF THE PHARMACOKINETICS SPECIALTY

Numerous studies on clinical pharmacokinetic monitoring have demonstrated positive clinical outcomes. The reader is directed to a comprehensive review of the evidence to support such definitive outcomes.[2] Some examples of positive clinical outcomes for theophylline monitoring cited in the comprehensive review include decreased length of stay[18,19] and decreased toxicity.[18] For *traditional* aminoglycoside monitoring, examples include decreased length of treatment,[20,21] decreased length of hospital stay,[20–24] decreased febrile periods;[21] decreased duration to return to normal or baseline temperature,[22,25,26] decreased duration to stabilize heart rate,[26] decreased duration to stabilize respiratory rate,[22] increased patient survival,[23,27–29] and decreased changes in serum creatinine values from baseline.[23] For digoxin monitoring, examples include decreased length of hospital stay[30] and decreased toxicity.[30,31] Examples of beneficial clinical outcomes for anticonvulsants include decreased average number of readmissions per patient within 3 months of discharge[32] and decreased percentage of patients experiencing generalized tonic–clonic seizures.[33] Such examples for vancomycin include decreased length of hospital stay[34] and decreased toxicity.[34,35]

Several of these studies evaluating the impact of clinical pharmacokinetic monitoring on patient outcomes[21,22,24,26,32] were also cited in a 1996 landmark paper by Shumock et al.[36] that summarized and critiqued original economic assessments of clinical pharmacy services published from 1988 to 1995. Of the 104 literature articles that were identified, 13% fell under the category of pharmacokinetic monitoring services (defined as "clinical pharmacy services that primarily involved evaluation of anticipated or actual serum drug concentrations and provision of subsequent dosing recommendations"). Two of the articles on pharmacokinetic monitoring calculated benefit : cost ratios of 75.84:1 (pharmacokinetic services for patients receiving aminoglycosides)[26] and 4.09:1 (computer-assisted aminoglycoside dosing),[24] respectively. Other notable findings of the pharmacoeconomic impact of pharmacokinetic monitoring services from individual institutions were as follows: charge avoidance of $500,000 annually;[37] despite an increased number of drug levels ordered, a decrease of $599 in hospital costs; increased rational ordering of serum drug concentration determinations leading to cost avoidance of up to $12,325;[38–40] decreased length of treatment;[22] decreased length of stay;[21,22,41,42] decreased febrile period;[21] decreased direct costs;[21] annual cost savings of $113,934;[22] reduction of $14,000 in drug costs associated with service;[41] savings of $3000;[39] decreased number of digoxin serum drug concentrations ordered;[43] overall cost savings of $100 after 1 year of the program;[32] equal cost of pharmacist monitoring and savings after 1 year;[44] $1311 savings per patient in the study group (computer-assisted aminoglycoside dosing);[24] and $490 savings per patient in the study group (pharmacist dosing of aminophylline).[42]

Several other examples of the value of pharmacokinetics services on patient or pharmacoeconomic outcomes are provided here.

Pharmacokinetic monitoring of cancer patients on methotrexate has been found to significantly reduce the incidence of serious toxicity and virtually eliminate death due to high-dose methotrexate.[45] Other examples for other drugs are discussed in a state-of-the-art paper on pharmacokinetic optimization of cancer chemotherapy and its effect on outcomes.[46]

An online pharmacy intervention program was developed to determine the value pharmacy brings to the medication use process to improve patient outcomes at the Memorial Sloan-Kettering Cancer Center, a 565-bed comprehensive cancer center in New York City. Of 2499 interventions within 1 year's time, the most common types were order clarification/change (18%), followed by pharmacokinetic consult (16%).[47] The authors concluded that "pharmacy interventions elevated the standard of care and prevented major organ damage and potentially life-threatening events," thus demonstrating the major role that pharmacists play in improving patient outcomes.

In a cost-effectiveness analysis of the impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcomes, Van Lent-Evers et al.[48] found shorter length of hospital stay ($p = 0.0450$), shorter duration of therapy ($p < 0.001$), fewer dosage adjustments ($p = 0.016$), and lower incidence of nephrotoxicity ($p = 0.003$) in the group with active pharmacy-based clinical pharmacokinetic monitoring compared with a control group of patients not guided by therapeutic drug monitoring.[48]

Although not directly related to patient or pharmacoeconomic outcomes, deserving of mention is an exploratory study comparing survey data from 127 matched pairs of clinical pharmacists and physicians working together.[49] Interestingly, both pharmacists and physicans rated pharmacokinetic monitoring similarly as an activity in which pharmacists were highly competent. Pharmacy specialists perceived their influence on prescribing to

be higher ($p = 0.015$) than that of generalists with respect to recommendations based on pharmacokinetics.[49]

In a study that determined associations among hospital characteristics, mortality rates, and staffing levels for professional health care workers in 3763 U.S. hospitals, Bond et al.[50] found that increased numbers of pharmacists in a hospital were associated with lower mortality rates. Although the reasons for this were unknown, the authors speculated that providing clinical pharmacy services such as pharmacokinetic dosing services, preventing and detecting adverse drug reactions, and admission drug histories may be responsible for improving patient care outcomes.[50]

Performing simple regression analysis on data from the 1992 National Clinical Pharmacy Services study,[51] Bond et al. found a significant ($p = 0.001$) association between provision of pharmacokinetic consultations and lower mortality rates. Further multiple regression analysis did not reveal a significant association ($p = 0.544$).[52] Subsequently, Bond et al.[53] evaluated direct relationships and associations among clinical pharmacy services, pharmacist staffing, and total cost of care in 1016 U.S. hospitals. Pharmacokinetic consultations were among seven clinical pharmacy services that were associated with lower cost of care ($p = 0.0001$), based on simple regression analysis. Further multiple regression analysis did not reveal a significant association ($p = 0.436$).[53]

MATERIALS USEFUL TO PRACTITIONERS

American Society of Health-System Pharmacists Statement on the Pharmacist's Role in Clinical Pharmacokinetic Monitoring:[1] This is a position statement that provides background information and lists responsibilities that should be a part of clinical pharmacokinetics services or monitoring conducted by all pharmacists. In addition, a list of responsibilities that should be assumed by pharmacists with specialized education, training, or experience in pharmacokinetics is provided.[1]

American Society of Health-System Pharmacists Supplemental Standard and Learning Objectives for Residency Training in Clinical Pharmacokinetics Practice:[54] This document provides comprehensive guidelines and objectives for residency training in clinical pharmacokinetics practice. The contents of the Preamble include sections on definition, purpose and philosophy, accreditation authority, qualifications of the program director, selection and qualifications of the resident, and content of the residency program. Both the Goal Statements and Associated Terminal and Enabling Objectives include sections on practice foundation skills, direct patient care, drug information, drug policy development, and practice management.[54]

PROFESSIONAL NETWORKING OPPORTUNITIES

A number of network opportunities are available within professional organizations. These include, but are not limited to, the following:

American Society of Health-System Pharmacists Section of Clinical Specialists Pharmacokinetics Specialty Network:[55] The Pharmacokinetics Specialty Network is available as one of 19 networking assemblies of ASHP's Section of Clinical Specialists, each of which is led by a facilitator. Modes of networking among pharmacokinetic specialists are via the listserv as well as at networking assemblies conducted during ASHP Midyear Clinical Meetings.

American College of Clinical Pharmacy Pharmacokinetics/Dynamics Practice Research Network (PRN):[56] The Pharmacokinetics/Dynamics PRN provides a mechanism for networking and collaboration, educational programming, and a forum in which ACCP members with similar interests can discuss pharmacokinetic and pharmacodynamic methods and research.

American Association of Pharmaceutical Scientists Pharmacokinetics, Pharmacodynamics and Drug Metabolism Section:[57] The Pharmacokinetics, Pharmacodynamics and Drug Metabolism Section provides an opportunity for AAPS members to present new developments and exchange ideas related to the field. The section is designed to bring together qualified individuals who are investigating or interested in pharmacokinetics, pharmacodynamics, and drug metabolism.

American Association of Pharmaceutical Scientists Population Pharmacokinetics and Pharmacodynamics Focus Group:[58] The AAPS Population Pharmacokinetics and Pharmacodynamics focus group is open to all individuals, not just members, who are interested in this focused area. The focus group is designed to serve as a vehicle for presentations, symposia, and other mechanisms of interchange of relevant ideas.

American Society for Clinical Pharmacology and Therapeutics Pharmacokinetics and Drug Metabolism

Section:[59] This is a new listserv (phk@lists.ascpt.org) established in June 2000 for Pharmacokinetics and Drug Metabolism Section members of the ASCPT. The goal is to facilitate communication for the section members.

Pharmacokinetic and Pharmacodynamic Resources:[60] The Pharmacokinetic and Pharmacodynamic Resources web site (http://www.boomer.org/pkin/) provides links to information about pharmacokinetics and pharmacodynamics. All individuals interested in discussing pharmacokinetics and pharmacodynamics with colleagues around the world are invited to subscribe to the listserv.

CONCLUSION

Although a number of studies have demonstrated significant positive outcomes from clinical pharmacokinetics services, the reader needs to be aware that several studies have shown clinical pharmacokinetic monitoring not to have a significant effect on specific patient outcomes. A few studies even found a negative effect on patient outcomes.[2] This equivocal result may reflect that conventional patient outcome indicators (e.g., length of hospital stay) may not be appropriate to evaluate the value of clinical pharmacokinetic service. In addition, specific outcome indicators are likely to vary from drug to drug. Thus, we need to define those patients who are most likely to benefit from clinical pharmacokinetic monitoring and incorporate this into our provision of pharmaceutical care, while minimizing the time and money spent on clinical pharmacokinetic monitoring that has limited value (e.g., monitoring of digoxin concentrations for efficacy assessment in patients with heart failure or atrial fibrillation). Specifically, we should provide clinical pharmacokinetics services in a particular situation only when the results of the drug assay will make a significant difference in the clinical decision-making process and provide more information than sound clinical judgment alone. The reader is directed to a decision-making algorithm for clinical pharmacokinetic monitoring in the twenty-first century.[2]

Historically, clinical pharmacokinetics as a specialty practice has focused on interpretation of measured drug concentration, and modification of dosage regimen when appropriate.

The practice is also mostly concentrated on a limited number of drugs that meet certain criteria for concentration monitoring. Although such criteria are necessary to ensure appropriate use of resources, they may not work in the real world setting (e.g., monitoring of digoxin concentrations mentioned previously). In addition, such criteria for therapeutic drug monitoring limit the practice and application of clinical pharmacokinetics to a small number of drugs, as well as imply that the specialty is purely a "concentration exercise." The authors would argue that clinical pharmacokinetics practice should expand beyond the traditional realm of therapeutic drug monitoring, in terms of concept as well as scope of service. For example, the fluoroquinolones are not drugs that typically require concentration monitoring. However, with the recent knowledge of Cmax to MIC and AUC to MIC ratios being important determinants of response, the fluoroquinolones may provide a good potential for this expanded role. There are obvious technical problems regarding assay availability and dose-limiting central nervous system toxicity, as well as the need for more evidence to apply these pharmacokinetic determinants of response in the clinical setting. However, the potential for characterizing drug efficacy (and toxicities) using pharmacokinetic parameters should be explored to expand the role of the clinical pharmacokinetic specialty beyond that of therapeutic drug monitoring.

The explosion of pharmacogenetic and pharmacogenomic research has been fueled by the tremendous amount of genetic data generated by the Human Genome Project. In the future, instead of targeting a patient's drug concentrations within a therapeutic range as in traditional clinical pharmacokinetic monitoring, we predict that pharmacists will likely be making dosage recommendations of certain drugs based on an individual patient's genotype. Given the waning use of traditional aminoglycoside therapy that has been the primary focus of pharmacokinetic monitoring over the years, pharmacogenetics-oriented monitoring of other drugs may well become the therapeutic drug monitoring of the future.

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Clinical Pharmacy Practice Guidelines (Society of Hospital Pharmacists of Australia)

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INTRODUCTION

Clinical pharmacy services are provided in nearly all hospitals in Australia as an integral component of the pharmacy service.[1] The Society of Hospital Pharmacists of Australia (SHPA) Standards of Practice for Clinical Pharmacy, published in 1996, is the key reference point for the provision of clinical pharmacy services to hospitalized patients in Australia.[2]

The fundamental components of the Standard are the statement of objectives of clinical pharmacy and the documentation of procedures for selected clinical activities. In addition, the issues of boundaries of clinical practice, training, and education are addressed. These guidelines have been utilized in policy development at local and federal government levels, in the accreditation of clinical pharmacy services, and as a key standard for undergraduate and postgraduate teaching.

HISTORY

In Australia, approximately 90% of all hospitals and 100% of major government-funded hospitals provide clinical pharmacy services to admitted patients.[1]

SHPA is the primary professional body that represents pharmacists practicing in Australian hospitals and similar institutions. Founded in 1941, the Society today has a membership of more than 1700 pharmacists practicing in all states and territories of Australia.

The mission of the Society is to promote and develop the practice of pharmacy in hospitals and related areas. The Society promulgates practice standards, position statements, and other documents designed to provide professional guidance to members. Within the Society, the Division of Specialty Practice overseas a number of expert committees relating to selected areas of practice. These expert committees are known as Committee of Specialty Practice (COSP). The COSP in clinical pharmacy has representatives from a range of clinical practice backgrounds and membership is by invitation. One of the responsibilities of the committee is to develop standards of practice for clinical pharmacy for the Society and review these at least every five years. The current Standards are an expansion of previously published SHPA guidelines on selected clinical pharmacy activities.[3–8] The standards published by the Society are not legally binding as in the event of conflict or overlap with applicable legislation, the requirements of the legislation prevail.

The SHPA Standards of Practice for Clinical Pharmacy have been developed for all patient care settings and define the minimum requirements for service provision. Standards of practice in specialty areas such as drug usage evaluation, oncology, psychiatry, and other areas of pharmacy practice relevant to clinical pharmacy have been ratified and should be read in conjunction.[9–13] In addition, the SHPA Code of Ethics offers direction in relation to professional conduct.[14]

MAJOR STATEMENTS/RECOMMENDATIONS

The fundamental components of the Standard are the statement of objectives of clinical pharmacy, the documentation of procedures for selected clinical activities, the guidance on staffing levels, and the defining of an intervention. The issues of boundaries of clinical practice, resources required, training, education, quality assurance, and documentation requirements are addressed.

The objectives of clinical pharmacy are stated and defined and three key points are worth attention. The emphasis of the definition was to stress that patient care must be the focus of clinical practice. Reference was made to "quality use of medicines" as this is one of the four central objectives of the National Medicines Policy in Australia.[15] Educational and research activities were included in the definition to demonstrate that these are core clinical pharmacy activities.

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DOI: 10.1081/E-ECP 120006367

Leading on from this definition is a section that outlines the extent and operation of a clinical pharmacy service. Components that are discussed include the issue of the frequency of monitoring of patients' drug therapy. Clinical pharmacists need to be involved in activities that could improve patient clinical outcomes but are not necessarily focused on individual patients, for example, drug usage evaluations and the formulation of care plans. Research was addressed specifically by statements that involvement is an essential component of contemporary clinical pharmacy practice and should include a focus on optimizing drug therapy as well as research on the practice of clinical pharmacy. Education is also affirmed as a key core activity of clinical pharmacy practice. Specific details are not included in the document but rather motherhood statements that emphasize the need for involvement in undergraduate and postgraduate clinical teaching.

The third major section of the guidelines is the classification of clinical pharmacy services as a number of discrete activities. A goal for each activity is stated and then a recommended procedure outlines the major generic components of the activity. The activities were presented in an order that is somewhat reflective of the provision of these services. The Standard provides direction on which activities should be performed routinely. This is reflected in statements relating to medication history interview, the monitoring of drug therapy, and the provision of medication counseling.

The guidelines provide direction to the various resources recommended for the efficient provision of a clinical pharmacy service. There is limited detail as the primary aim was to briefly describe some selected components that should be considered rather than an attempt to quantify.

During the formulation and ratification of the guidelines, overwhelming input from members of the Society requested that the committee formulate a guide to staffing structure for the provision of a clinical service to particular clinical subspecialties. The document incorporates a guide to the ratio of pharmacists to patient bed numbers. These figures have not been substantiated by any objective measure or structured benchmarking study, but are based purely on consensus of the members of the Society.

Documentation of clinical service is featured and focuses on the very broad requirements of documenting actual activities performed as well as clinician documentation in the patient medical record. One of the key issues addressed is the defining of an intervention. The definition states that an intervention is "any action by a pharmacist that directly results in a change in patient management or therapy." By definition, the change must have occurred rather than have been merely proposed, and non-drug-related changes that impacted on patient management are included.

INFLUENCE AND RELEVANCE

These guidelines have been utilized in policy development at local and federal government levels, in the accreditation of provision of clinical pharmacy services, as a key standard for undergraduate and postgraduate teaching, and as a benchmark for practice.

The SHPA Standards of Practice for Clinical Pharmacy was one of the reference documents used in the formulation of the national guidelines to ensure continuity of medication management through hospital admission and treatment and postdischarge.[16] These guidelines were prepared by the Australian Pharmaceutical Advisory Council (APAC), which advises the Commonwealth Government of Australia on a wide range of pharmaceutical policy issues. The council includes representatives of major professional, industry, consumer, and media organizations as well as government members. The council published the guidelines in 1998, and they consist of broad principles on which standard procedures for individual institutions can be based, with the aim of ensuring continuity of medication management through hospital admission, treatment and postdischarge.

In another initiative by APAC, an integrated best-practice model for medication management in residential aged care facilities was developed.[17] One of the recommendations was that residents' medication be reviewed with cooperation between the prescriber and accredited pharmacists. Incorporated in the APAC model are guidelines for the performance of comprehensive medication review developed from the SHPA Standards of Practice for Clinical Pharmacy. Following on from this, the Commonwealth government agreed to reimburse accredited pharmacists to perform medication review services for nursing homes. Pharmacists can obtain accreditation through a number of mechanisms, including SHPA and also the Australian Association of Consultant Pharmacy (AACP). The AACP practice guidelines for the comprehensive medication review in residential care facilities utilize the Standard.

The SHPA Standards of Practice for Clinical Pharmacy are used as a reference point for benchmarking the provision of clinical pharmacy services in hospitals in Australia. An independent not-for-profit organization, the Australian Council of Healthcare Standards (ACHS), accredits healthcare organizations

through a process evaluation and quality improvement program. The Standards have been used as a template for developing standards within the ACHS accreditation process for specifying the fundamental requirements for pharmacy services.

The structure of the definitions of the clinical activities has been incorporated within the national standards for classification in health in Australia. SHPA collaborated with the Australia National Centre for Classification in Health (NCCH) to develop pharmacy procedure codes within the International Statistical Classification of Diseases and Health Related Problems Australian Modification.[18] The classification has subsequently been piloted in 28 hospitals to develop a standard approach to the documentation of clinical services to individual patients.[19]

Other applications include the use of the intervention definition in projects incorporating evaluation of clinical pharmacists' activities. SHPA recently completed a prospective multicenter study of pharmacist-initiated changes to drug therapy and patient management in acute care government-funded hospitals in Australia. This was a prospective study performed in eight hospitals to examine resource implications of pharmacists' interventions and was assessed by an independent, multidisciplinary clinical panel. Results of the study are to be published soon.

The SHPA Standards of Practice for Clinical Pharmacy have been utilized extensively in a range of settings ranging from undergraduate and postgraduate training to experiential clinical teaching. Practical experience placements are incorporated into the various undergraduate curriculums, with students practicing individual clinical skills using the SHPA Standards of Practice for Clinical Pharmacy as the basis for these activities.

In addition to undergraduate teaching, the Standard has been utilized in developing training programs for pharmacy interns. In Australia, there is some variation in the requirement for obtaining Pharmacy Board registration. In most cases, this requires completion of the B Pharm and then a period of traineeship or internship followed by a Pharmacy Board examination. Guidelines have been developed for the hospital traineeships/internships that are based on the Standards. In 1999, a clinical residency program commenced in Victoria, the second-largest state in Australia. The program is structured around a more advanced level of clinical experiential teaching based on the Standard.

The current SHPA Standards of Practice for Clinical Pharmacy published in 1996 are under review. The revised document will be circulated extensively to the various members of SHPA for comment prior to adoption and publication. The new version will be available toward the end of 2002.

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PROFESSIONAL DEVELOPMENT

Clinical Pharmacy Scientist

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INTRODUCTION

A clinical pharmaceutical scientist is an independent investigator with education and training in pharmacotherapeutics who utilizes contemporary research approaches to generate new knowledge relevant to drug behavior in humans, to therapeutic interventions, and/or to patient outcomes.

The spectrum of research conducted by the community of clinical pharmaceutical scientists (CPSs) is broad (Fig. 1), with human research being common to all, as indicated by the shaded spheres of clinical research and outcomes research. Some clinical scientists may spend their entire careers focused on human interventional or observational trials. However, CPSs may also extend the programmatic scope of their work into adjacent research spheres, including preclinical research. Fig. 1 also demonstrates that, although individuals who spend their entire careers exclusively in the preclinical sphere are indeed pharmaceutical scientists, they do not fit the definition of a clinical pharmaceutical scientist. It is the nature and the scope of research that defines the clinical pharmaceutical scientist.

ORIGINS AND EVOLUTION OF THE CONCEPT

The term *clinical pharmaceutical scientist* was originally developed within the profession of pharmacy and was applied to pharmacy practitioners who became scientists. The concept of a CPS originated with the Millis Commission in 1975, which described the need for "people who are equally skilled and trained in a science and in pharmacy practice." This commission proposed the vision of "training skilled pharmacy practitioners in research to increase the number and variety of clinical pharmacists."[1] Since the original definition, the concept has evolved, and several subsequent definitions have been published (Table 1). These reflect not only the evolution of the CPS, but also how the profession of pharmacy has changed.

Since the first definition of the CPS, there have been substantial changes in the arenas of both clinical care and research. The way that pharmacists interact with patients has changed—the clinical context has matured from pharmacy practice to clinical pharmacy, and subsequently to pharmaceutical care. Managed care has emerged, and with it has come a greater focus on patient outcomes and on quality and cost of care. Pharmacokinetics and pharmacodynamics, which once represented cutting edge research, have become basic skills critical to the drug development process. An incredible array of technological advances has increased the spectrum of research possibilities. Finally, the mapping of the human genome has opened the vista of genetic research to better understand a patient's predisposition to both the beneficial and adverse effects of specific pharmaceutical interventions.

Together, these changes have expanded the spectrum of research opportunities for clinical pharmaceutical scientists and have fostered the continued evolution of the definition. The term *translational research* has evolved to define scientific endeavors that provide a critical link between research theory and human application. The result is that today, there is "variety" in the types of clinical pharmaceutical scientists to be found, which is in fulfillment of the Millis Commission imperative.

EVOLUTION OF TRAINING

Historically, some CPSs began their careers as clinical pharmacists who had earned a postbaccalaureate degree (PharmD or MS); in their pursuit of answers to therapeutic questions, they turned to scientific endeavors and conducted clinical research, often in the areas of pharmacokinetics and pharmacodynamics. These experiences sometimes resulted in individuals developing laboratory-

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006354

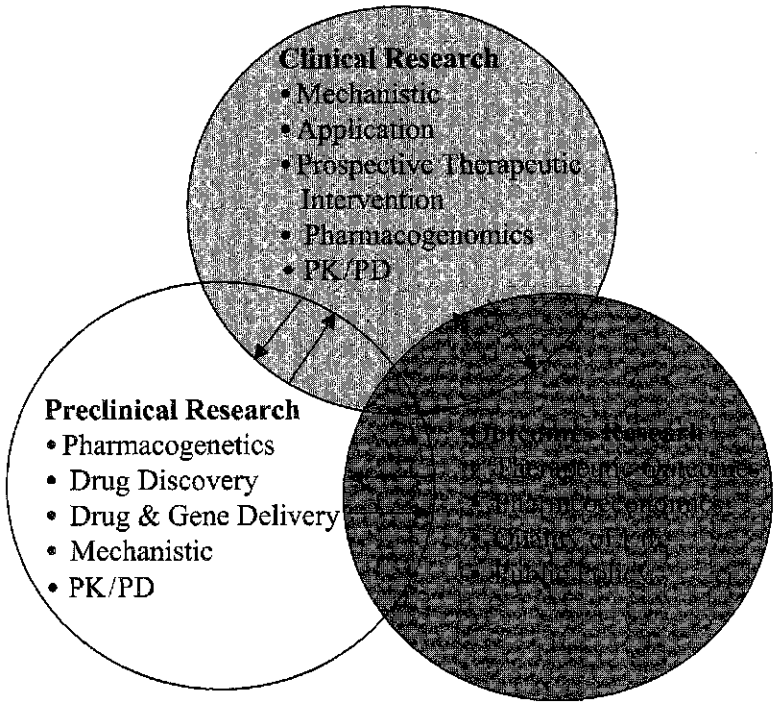

Fig. 1 This figure represents the continuum of research endeavors within the pharmaceutical sciences. The shaded areas represent the research areas encompassed by the definition of a CPS. The arrows indicate the potential movement from one sphere of research to another. The overlap with genetics, discovery, drug delivery, and animal mechanistic studies represent areas of translational research that provide the critical link between research theory and human application. Abbreviation: PK/PD, pharmacokinetics/pharmacodynamics.

based research as a means of gaining mechanistic or theoretical insight. Other clinical pharmaceutical scientists began their careers in the research laboratory and extended their research into normal volunteer and patient studies; these were often individuals with PhD degrees. Both career paths resulted in the generation of a CPS, and both were essentially "bootstrap" methods of becoming a clinical scientist.

The initial formal CPS training programs emerged in the 1980s. These programs required that the trainees conduct related patient-oriented and laboratory research. Historically, most of these programs were fellowships, although a few clinically oriented MS and PhD programs also emerged. Although most educational and training programs were in schools of pharmacy, some excellent fellowships are found in research institutes and health care organizations.

CURRENT EDUCATIONAL BACKGROUND AND TRAINING OPTIONS

Like the definition of the CPS, the background education and training options for becoming a CPS have also evolved. Common to most current CPS programs is the requirement for training in clinical pharmacotherapeutics. Stated in this way, clinically trained health care professionals other than pharmacists have the potential to become CPSs, given that they have an interest in developing research careers within the clinical pharmaceutical sciences. It is the nature and scope of research and not professional background that serves as the foundation for the definition of the CPS.

As stated in the definition, a CPS *is an independent investigator with education and training in pharmacotherapeutics who utilizes contemporary research approaches to generate new knowledge relevant to drug behavior in humans, to therapeutic interventions, and/or to patient outcomes.*

CPS training options that have been developed since the mid-1970s are summarized in Table 2. Each CPS training option has unique advantages and disadvantages, some of which have been debated previously.[3,8,9] Despite the differing opinions on the best method of training, the goal of these training programs is to develop individuals with the skills and confidence to conduct clinical research within their chosen career path.

Table 1 Published definitions of clinical pharmaceutical scientists

Year	Definition	Author
1975	People who are equally skilled and trained in a science and in pharmacy practice. The goal was to train skilled pharmacy practitioners in research to increase the number and variety of clinical scientists.	Millis Commission[1]
1984	Clinically experienced pharmacist capable of initiating and completing drug related research.	Smith et al.[2]
1987	1) An independent investigator conducting research relevant to the behavior of drugs in man. 2) Person has formal training as a clinical pharmacist.	Evans[3]
1987	A balanced clinical scientist who responds to clinical needs of patients and initiates research. Person has a balance of clinical and scientific skill.	Smith[4]
1987	Pharmacist with clinical skills, coupled with a sufficient background in pharmaceutics to perform clinical phamacokinetics and pharmacodynamics research.	Juhl and Kroboth[5]
1987	An individual with clinical service responsibilities who conducts clinical trials on human subjects and is the PI on grants.	Schwartz[6]
1991	A pharmacy-trained specialist who independently derives new knowledge through observation, study, and experimentation focused on drug therapy outcomes in patients, and the factors and mechanisms determining those outcomes.	Blouin et al.[7]
2001	An independent investigator with education and training in pharmacotherapeutics who uses contemporary research approaches to generate new knowledge relevant to drug behavior in humans, therapeutic interventions, and/or patient outcomes.	Kroboth et al.

Fellowship programs have provided advanced practice experience for clinicians for decades and have prepared them for board certification in areas of specialty in pharmacy and medicine.[10] Those individuals who desire a research component to their experience have either added an additional 1 to 2 years of training or sought mentors who provided a large research component to their core experiences. In the early 1980s and the 1990s, a small number of institutions developed postdoctoral graduate programs in the clinical pharmaceutical sciences.

Table 2 Clinical pharmaceutical scientist training options

Training option	Typical duration (yr)	Goal of training
Certificate in clinical pharmaceutical research	1	Develop individuals capable of conducting human interventional or observational research.
Master's in clinical pharmaceutical research	2–3	Develop individuals capable of designing and conducting human interventional or observational research.
Fellowship training	2–3	Develop independent scientists capable of designing and conducting clinical pharmaceutical research within academia, industry, or government.
PhD in clinical pharmaceutical sciences	4–5	Develop independent scientists capable of designing and conducting clinical pharmaceutical research within academia, industry, or government.

Some of these programs conferred an MS degree (e.g., University of Iowa, University of Minnesota), whereas others conferred a PhD (University of Pittsburgh, Virginia Commonwealth University, University of Kentucky). The core content of fellowship, MS, and PhD programs is similar, with the primary difference being the greater breadth and depth of experience associated with the PhD programs, which is paralleled by the greater duration of training.

Certificate programs in clinical pharmaceutical research have only emerged more recently. These are usually offered as a 1-year or less training option. Many of these programs provide graduate academic courses in which the individual can develop the skills to conduct clinically oriented research. Typically, these programs are very focused on human clinical interventional or observational studies. Independent research skills are limited due to the short training period.

The purpose of an educational program is to provide the optimal experience that will develop the skills for that individual to succeed within this chosen career. However, success is predicated not only on training, but also on the innate motivation and talents of the individuals, as well as their commitment to lifelong learning and perseverance in research after the formal training is complete. Each of the training options identified has resulted in successful CPSs. The decision as to the "best" training option is highly individualized and dependent on a multitude of factors, including the given student's career goals and aspirations. It is important for interested students to evaluate each training option extensively, realizing that the degree of development and the ability to conduct independent research increases directly with the duration and intensity of the various training options.

SKILL SETS

The world in which science is conducted has changed, and so have the skills necessary for scientists to function effectively. In a report published in 1995, essential skills and characteristics of scientists were addressed by The Committee on Science, Engineering, and Public Policy (COSEPUP), which was a joint committee of the National Academy of Science, National Academy of Engineering, and the Institute of Medicine.[11] The COSEPUP report states that "a world of work that has become more interdisciplinary, collaborative, and global requires young people who are adaptable, flexible, as well as technically proficient."[11] Subsequently, the 1996 report of the Research and Graduate Affairs Committee of the American Association of Colleges of Pharmacy emphasized the demand for "scientists (who) possess excellent verbal and written communication skills, team-building aptitudes, critical thinking, problem-solving skills, leadership ability, and scientific integrity."[9]

The primary goal of CPS training programs is to develop critical thinking, clinical acumen, and technical skills in a specialty research field, so as to develop the individual's ability to contribute to the knowledge that serves as the basis of clinical pharmaceutical science. It has been stated that "for the most part, graduate education has produced technical proficiency and mastery of a specific discipline."[9]

The common denominator for all training options, as well as for each research sphere (clinical, outcomes, and preclinical), is the skill set that one must acquire to successfully establish a clinical or translational research program. These skill sets can be grouped into six major categories. These categories include, but are not limited to, literature tracking and evaluation, critical scientific thinking and creativity, behavioral development, communication skills, technical proficiency, and research ethics and integrity. Mechanisms of attaining these skills vary with the different training options; however, the majority of these skills are attained via combination of graduate-level courses and mentored research experiences. Note that the role of advising and mentoring young scientists is viewed as sufficiently important that the National Academy of Sciences, National Academy of Engineering, and Institute of Medicine convened a committee that published a document regarding advising in 1997.[12]

Literature Tracking and Evaluation

The core of scientific research is based on the ability to review large volumes of published literature. To effectively pursue these research endeavors, the CPS must develop the ability to find, interpret, and critique the scientific literature. The trainee must become adept at using the existing body of information as the foundation for well-planned research. Once the research direction has been set, continual tracking of the literature is critical to maintaining currency and a successful research program.

Critical Scientific Thinking and Creativity

The development of critical and independent scientific thinking is paramount to the success of building a research program within each CPS research sphere. Using published literature as the foundation, scientists must be able to identify the next frontier for scientific exploration. They must also integrate the results of their own expe-

riments with relevant existing literature in an iterative process of literature tracking, assimilation, and creativity to form the basis of new research ideas, develop new hypotheses, and design methods to test their validity. It is this creative process that requires critical scientific thinking that leads to new scientific discoveries. Implicit in hypothesis generation and study design is the ability to use accepted methods or develop new technology to quantify study endpoints.

Like most skills, this skill is best honed by practice. Through exposure to the ongoing work of several scientists and peers, the development of these skills and characteristics can be enhanced.

Behavioral Development

As discussed previously, the CPS is a clinically trained individual capable of conducting independent research. The combined clinical and research educational background ideally facilitates interactions of the CPS with both researcher and clinician colleagues, thereby developing a collaborative and interdisciplinary team approach to develop and test research hypotheses. For the CPS to develop both independent and collaborative research, it is critical to develop decision-making, problem-solving, team building, and leadership skills. These skills are not only important for collaborative development, but also for the development of leadership and managerial skills that will be necessary for the CPS to effectively supervise research assistants, graduate students, and postdoctoral students, and to lead a team of investigators. For CPSs or any other scientist to develop these traits, trainees should ideally be exposed to diverse research environments where scientists exhibit these traits.[9]

Communication Skills

CPSs must develop the ability to effectively communicate their ideas to colleagues, collaborators, and students, as well as granting agencies, regulatory agencies, and peer-reviewed publication. Frequent writing experiences enhance written skills. Venues including the preparation of Institutional Review Board and Institutional Animal Care and Use Committee proposals, grant applications, and manuscripts are essential components of the training experience. Peer review of manuscripts for journals and report preparation are also vehicles for enhancing written communications skills. Frequent written communication is essential. All written materials should be viewed as vehicles for enhancing communications skills, providing that a mentor gives feedback.

Frequent oral presentations to peer and mixed audiences develops verbal communication skills. Large- and small-group teaching and research presentation skills each require different talents that should be developed during the training period. Furthermore, the ability to verbally defend one's research ideas and results must be developed irrespective of the clinical pharmaceutical training path that has been chosen. Mastery of the ability to verbally defend one's research occurs only after the trainee has fully developed multiple other skill sets including critical thinking, hypothesis derivation, literature mastery, and technical proficiency.

Technical Proficiency

Concordant with hypothesis generation and study design development are the processes associated with method establishment and/or development, data generation, and data analysis, all collectively referred to as technical proficiency. Establishing a method for generating data using previously established methods allows for general technical skill development, as do data analysis and interpretation. These skills are generally obtained using an apprenticeship technique, which involves learning from someone already working in the laboratory. However, it is important for the individual to develop technical mastery of the methods used within the mentor's laboratory, as well as be able to identify, establish, and validate valuable methods described in the literature. This develops confidence to develop de novo techniques, which can move the entire discipline forward. Similarly, to complete the process, the appropriate statistical comparisons must be planned and applied to interpret the results of the tested hypotheses.

Research Ethics and Integrity

Ethics and integrity associated with the conduct of research is important in the development of every scientist. However, the direct human impact of the research adds a layer of complexity to the training of a CPS. Federal regulations mandate that study protocols be carefully evaluated for subject/patient safety by the investigator and the local Institutional Review Board. Regulations also mandate that all scientists funded by the National Institutes of Health (NIH) provide certification of training in the protection of human subjects. This training can be obtained either locally or through the NIH Office of Human Subjects Research, which maintains a web site for computer-based training on the

"Protection of Human Research Subjects." The URL for this site is http://ohsr.od.nih.gov/cbt/.

Concerns regarding confidentiality of patient information have heightened, particularly with the advent of human genetic research. There are also ethical issues that relate to accuracy of data collected and its security in a database, which relates to either technical proficiency in database management or the knowledge that a database manager needs to be part of the investigative team.

CAREER OPTIONS

The demand for researchers who focus on the clinical pharmaceutical sciences has exceeded the supply. Individuals graduating from CPS programs have secured successful careers within academic, industrial, and governmental institutions (Fig. 2). Academic institutions are major employers of CPSs within the clinical or basic science divisions in the various health-related schools. The CPSs' unique blend of clinical and research skills allow these individuals to develop interdisciplinary collaborations and thus are aggressively sought by research intensive institutions and those that are expanding their research focus.

Similarly, these individuals are capable of functioning in the preclinical or clinical areas of drug development within the pharmaceutical industry. In particular, the CPS has unique talents to contribute to the decision-making process and study design at the preclinical/clinical interface, which is a critical juncture of the drug development process. In addition to the traditional pharmaceutical industry, contract research organizations and site management organizations have become essential contributors to the drug, biological, and device development process. Many CPSs who have experience within the pharmaceutical industry have guided the growth and development of this industry. It is not surprising that the design, monitoring, analysis, and evaluation functions provided by these organizations draw heavily on the strengths of the CPS.

CPSs are prime candidates for positions in governmental and regulatory agencies. The CPSs' critical thinking and analysis skills, plus their practical experience in conducting clinical investigations, are highly desirable attributes for individuals entrusted with the evaluation of

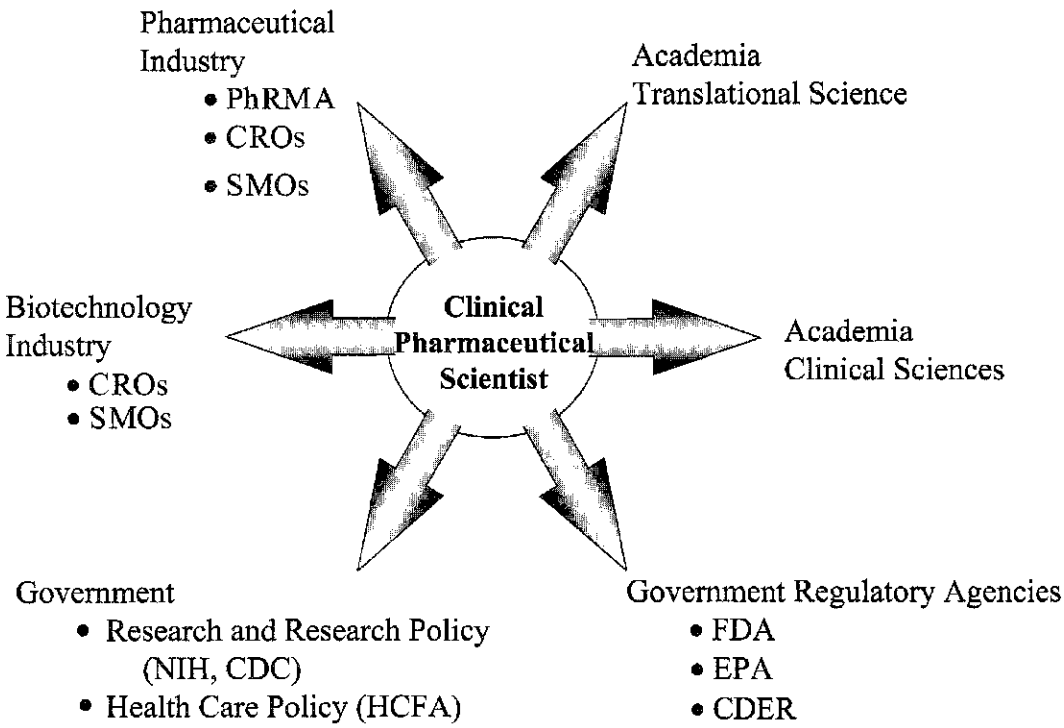

Fig. 2 This figure represents the career options for individuals interested in the clinical pharmaceutical sciences. Abbreviations: PhaRMA, Pharmaceutical Research Manufacturers; CROs, Contract Research Organizations; SMOs, Site Management Organizations; NIH, National Institutes of Health; CDC, Center for Disease Control and Prevention; HCFA, Health Care Financing Administration; FDA, Food and Drug Administration; EPA, Environmental Protection Agency; CDER, Center for Drug Evaluation Research; CBER, Center for Biological Evaluation Research.

the efficacy and safety of new drugs, biologicals, and devices in agencies such as the Center for Drug Evaluation Research, Center for Biological Evaluation Research, Environmental Protection Agency, and so on. Governmental health policy decisions are often based on critical review of scientific and economic evidence, along with a projection of their impact on the health care system. The CPS is similarly well suited to engage in this critical policy decision-making process at the national or local level.

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Cochrane Library, The

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INTRODUCTION

The Cochrane Library is a relatively new and growing electronic library that provides more than 850 summaries of published literature about pharmaceutical and other interventions to improve health. The Library adds new titles four times a year to its cumulative online and CD versions (the latter, available by subscription, offers more databases). The Library's 2000 Issue 3 contains evidence on dozens of clinical dilemmas, such as antibiotic treatment for traveler's diarrhea, antileukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma, opioid antagonists for alcohol dependence, and bromocriptine versus levodopa in early Parkinson's disease. The Cochrane Library also updates earlier reviews when important new evidence becomes available. Among the newest updates are tacrine for Alzheimer's disease, tricyclic and related drugs for nocturnal enuresis in children, and nicotine replacement therapy for smoking cessation.

BRIEF HISTORY

The Library is the product of a grassroots network, the Cochrane Collaboration, which began in 1993. This international, nonprofit organization represents a worldwide network of more than 4000 healthcare professionals, researchers, and consumers working together toward a similar goal: to prepare, maintain, and disseminate systematic reviews of the effects of healthcare.[1]

One way to begin understanding the Collaboration is to read their ten guiding principles: 1) Maintain a collaborative spirit. 2) Build on the enthusiasm of individuals by encouraging people of different expertise, backgrounds, and culture to participate. 3) Avoid duplication by encouraging international collaboration and maximizing efforts. 4) Minimize bias by using rigorous scientific methods. 5) Keep up-to-date by assuring that Cochrane Reviews are updated as new evidence becomes available. 6) Strive for relevance by selecting outcomes that are clinically useful. 7) Promote worldwide access. 8) Ensure quality by developing systems for quality control and quality improvement. 9) Assure continuity of the Collaboration infrastructure. 10) Enable wide participation by reducing barriers to contributions.

The Cochrane Collaboration is named after Archie Cochrane, a British epidemiologist. He emphasized that the effectiveness of healthcare interventions should be based on evidence from randomized controlled trials. He argued that evidence-based healthcare could encourage the wise use of resources. Cochrane also recognized that people who want to make informed decisions about healthcare did not have access to reliable reviews of the available evidence when in 1979, he wrote: "It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials."[2]

Even today, healthcare providers, consumers, researchers, and policymakers are overwhelmed by the vast amount of published research. Too often, the results of randomized controlled trials are ignored or lost in the information overload and helpful interventions are not identified promptly, while useless healthcare practices are continued. Review articles are needed to summarize all the relevant findings on a given topic or in a given field.[3] Systematic reviews, as suggested by Archie Cochrane, can help direct current therapeutic decisions and plan future research.

COLLABORATION STRUCTURE

Steering Group

A steering group of 14 elected members—clinicians, consumer advocates, researchers, and administrators representing all Cochrane entities—provide guidance to the Collaboration.

Cochrane Centers

The Cochrane Collaboration's two main entities are Cochrane Centers and Collaborative Review Groups (Fig. 1). Spanning the globe are 14 Cochrane Centers: Australasian,

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006288

Brazilian, Canadian, Chinese, Dutch, French, German, Italian, Nordic, North American, South African, South American, Spanish, and United Kingdom. Each center has general responsibilities, such as helping to maintain a directory of contributors to the Collaboration, offering training in the process of producing a Cochrane review, and coordinating handsearches for healthcare journals. The centers are not responsible for preparing and/or maintaining systematic reviews. This is the role of the Collaborative Review Groups.

Cochrane Collaborative Review Groups

A review group is formed by researchers, healthcare professionals, consumers, and others who share a common interest in a particular health problem. As of November 2000, about 50 review groups cover the major areas of healthcare (Table 1). The groups' core function is to prepare systematic reviews that are evidence-based, internationally developed, quality controlled, and clinically useful. Creating a Cochrane review involves the systematic assembly, critical appraisal, and synthesis of all relevant studies that address a specific clinical question. Reviewers use strategies that limit bias and random error.[4] These strategies include a comprehensive search for potentially relevant articles and selection of relevant articles, using explicit, reproducible criteria. Reviewers critically appraise research designs and study characteristics during synthesis and interpretation of results. When appropriate, they integrate the results using meta-analysis. The unique value of Cochrane reviews is the commitment to regular updating. Reviews published in journals are often out-of-date by the time they are published. By updating reviews as new evidence becomes available, Cochrane Colla-

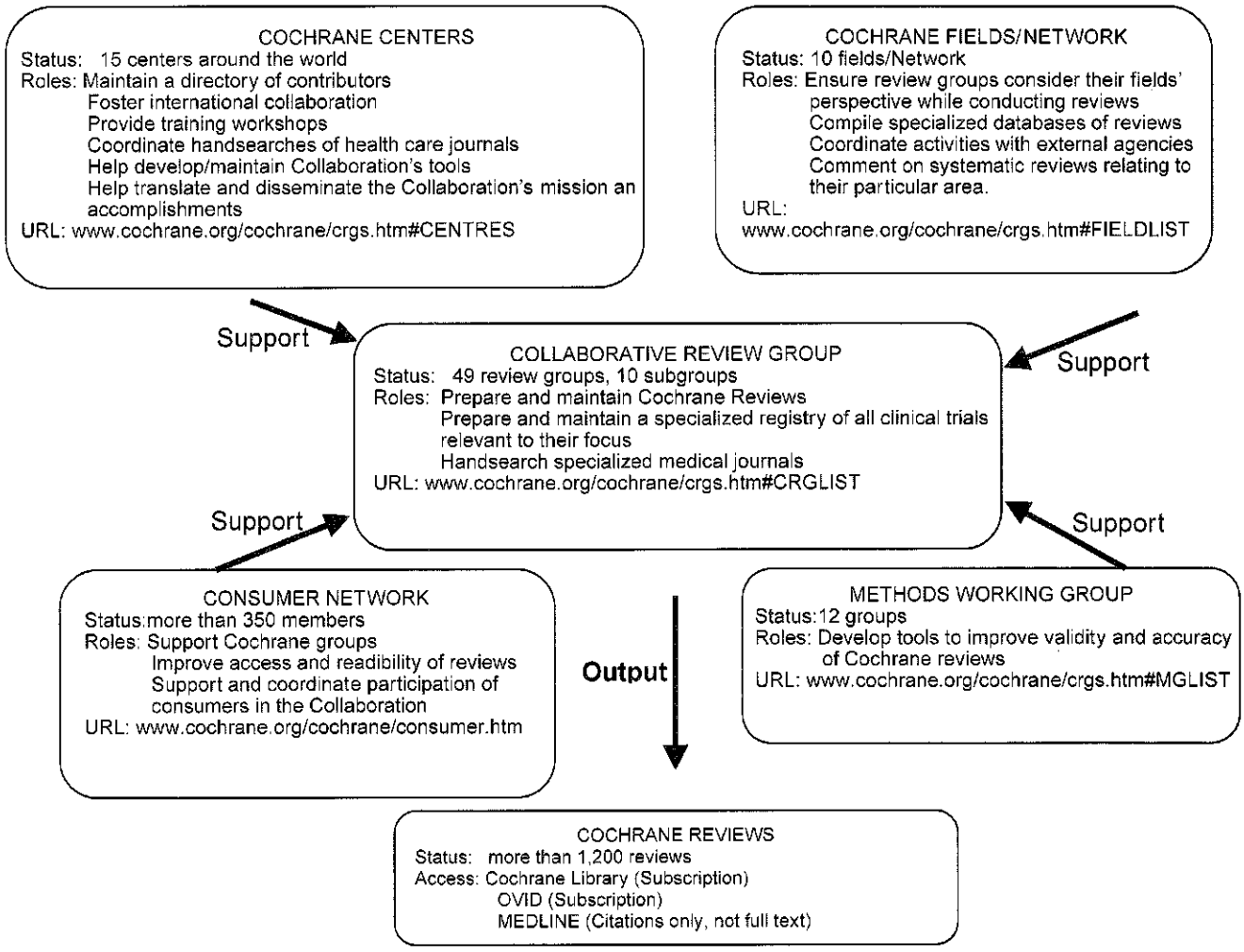

Fig. 1 The Cochrane collaboration structure.

Table 1 Cochrane collaborative group

Focus (No. of completed reviews)	URL address (assessed November, 2000)
Acute respiratory infection group (26)	http://nceph.anu.edu.au/user/rnd868/arigroup.html
Airways group (53)	http://www.cochrane-airways.ac.uk
Anesthesia group (2)	http://www.cochrane-anaesthesia.suite.dk
Back group (15)	http://www.iwh.on.ca/Pages/Cochrane/index.htm
Breast cancer group (4)	Not available
Colorectal cancer group (2)	http://www.cccg.dk
Consumers and communication group (2)	Not available
Cystic fibrosis and genetic disorders group (21)	http://web.bham.ac.uk/walterss/CFcochrane1.htm
Dementia and cognitive Impairment group (20)	http://www.jr2.ox.ac.uk/cdcig
Depression anxiety and neurosis group (10)	www.ccdan.auckland.ac.nz
Developmental, psychosocial and learning problems (5)	Not available
Drugs and alcohol group (5)	Not available
Ear, nose and throat disorders group (3)	http://www.entgroup.demon.co.uk/
Effective practice and organization of care group (17)	http://www.abdn.ac.uk/public_health/hsru/epoc/
Epilepsy group (7)	http://www.liv.ac.uk/epilepsy
Eyes and vision group (8)	http://www.archie.ucl.ac.uk
Fertility regulation group (6)	Not available
Gynaecological cancers group (16)	http://www.soton.ac.uk/~jps/gyn1.htm
Haematological malignancies group	Not available
Heart group (3)	http://www.epi.bris.ac.uk/cochrane/heart.htm
Hepato-biliary group (4)	http://inet.uni2.dk/~ctucph/chbg/index.htm
HIV/AIDS group (4)	http://hivinsite.ucsf.edu/cochrane/
Hypertension group (3)	Not available
Incontinence group (14)	http://www.otago.ac.nz/cure/
Infectious diseases group (38)	http://www.liv.ac.uk/lstm/nwc-id1.html
Inflammatory bowel disease group (7)	http://hiru.mcmaster.ca/cochrane/centres/canadian/IBD/IBD.htm
Injuries group (18)	http://www.cochrane-injuries.ich.ucl.ac.uk
Lung cancer group (2)	http://www.cochrane.es/English/LCG/
Menstrual disorders and subfertility group (44)	Not available
Metabolic and endocrine disorders group (5)	http://www.uni-duesseldorf.de/WWW/MedFak/MDN/Cochrane/ccset.htm
Movement disorders group (11)	Not available
Multiple sclerosis group	Not available
Musculoskeletal group (30)	http://www.arthritis.ca/cmsg/
Musculoskeletal injuries group (29)	Not available
Gout subgroup	
Lupus erythematous subgroup	
Osteoarthritis subgroup	
Osteoporosis subgroup	
Pediatric rheumatology subgroup	
Rheumatoid arthritis subgroup	
Scleroderma subgroup	
Soft tissue rheumatism subgroup	
Spondylarthropathy subgroup	
Vasculitis subgroup	
Neonatal group (91)	http://hiru.mcmaster.ca/cochrane/centres/canadian/neonatal/
Neuromuscular disease group (3)	Not available
Oral health group (3)	http://www.cochrane-oral.man.ac.uk
Pain, palliative care and supportive care group (8)	http://www.jr2.ox.ac.uk/Cochrane/
Peripheral vascular diseases group (14)	http://www.med.ed.ac.uk/pvd/
Pregnancy and childbirth group (161)	Not available

(*Continued*)

Table 1 Cochrane collaborative group (*Continued*)

Focus (No. of completed reviews)	URL address (assessed November, 2000)
Prostatic and urologic cancers group (7)	Not available
Renal group (4)	Not available
Schizophrenia group (52)	http://cebmh.warne.ox.ac.uk/csg/
Skin group (6)	http://www.nottingham.ac.uk/~muzd/index.htm
STD group	Not available
Stroke group (44)	http://www.dcn.ed.ac.uk/csrg/
Tobacco addiction group (20)	http://www.dphpc.ox.ac.uk/cochrane_tobacco/index.html
Upper gastrointestinal and pancreatic diseases group (7)	Not available
Wounds group (8)	http://www.york.ac.uk/depts/hstd/centres/evidence/ev-intro.htm#cochrane-wounds-group

borative Review Groups seek to provide the current best evidence for healthcare decision makers.

To create a comprehensive review on a given topic, Cochrane reviewers need access to all relevant randomized controlled trials. To assist the reviewers in this process, each Collaborative Review Group maintains a specialized registry of all (English and non-English; published and unpublished) randomized controlled trials pertinent to its particular focus. Trials are identified several ways: 1) electronic and manual searching of bibliographic databases, 2) contacting the pharmaceutical industry for unpublished trials, 3) handsearching hundreds of medical journals.

Three other Cochrane entities have much broader interests and focus on other dimensions other than specific healthcare problems. These are fields, methods groups, and networks.

Cochrane Fields

Fields serve to ensure that Collaborative Review Groups consider healthcare issues other than interventions, e.g., healthcare settings, types of consumers, and types of providers. For example, the field devoted to the healthcare of elderly people does the following: 1) assist in the handsearching activity of specialist journals, 2) ensure that Collaborative Review Groups address their issues and concerns, 3) compile a specialized database of reviews relevant to elder healthcare, and 4) establish internal and external partnerships.[5] A Cochrane Pharmaceuticals Field is being considered.

Cochrane Methods Groups

The Collaborative Review Groups are further assisted by Cochrane Methods Groups, which develop tools and assess new methodologies to improve the validity and accuracy of systematic reviews. For example, the informatics methods group played an important role in the development of the review manager software (REVMAN).[6] The Cochrane review manager software assists Cochrane reviewers in conducting reviews (submitting review protocol, entering data for analysis, and writing results) in the structured format for publication in the Cochrane Library.

Consumer Network

Consumers, users of the healthcare system, participate throughout most entities of the collaboration. Consumers' input and feedback helps identify clinical questions that

Table 2 How to subscribe to the Cochrane Library

Update Software Ltd. Summertown Pavilion, Middle Way, Oxford OX2 7LG, U.K. Tel.: +44-1865-513902 Fax: +44-1865-516918 E-mail: info@update.co.uk URL address for information on the Cochrane Library: www.cochrane.org/cochrane/cdsr.htm	Update Software Inc. 936 La Rueda Vista, California 92084, U.S.A. Tel.: +1-760-727-6792 Fax: +1-760-734-4351 E-mail: info@updateusa.com

Table 3 Information on Cochrane Centers

Australasian Cochrane Centre
Monash Institute of Public Health and Health Services Research, Monash Medical Centre, Locked Bag 29, Clayton Vic 3168, Australia
Tel.: +61-3-9594-7350
Fax: +61-3-9594-7554
E-mail: cochrane@med.monash.edu.au

Canadian Cochrane Centre
Health Information Research Unit, McMaster University Medical Centre, 1200 Main Street West, Hamilton Ontario L8N 3Z5, Canada
Tel.: +1-905-525-9140 ext. 22738
Fax: +1-905-546-0401
E-mail: cochrane@fhs.mcmaster.ca

Centro Cochrane do Brasil
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Tel.: +55-11-575-2970
Fax: +55-11-570-0469
E-mail: cochrane.dmed@epm.br

Centre Cochrane Français
Centre Léon Bérard, 28 Rue Laënnec, 69373 Lyon Cedex 08, France
Tel.: +33-478-78-28-34
Fax: +33-478-78-28-38
E-mail: ccf@upcl.univ-lyon1.fr

Centro Cochrane Iberoamericano
(Formerly called Centro Cochrane Español)
Hospital de la Santa Creu i Sant Pau, Casa de Convalescència, Sant Antoni M. Claret 171, 08041 Barcelona, Spain
Tel.: +34-93-291-95-27
Fax: +34-93-291-95-25
E-mail: Cochrane@cochrane.es

Centro Cochrane Italiano
Mario Negri Institute, Via Eritrea 62, 20157 Milano, Italy
Tel.: +39-02-39014327
Fax: +39-02-33200231
E-mail: cochrane@irfmn.mnegri.it

Deutsches Cochrane Zentrum
Abteilung für Medizinische Informatik, Institut für Medizinische Biometrie und Medizinische Informatik, Stefan Meier Str 26, D-79104 Freiburg i. Br, Germany
Tel.: +49-761-203-6715
Fax: +49-761-203-6712
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Dutch Cochrane Centre
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New England Cochrane Center
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Tel.: +1-617-636-5133
Fax: +1-617-636-8023
E-mail: cochrane@es.nemc.org
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Fax: +1-401-863-9944
E-mail: cochrane@brown.edu

Nordic Cochrane Centre
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Fax: +45-35-45-7007
E-mail: general@cochrane.dk

San Francisco Cochrane Center
University of California, San Francisco, Suite 420, Box 0613, 3333 California Street, San Francisco, California 94118, U.S.A.
Tel.: +1-415-502-8204
Fax: +1-415-502-0792
E-mail: sfcc@sirius.com

South African Cochrane Centre
Medical Research Council, Francie van Zijl Drive, Parowvalley, PO Box 19070, Tygerberg, 7505 Cape Town, South Africa
Tel.: +27-21-938-0438
Fax: +27-21-938-0836
E-mail: cochrane@eagle.mrc.ac.za

(*Continued*)

Table 3 Information on Cochrane Centers (*Continued*)

Chinese Cochrane Centre The First University Hospital, West China University of Medical Sciences, Chengdu, Sichuan 610041, P.R. China Tel.: +86-28-5422078/5422079 Fax: +86-28-5582944 E-mail: cochrane@public.sc.cninfo.net	**U.K. Cochrane Centre** Summertown Pavilion, Middle Way, Oxford OX2 7LG, U.K. Tel.: +44-1865-516300 Fax: +44-1865-516311 E-mail: general@cochrane.co.uk

matter. Consumers also help disseminate and translate the results of Cochrane reviews to a broader audience.

THE COCHRANE LIBRARY

Cochrane reviews are the key component of the Cochrane Library, but not its only jewel. In addition to the Cochrane Database of Systematic Reviews (CDSR), there are three other databases: Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effectiveness, and Cochrane Review Methodology Register.

Cochrane Database of Systematic Reviews

Once completed, Cochrane reviews undergo internal and external peer review before electronic publication. More than 850 Cochrane reviews are currently available (2000, Issue 3) with more than 750 reviews in progress. As new reviews are added with each issue of the Cochrane Library, eventually all areas of healthcare will be covered.

The Cochrane Controlled Trials Register

The Cochrane Controlled Trials Register contains bibliographic details of more than 270,000 controlled trials identified by contributors to the Cochrane Collaboration. The register aims to be the most comprehensive source of trials to assist the reviewers in conducting systematic reviews. To accomplish this goal, contributors around the world systematically handsearch healthcare journals to identify randomized controlled trials (published and unpublished). The handsearching efforts are done in collaboration with the National Library of Medicine (MEDLINE) and Reed Elsevier (EMBASE). More than 50,000 trials have been identified as randomized controlled trials and sent for proper tagging in MEDLINE and EMBASE. Each Collaborative Review Group's specialized registry is included and respectively tagged in the Cochrane Controlled Trials Register.

The Database of Abstracts of Reviews of Effectiveness (DARE)

This database, produced by the National Health Services Center for Review and Dissemination at the University of York, contains more than 2500 structured abstracts of good-quality published reviews about the effectiveness of health interventions. The database also can be accessed free on the Internet at www.york.ac.uk/inst/crd.

The Cochrane Review Methodology Register

This bibliographic database of more than 1300 references addresses methodological aspects relevant to conducting systematic reviews. It assists novice reviewers in finding good-quality articles summarizing important methodological challenges encountered in conducting systematic reviews.

The Cochrane Library represents one of the most comprehensive sources of evidence about healthcare. The Library can be purchased via subscription by contacting Update Software (Table 2). OVID Technologies includes the Cochrane Database of Systematic Reviews as one of their subscription databases. The National Library of Medicine's MEDLINE also indexes Cochrane Reviews. This allows MEDLINE users to identify Cochrane Reviews relevant to their search strategies.[7]

FUNDING SOURCES

Most Collaboration members contribute time and effort without monetary compensation. More than 4000 volunteers help prepare, maintain, and disseminate Cochrane Reviews. Over the past seven years, a long list of government agencies, foundations, universities, and others have provided financial support, though the level of support varies considerably. The Collaboration is exploring ways to secure continuing financial support for its infrastructure to achieve sustainability.

PARTICIPATION

Expertise or interest in a particular healthcare field is the qualification requirement for a Cochrane reviewer or an editor for a Collaborative Review Group. Expertise in statistics or trial methodology qualifies membership in a Methods Working Group. Most review groups and Centers welcome volunteer handsearchers and will provide the necessary training and support. The Italian Cochrane Center coordinates the efforts of people willing to translate reports of non-English medical trials for those preparing Cochrane reviews. Membership in a Cochrane entity is not based on formal qualifications. There are no membership fees. The key requirements are a willingness to volunteer and a sharing of the Collaboration's goals and collaborative spirit. Additional information on participation can be obtained by contacting the nearest Cochrane Center (Table 3).

NOTE ADDED IN PROOF

This article was written and submitted in early 2001. The author expects to submit a fully updated version of this article, available online, in the first quarter of 2003.

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Collaborative Drug Therapy Management by Pharmacists (ACCP)

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INTRODUCTION

The traditional system of providing drug therapy to patients, in which only certain health care professionals are authorized to initiate drug therapy, is under attack at many levels. The processes of drug prescribing, dispensing, administration, monitoring, and dosage adjustment, as practiced in this traditional system, occur in a disjointed fashion that frequently results in avoidable drug-related problems that contribute significantly to poor patient outcomes and increased medical costs.[1]

Collaborative drug therapy management, characterized by an interdisciplinary approach to patient care, is emerging as a solution that can maximize the patient's health-related quality of life, reduce the frequency of avoidable drug-related problems, and improve societal benefits from pharmaceuticals. In this approach to care, drug therapy decision making and management are coordinated collaboratively by pharmacists, physicians, other health care professionals, and the patient.

Many pharmacists with sufficient clinical training have or are willing to assume this level of responsibility for the patients they serve. When participating in collaborative drug therapy management, pharmacists share the responsibility for patient outcomes, not just by providing basic dispensing functions and drug information services, but by solving patient- and medication-related problems and by making decisions regarding drug prescribing, monitoring, and drug regimen adjustments.

This statement represents the position of the American College of Clinical Pharmacy (ACCP) on the role of pharmacists in collaborative drug therapy management. Furthermore, a model for collaborative management of drug therapy is described and endorsed as a way to enhance the quality of patient care within health care systems.

ACCP POSITION STATEMENT

The ACCP advocates the role of qualified pharmacists as capable collaborative drug therapy managers. Furthermore, ACCP supports the pharmacists' role in collaborative drug therapy management to improve patient outcomes and increase efficiencies in the health care system. To participate in collaborative drug therapy management, pharmacists must have access to patients and patient health information, conduct patient assessments, document activities, and undergo quality assurance programs on these activities. Scope of practice statements, identifying pharmacists' professional authority and responsibility, will be based on the pharmacist's credentials and the nature of the collaborative arrangement within the health care environment or system.

HISTORY OF PHARMACIST PRESCRIBING IN THE UNITED STATES

Regulation of pharmacist prescribing in the modern health care system of the United States can be traced to passage of the Federal Food, Drug, and Cosmetic (FDC) Act of 1938. This act was introduced to address concerns surrounding the availability of a growing therapeutic armamentarium of antimicrobial agents, led by introduction of the sulfonamides in 1935. Following a disaster in which 107 people died from consuming a toxic base used to compound a sulfanilamide elixir, Congress passed the FDC Act of 1938. The Food and Drug Administration (FDA) then issued regulations to enforce this legislation. The 1938 act deemed as misbranded any drug that failed to carry adequate directions for use or failed to warn patients about potential lack of safety. Any drug could be exempt from the requirement of adequate directions for

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DOI: 10.1081/E-ECP 120006410

use if, because of its potential for toxicity or misuse, it was to be used under the supervision of a physician. Regulations mandated these exempted agents carry the wording, "Caution: to be used only by or on the prescription of a physician, dentist, or veterinarian." Another provision was the working, "Warning—may be habit forming," required on certain narcotic and hypnotic drugs. These regulations became the forerunner to our present-day system for designating prescription drugs and controlled substances. Until this time, pharmacists had been able to prescribe medications legally.

The activity of pharmacists refilling, and thereby continuing, a patient's medications without authorization from the patient's physician was a secondary issue in the 1938 FDC debates. Although not defined as unlawful in 1938, the practice of pharmacists providing refills of medications directly to patients was not favored by the FDA. No definition had differentiated a prescription drug from a nonlegend, over-the-counter, drug. The two classes of drugs were not legally differentiated until passage of the Durham–Humphrey Amendment in 1951. At that time, it became illegal for pharmacists to refill legend drugs without authorization from the patient's physician.[2,3] Thus, the practice of physician prescribing and pharmacist dispensing became law. Many regulations endorsed by today's state boards of pharmacy are resultant attempts to define these distinctions clearly.

During this same period, the preparation of medications was increasingly assumed by pharmaceutical manufacturing companies, thereby lessening the role of individual pharmacists in production manufacturing. Thus, pharmacists were no longer taking an active role in initiating or continuing prescription drug therapy, and were also spending less time in the final preparation of the pharmaceutical product.

In the 1960s and 1970s, pharmacists began to assume roles as direct patient care providers in rural settings within the Indian Health Service. The activity of pharmacist prescribing was first documented in this setting. As early as 1977, Brands described pharmacist practitioners in the Indian Health Service who were trained to diagnose and treat acute, self-limiting diseases and chronic diseases in ambulatory patients.[4] A 1-year review of patients cared for by this arrangement found that 70% of the patients in this group were cared for solely by pharmacists. Quality of care was satisfactory and patient acceptance was excellent. In a similar fashion, Erickson described a program in the same Indian Health Service setting that demonstrated pharmacists were able to provide patient monitoring between physician visits and were also able to extend the interval between physician visits.[5]

In 1972, individual states began exploring the issue of pharmacist prescribing, heralded by the Health Manpower Experimental Act of 1972, a unique experiment in California. Health Manpower Pilot Projects were created with the purpose of training students of the allied health professions in areas that were then beyond their legal scope of practice. To include prescribing by pharmacists, nurses, and physician assistants in these pilot projects, the California Assembly Bill 717 was introduced in 1977, with a provision for sunsetting in 1983. The bill authorized prescriptive authority only to those directly involved with the pilot projects. The project was so successful in saving health care dollars[6] that the California Pharmacists Association, with assistance from the California Society of Hospital Pharmacists, introduced legislation in 1981 to enable prescribing by all pharmacists in the state. This legislation allowed registered pharmacists functioning in licensed acute and intermediate health care facilities to adjust the dosage of a patient's drug regimen pursuant to a prescriber's authorization, order laboratory tests, perform physical assessments, and administer medications. This law has been expanded twice since then and now enables pharmacists to initiate drug therapy (1983) and expands the types of practice sites to include clinics and systems licensed as health care service plans (e.g., managed care organizations; 1994). The specific duties outlined by each protocol are site- and practice-specific. Traditionally, they have ranged from pharmacist-managed nutritional support prescribing in the inpatient setting to antihypertensive medication management in the outpatient setting.[7–10]

Eventually, pharmacists have gained recognition as drug therapy experts at the national level. In 1974, the Department of Health, Education, and Welfare enacted a drug regimen review regulation for nursing homes in an attempt to improve the quality of drug prescribing in that health care setting. In 1984, Thompson and associates published the results of a study of clinical pharmacists who prescribed under physician protocol in a skilled nursing facility.[11] The findings of this controlled study indicated that patients in the prescribing clinical pharmacists' group had significantly fewer deaths, more patients discharged to lower levels of care, and fewer drugs per patient than the patients in the traditional care group. The estimated health care savings due to clinical pharmacists prescribing in a skilled nursing facility were $70,000 annually (in 1984 dollars) for every 100 beds.

Legislation enabling pharmacists to prescribe under protocol was first passed in the state of Washington in 1979. Since then, it has been amended several times to clarify or expand the types and numbers of protocols. Currently, the Washington State Board of Pharmacy has

Table 1 Attributes of state and federal regulations governing pharmacist prescribing

State	Arkansas	California	Florida	Indiana	Kentucky	Michigan	Mississippi
Year	1997	1981	1986	1996	1996	1991, under state public health code	1987
Types of Collaborative Practice Agreements	Protocol for each specific patient	Policies, procedures, protocols	Formulary only; legislation to establish protocols introduced in 1997	Policies, procedures, protocols	Collaborative care agreements	Responsibility delegated by MD or DO	Guidelines, protocols
Level of Review or Approval Required	Physician	Facility	None	Hospital and admitting practitioner	Yet to be determined by Board of Pharmacy	None	Board of Pharmacy
Medications Included	All	All	Specified formulary only; no narcotics or injectables	All, except narcotics	All; narcotics not specified	All, except C-II drugs and anabolic steroids	All
Environments	All settings	Licensed health care facilities, licensed clinics, providers who contract with licensed health care service plans	Pharmacies	Acute care settings, private mental health institutions	All settings	All settings	Institutional settings; in outpatient settings, specific signed protocols required for each patient
Educational Requirements/ Demonstrated Competencies	Those completing diabetes mellitus training eligible for reimbursement from insurance companies	Clinical residency or clinical experience as specified by the facility	No additional	No additional	No additional	None specified	Study course (of at least 20 CEUs) approved by Board of Pharmacy
Other Aspects Addressed	Completion of course approved by Board of Pharmacy enables pharmacist to administer certain medications, including immunizations and vaccinations, to patients age 18 yr or older	Administering injections; patient assessment; laboratory tests; initiating and adjusting drug regimens	No pregnant or nursing women; only drug supplies for less than 34 d; no refills	Changing duration of therapy, drug strengths, dosage forms, frequencies or routes of administration; stopping and adding drugs	Physical assessment; ordering clinical tests; initiating, continuing, or stopping drug therapy; drug modification and monitoring; therapeutic interchange	Pharmacist must record the name of the delegating MD or DO on the prescription	Initiating and modifying drug therapy

Table 1 Attributes of state and federal regulations governing pharmacist prescribing (*Continued*)

Nevada	New Mexico	North Dakota	Oregon	South Dakota	Texas	Washington	Federal government
1990	1993	1995	1980	1993	1995	1979	1995
Protocols	Protocols	Collaborative agreement with licensed physician	Protocols or on a case-by-case basis	Protocols	Written protocols with specific physicians	Protocols	Protocols within scope of practice
Available for inspection by Board of Pharmacy	Board of Pharmacy approves practitioner license	Board of Pharmacy and Board of Medical Examiners	None	Practitioner or the legal authority of the licensed health facility	Must be available for inspection by Board of Pharmacy	Board of Pharmacy	Appropriate facility-based authorizing body or chief of staff
All, except narcotics	All	All, except narcotics	All	All, except narcotics	All	All	All, except narcotics
Licensed medical facilities (hospitals, hospices, managed care settings, home health care, skilled nursing facilities)	All settings	Institutional settings (hospitals, skilled nursing facilities, swing bed facilities)	All settings	All settings	All settings	All settings	All settings
No additional	Additional training equivalent to that of a physician assistant (60 hr of physical assessment; 9 mo of clinical experience or MD preceptorship)	No additional	No additional	No additional	Specific clinical continuing education	No additional	MS degree, PharmD degree, accredited residency, specialty board certification, or 2 yr of clinical experience
Initiating, modifying, and monitoring drug therapy	Monitoring drug therapy; ordering laboratory tests; patient assessment; prescribing and modifying drug therapy	Pharmacist must notify physician when they initiate or modify drug therapy	Further rulings expected in 1997	Administering, initiating, and modifying drug therapy; research investigators	Written protocol defined as a physician's order, standing order, standing delegation order, or other protocol	Initiating and modifying drug therapy; protocols must be renewed every 2 yr	No protocol or cosignature required within scope of practice; policies required to assure practice is within identified scope of practice

over 70 protocols on file, conducted by over 425 pharmacists practicing in 60 locations throughout the state. Although the protocols were initially used in institutions, most are now used in managed care and community settings. In clinic settings, these protocols have been found to create efficiencies in prescribing antimicrobial and anticoagulation regimens.[12,13] In the community pharmacy setting, protocols are used for prescribing refills and for monitoring drug therapy of chronic disease states.

The third state to provide prescriptive authority to pharmacists was Florida. Taking a different approach, the Florida legislature created a third class of drugs in 1986. In contrast to the California and Washington provisions for prescribing under protocol, Florida pharmacists enjoy independent prescribing from within a limited formulary. Certain drugs within the following categories are included in this formulary: oral, urinary, and otic analgesics; hemorrhoid medications; antinausea preparations; antihistamines and decongestants; anthelmintics; topical antifungals and antimicrobials; topical antiinflammatory preparations; otic antifungals and antimicrobials; keratolytics; vitamins with fluoride; lindane shampoos; antidiarrheals; smoking cessation products; and ophthalmics. The formulary is subject to specific conditions spelled out in the state's pharmacy practice act. The legislation has been amended frequently.[14]

In 1995, the Veterans Health Administration (VHA) updated the granting of prescribing authority for practitioners in the Veterans Affairs (VA) system. "General guidelines for establishing medication prescribing authority for clinical nurse specialists, nurse practitioners, clinical pharmacy specialists, and physician assistants," VHA Directive 10-95-019, reviews and clarifies the prescribing role of these practitioners within the VA health care system. Clinical pharmacy specialists are defined as those with Master of Science or Doctor of Pharmacy degrees, pharmacists who have completed an accredited residency, specialty board-certified pharmacists, or pharmacists with equivalent experience. The scope of practice for each type of practitioner is determined by the practice site. The scope of practice statement identifies each individual's prescriptive authority and describes routine and nonroutine professional duties and general areas of responsibility. Prescriptions written by authorized practitioners within their approved scope of practice do not require a physician cosignature. Because states cannot regulate the activities of the federal government or its employees when acting within the scope of their employment, state laws and regulations related to medication orders and prescriptions do not affect scope of practice statements in the VA system.

With early models in place and numerous studies documenting success, momentum has mounted to support the pharmacist's role in collaborative drug therapy management. States are continuing to enact or pursue legislation to enable pharmacists to prescribe as part of collaborative drug therapy management agreements. Currently, 14 states and the federal government have enacted legislation allowing some form of collaborative prescribing for pharmacists. Table 1 provides some specific attributes of these laws.

IMPACT OF PHARMACISTS PERFORMING COLLABORATIVE DRUG THERAPY MANAGEMENT

Since the late 1970s, many studies have been published that document the success of pharmacists' management of specific types of patients, drugs, disease states, and specific patient problems and issues. Outcomes measured have included increased patient safety and satisfaction, reduced health care costs, and improved efficiencies.[15–22]

Recently, a summary and critique of 104 studies that assessed the economic outcomes of clinical pharmacy services from 1988–1995 was published.[23] The clinical pharmacy services evaluated could be classified into four main categories—disease state management (4%), general pharmacotherapeutic monitoring (36%), pharmacokinetic monitoring (13%), and targeted drug programs (47%). The services were provided in a variety of health care settings, including university, community, and government hospitals; health maintenance organizations; and community pharmacies.

Outcomes, or consequences, of the services described were considered in all 104 papers. Nineteen (18%) of the papers were found to be full economic analyses because they considered two or more alternatives to care and measured both input costs and outcomes. The most common outcomes measured were drug costs avoided, length of hospital stay, use of nonpharmaceutical resources, rates of adverse drug reactions, frequency of pharmacist-driven therapeutic interventions, and qualitative changes in prescribing patterns. In 93 (89%) of the papers, beneficial financial impacts of clinical pharmacy services were described.

In seven papers, the study design was sufficiently rigorous to allow the results to be expressed as a benefit-to-cost ratio. The calculated benefit-to-cost ratios for these seven studies ranged from 1.08:1 to 75.84:1 (mean 16.7:1). In other words, for every dollar invested in clinical pharmacy services, on average, $16.70 of benefit was realized. Overall, the body of literature contains a wealth of information pertinent to the value of the clinical practice of pharmacy.

EVOLVING VIEW OF HEALTH CARE

In November 1995, the Pew Health Professions Commission released its third report describing the future of the health professions in the United States.[24] The changes foreseen by the Pew Commission come from the backdrop of failed government-driven health care reform and the emergence of market-driven health care reform. Table 2 illustrates the shifting paradigm in health care as outlined by the Pew Commission.

The driving force behind health care reform in the United States is the trillion-dollar health care market and the rate of growth of this market. The rate of growth of health care resource utilization competes for other needed programs in both the private and public sectors. These expenditures are brought to the forefront by the fact that, compared with all other industrialized countries, the United States spends more of its gross national product on health care (nearly $3000/person versus $2000/person or less in all other countries), yet realizes no proportional improvement in quality of life.[25] In a market-driven health care economy, three principal values exist: 1) holding or lowering costs; 2) increasing patient satisfaction; and 3) improving the quality of patient outcomes.

The shift to create this new system will be accomplished by more integration and collaboration, as opposed to fragmentation. The steps in this change are occurring at an increasingly rapid pace. This is evidenced by the current movement of health care into a managed care environment. What these changes mean for health care systems and for pharmacists, in particular, are not absolutely clear, but the implications are that the next generation of health professionals will be practicing in an environment that is more intensively managed. In addition, exploration into changing the roles of health professionals to provide a more diverse skill mix within the health care team and more efficient delivery of integrated health care appears to be essential.

Table 2 The shifting paradigm in health care

1945–Present	Future
Specialization	Primary care
Cost unaware	Cost accountable
Technology driven	Humanely balanced
Institution based	Community focused
Professionally driven	Managerially driven
Individual care	Population health
Acute	Chronic
Treatment	Management and prevention
Individual providers	Team providers
Competitive	Collaborative

The Pew Commission has suggested that to meet these challenges, health professionals will have to redesign the way their work is organized, reregulate the ways in which they are permitted to practice, right-size the health professional workforce, and restructure health professional education.

This reregulation of health professions has direct bearing on the need for collaborative drug therapy management and prescriptive authority for pharmacists. As discussed earlier, our present prescriptive authority regulations evolved to protect consumers from misbranded and dangerous medications. However, at this juncture, the current process of drug prescribing, dispensing, administration, and consumption may, in fact, actually provide barriers to effective and efficient health care delivery. Current practice acts do not recognize overlapping or innovative scopes of practice based on demonstrated competency.[24] In addition, the current health care system is not oriented toward managing and monitoring chronic medication therapy. Rather, the focus has traditionally been toward managing acute medical events.[26]

Although pharmacists have traditionally assessed patients and assisted in drug therapy decision making, they have been given little autonomy to manage common and chronic disease states without the direct concurrence of a physician. Without authority to initiate and change medication regimens, many pharmacists must still contact a licensed prescriber as a step in solving drug-related problems they have identified. Scope of practice statements defining professional duties and general areas of responsibility are a logical way to improve access and continuity of patient care. Once considered only a hindrance to practicing disease and drug management, the inability of pharmacists to prescribe medications may well be considered both time and cost impediments to the delivery of quality and cost-efficient patient care in evolving health care delivery systems.

Pharmacy has embraced the philosophy that the provision of pharmaceutical care represents the principal mission of the profession.[27] Core activities of pharmacists who provide pharmaceutical care include the following: 1) participating in drug therapy decisions; 2) selecting drug products; 3) determining doses and dosage schedules; 4) preparing and providing drug products; 5) providing drug information and education; and 6) monitoring and assessing outcomes of drug therapy.

These types of activities can help solve significant problems in our health care system. Some examples of tasks associated with the provision of pharmaceutical care are listed in Table 3.[28] Many of these examples are necessary to help patients to use their medications

Table 3 Tasks associated with provision of pharmaceutical care

Interview patients to obtain information pertinent to product selection, dosage determination, and usage of current and past prescription and over-the-counter products.
Initiate requests for, or perform, and interpret results from appropriate laboratory and other diagnostic studies needed to select, initiate, monitor, and modify drug therapy.
Renew or rewrite prescriptions for continuation of drug therapy in accordance with established therapeutic endpoints or patient appointment status.
Measure vital signs and perform physical examinations of relevant organ systems and other patient assessments for the purpose of initiating, monitoring, and adjusting drug therapy.
Evaluate the patient's responses to therapy.
Provide oral and written recommendations for corrective actions for drug-related problems.
Document all patient care activities through orders and notes in the patient's medical record.
Select, initiate, monitor, continue, modify, and administer medication therapy to prevent disease or adverse reactions; resolve drug-related problems; or improve cost effectiveness.
Implement treatment guidelines, protocols, formulary changes, or critical pathways for therapy, as approved by an authorized health system provider or committee.
Provide patient education, identify expected outcomes of therapy, select monitoring parameters, and develop follow-up plans for drug therapy.
Provide direct patient care for appropriate disease management, either under protocol, policy, or guidelines.
Provide highly specialized inservice education and training to other health care professionals.
Develop medication use evaluation criteria and other quality improvement measures to assess the use of drug therapy by other providers.
Design, conduct, and coordinate clinical research projects under FDA guidelines and procedures of the institutional review board.

(Adapted from Ref. [28].)

optimally, but are prohibited by some state pharmacy statutes and regulations.

EVOLVING VIEW OF PRESCRIBING

Defining Prescribing

Today, prescribing is no longer the act of writing medication instructions. Prescribing encompasses multiple complex tasks, and as a term, it inadequately describes the numerous activities needed to provide drug therapy that achieves the defined outcomes that improve a patient's quality of life. The process of prescribing is more appropriately described by a broad set of activities that include selecting, initiating, monitoring, continuing, modifying, and administering drug therapy. Table 4 provides definitions of these prescribing activities. To select, initiate, and monitor drug therapy, the practitioner must be able to order and interpret laboratory tests, and perform patient assessments related to drug therapy management. This set of prescribing activities suggests that the focus of a practitioner's responsibility is on drug therapy management to improve patient outcomes.

Table 4 Definitions of prescribing activities

Select	When pharmacotherapy is necessary, and after review of an individual patient's history, medical status, presenting symptoms, and current drug regimen, the clinician chooses the best drug regimen among available therapeutic options.
Initiate	After selecting the best drug therapy for an individual patient, the clinician also determines the most appropriate initial dose and dosage schedule and writes an order or prescription.
Monitor	Once drug therapy is initiated, the clinician evaluates response, adverse effects, therapeutic outcomes, and adherence to determine if the drug, dose, or dosage schedule can be continued or needs to be modified.
Continue	After monitoring the current drug therapy of a patient, the clinician decides to renew or continue the same drug, dose, and dosage schedule.
Modify	After monitoring a patient's drug therapy, the clinician decides to make an adjustment in dose and/or dosage schedule, or may add, discontinue, or change drug therapy.
Administer	Regardless of who initiates a patient's drug therapy, the clinician gives the drug directly to the patient, including all routes of administration.

Defining Collaborative Relationships

Some individuals have advocated that pharmacists be granted independent prescriptive authority—that is, authority to prescribe medications independent of a defined collaborative relationship with an individual physician or medical group. Indeed, the system operative in Florida represents a form of independent prescriptive authority for pharmacists, albeit limited to a select formulary of drugs. Others have argued that pharmacists should function in a dependent role where prescriptive authority is delegated by a physician or other independent prescriber to another health care professional whom that prescriber believes possesses the professional skills and judgment necessary to perform these delegated duties.

However, the terms *dependent* and *independent prescribing authority* do not adequately reflect the collaborative relationship needed for pharmacists to contribute fully to the drug use process. A collaborative practice maximizes physician training and expertise in diagnosis, and pharmacist training and expertise in drug therapy and disease management. In most successful examples, the pharmacist and the physician have entered into a collaborative practice agreement or protocol under which the physician diagnoses and may make an initial treatment decision, and then authorizes the pharmacist to select, monitor, modify, and discontinue medications as necessary to achieve favorable patient outcomes. The physician and pharmacist then share the risk and responsibility for patient outcomes.[29]

Two additional factors support collaborative, rather than independent, management of patients by pharmacists. First, pharmacists have limited training in diagnosis. While physical diagnosis is a systematic process of organ system review, the pharmacist's assessment of physical findings is often targeted to a specific organ system or disease state. Except for acute self-limiting diseases or conditions identified during drug therapy monitoring, such as adverse drug reactions or inadequate responses, pharmacists are not trained to be diagnosticians. Second, a collaborative environment is the nature of current and future health care delivery systems. In fact, the future holds a marked increase in the extent of collaborative and managed health care delivery for all providers. All health care providers will be interdependent and will function in a collaborative fashion. The debate regarding dependent versus independent practice should be put to rest; instead, pharmacists should strive for collaboration with shared responsibilities and risks.

Prescriptive authority is not necessary to perform many duties involved in selecting, initiating, monitoring, continuing, modifying, and administering drug therapy. Nor is the ability to initiate drug therapy a prerequisite condition for pharmacists to establish a therapeutic relationship with a patient, solve drug-related problems, assume responsibility for therapeutic outcomes, or improve a patient's quality of life. However, when legally available, initiating drug therapy changes through collaborative drug therapy management agreements makes provision of care easier, more efficient, and convenient. Given the complexity of drug therapy decision making, evolving health care systems, and historic development of prescriptive authority, it may benefit society to review the scopes of practice of all health professionals, including the efficiencies gained by a collaborative health care team.

This discussion has focused on collaboration between pharmacists and physicians. However, optimal patient care and efficiency are most likely to result when effective collaboration exists among all the health professions. For example, there is no reason why nurse practitioners and pharmacists, or physician assistants and pharmacists, cannot collaboratively provide care for many patients with acute and chronic illnesses.

REQUIREMENTS FOR COLLABORATIVE DRUG THERAPY MANAGEMENT

For pharmacists to participate effectively in collaborative drug therapy management in a timely and cost-efficient manner, several conditions must exist: 1) a collaborative practice environment; 2) access to patients; 3) access to medical records; 4) knowledge, skills, and ability; 5) documentation of activities; and 6) compensation for their activities.

Collaborative Practice Environment

The pharmacist wanting to participate in collaborative drug therapy management first needs to identify a physician or practitioner group who wants to collaborate with the pharmacist. The physician or health system will identify patient populations, disease states, specific drugs, and certain drug-related issues in which other health professionals want to practice collaboratively with pharmacists. A description of routine and nonroutine professional duties and general areas of responsibility become the approved scope of practice for that pharmacist. The physician or health system needs to be willing to share responsibility for the pharmacist's actions. The environment may be an acute care hospital, a transitional care facility, a nursing home, a clinic, or a community pharmacy, as long as the remaining conditions are also met.

Table 5 Areas and content of core pharmacy curriculum adopted in 1997 by the American Council on Pharmaceutical Education

Biomedical Sciences	Anatomy, physiology, pathophysiology, microbiology, immunology, biochemistry, molecular biology, biostatistics
Pharmaceutical Sciences	Medicinal chemistry, pharmacognosy, pharmacology, toxicology, pharmaceutics, biopharmaceutics, pharmacokinetics
Behavioral, social, and administrative pharmacy sciences	Health care economics, pharmacoeconomics, practice management, communications, pharmacy history, ethics, social and behavioral applications and laws of practice
Pharmacy practice	Dispensing, drug administration, epidemiology, pediatrics, geriatrics, gerontology, nutrition, health promotion and disease prevention, physical assessment, emergency first care, clinical laboratory medicine, clinical pharmacokinetics, patient evaluation and ordering medications, pharmacotherapeutics, disease state management, outcomes documentation, self care and nonprescription drugs, drug information and literature evaluation
Professional experience	Introductory and advanced practice experiences throughout the curriculum as a continuum, in a variety of practice settings

(Adapted from Ref. [30].)

Access to Patients

Direct communication with patients is imperative for pharmacists to function successfully as collaborative drug therapy managers. In fact, it is best to establish an agreement with the patient describing the ideal conditions under which care should be rendered. Within this relationship, the patient grants the pharmacist responsibility, and the pharmacist in turn promises competency to perform the service, along with a willingness to assume responsibility, to the patient. This agreement codifies the direct relationships between patients and pharmacists, and heightens awareness of both groups to the responsibility assumed by the pharmacist in caring for the patient. The goal should be the establishment of a permanent and ongoing relationship that takes place over time. These relationships should complement, but not replace, those of patients and physicians.

Access to Medical Records

Access to a patient's medical records is essential to the provision of collaborative drug therapy management. In fact, it is only under these conditions, wherein the pharmacist has adequate knowledge of the patient and the patient's history, disease states, drug therapy, and laboratory and procedure results, that quality care can be rendered. Much work is being done in this area, via computerization of medical records and network facilitation of electronic data, to ensure this key element is in place to facilitate patient care by health care providers.

Knowledge, Skills, and Ability

In many ways, the pharmacist is uniquely trained for the task of collaborative drug therapy management. Contemporary pharmacy education has provided pharmacists with more extensive and indepth training in pharmacology and drug therapy management than any other health professional. Other health professionals who have prescriptive authority, such as nurse practitioners and physician assistants, have far less education in drug therapy management. Areas and examples of core curricula required under the 1997 American Council on Pharmaceutical Education requirements for Doctor of Pharmacy programs are listed in Table 5.[30]

Documentation of Activities

When pharmacists participate in any aspect of collaborative drug therapy management, they must document their activities in the patient's medical record. This information should, in turn, be available to other care providers within the health care system. Within the collaborative drug therapy management agreement, the frequency of communication with the collaborative team should also be established.

Compensation

In a vertically integrated managed health care system, the historical fee-for-service system of compensation is not operative. Therefore, pharmacists, either as primary care providers or as disease management specialists within a provider group, should expect to join with other health professionals on a collaborative team. Within a managed care contract, the pharmacist, along with other team members, assumes risk and responsibility for providing health care to patients in that system. Compensation from managed care payers will be on a contractual basis for team services. Demonstration of improved

outcomes will be integral to continuing contracts.[31] Specific duties and privileges will be defined by the scope of practice within the specific health care system, partly based on the mix of health care providers present and the type of patients for whom the system provides care. Collaborative drug therapy management will not lead to a fee-for-service form of compensation for clinical pharmacy services within a managed care environment. It is possible that it may do so in other types of health care systems.

COMPETENCIES, SETTING, CREDENTIALING, AND QUALITY ASSESSMENT

Competence assessment is essential when pharmacists assume collaborative drug therapy management activities, especially when such activities are new. Many methods exist to certify competence, such as granting clinical privileges or determining scope of practice in a health system via committee,[32] completing certificate programs for specific disease states, demonstrating knowledge and patient care skills, or earning national certification in a specialty via competency-based processes. The nature of the collaborative relationship will determine the appropriate mechanism for assessing competence. In addition, competencies may vary based on which prescribing activities are needed or how the scope of practice for each pharmacist is written. For example, initiating and modifying drug therapy may require competencies different than those necessary for administering, continuing, or monitoring drug therapy.

Pharmacists, by nature of their education and licensure, should be able to perform many of these functions without any additional demonstration of competence. The entire spectrum of prescribing activities is appropriate for any qualified licensed pharmacist in any practice setting as long as a collaborative relationship with other health care providers is established, access to relevant patient information exists, and ongoing competence and quality are assessed.

Pharmacists engaged in collaborative drug therapy management activities should be held accountable to the same quality assurance monitors and measures as other health professionals in their setting. Thus, supervision and quality assessment of activities are setting specific and will differ greatly among settings and health systems. Mechanisms to measure and ensure quality should be developed and put into place at the time the collaborative arrangement is established. These mechanisms should follow the same outline as those developed and used for other health professionals.

CONCLUSION

The practice of pharmacy and the provision of health care in the United States have changed dramatically over the past 60 years. Reports in the literature documenting pharmacists functioning in primary care roles and as prescribers of medications appeared as early as the 1970s. Reports of these early efforts, now renamed as efforts in collaborative drug therapy management, have demonstrated increased efficiencies in the health care system, while maintaining quality of care and patient satisfaction. At least 14 states and the federal government have authorized some form of pharmacist involvement in collaborative drug therapy management, and many other states are seeking to institute enabling legislation and regulations. Opportunities for pharmacists to increase efficiencies, decrease drug-related morbidity, and improve patient outcomes are abundant.

Not only has the role of the pharmacist evolved, but market-driven forces have caused the entire health care system in the United States to become more collaborative in nature. Pharmacists now have an opportunity to participate in collaborative drug therapy management and contribute to the quality of patient care in concert with other health care professionals.

To function successfully in a collaborative environment, the pharmacist must practice in a setting where teamwork is fostered, be able to establish a convenantal relationship with the patient, and have access to the patient's medical records. Because collaborative drug therapy management involves multiple complex tasks, the process may be more easily defined by describing the activities involved in the process—selecting, initiating, monitoring, continuing, modifying, and administering drug therapy. Ideally, these responsibilities should also include ordering, performing, and interpreting medication-related laboratory tests and procedures, along with performing patient assessment tasks related to drug therapy. By virtue of their extensive training in all relevant aspects of drug therapy management, pharmacists are well qualified and well equipped to provide collaborative drug therapy management services to patients.

Collaborative drug therapy management is most successful when the nature of the collaborative arrangement, the competencies and credentialing required, and the quality assurance checks that will be used to assess performance are defined at the outset in each specific setting.

In this era of rapid evolution in health care, the provision of collaborative drug therapy management by pharmacists can contribute to the efficacious, efficient, and cost-effective use of health care resources to improve patient outcomes in the United States.

ACKNOWLEDGMENTS

The authors want to acknowledge the contribution of Jeffrey C. Fay, PharmD, in preparing Table 1.

From *Pharmacotherapy* 1997, 17(5):1050–1061, with permission of the American College of Clinical Pharmacy.

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Collaborative Practice Agreements (Collaborative Drug Therapy Management)

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INTRODUCTION

This article examines how the practice of pharmacy can be improved by the legal and institutional recognition of Collaborative Drug Therapy Management (CDTM). Further, the development of Collaborative Practice Agreements or defining a specific Scope of Practice that allows the pharmacist and other health professionals to focus more on integration and collaboration is discussed.

DEFINITIONS

Pharmaceutical care: The responsible provision of drug therapy for the purpose of achieving a definite outcome that improves the patient's quality of life.[1]

Collaborative Drug Therapy Management (CDTM): The provision of pharmaceutical care in a collaborative and supportive practice environment that allows the qualified pharmacist legal, regulatory, and ethical responsibility to solve drug related problems when discovered.

Scope of practice: The boundaries within which a health professional may practice. For pharmacists, the scope of practice is generally approved by the board, agency, or committee that regulates the profession in a given state or organization.

Credentialing: The process by which an organization or institution obtains, verifies, and assesses a pharmacist's qualifications to provide patient care services.

Privileging: The process by which a healthcare organization, having reviewed an individual healthcare provider's credentials and performance and having found them satisfactory, authorizes that individual to perform a specific scope of patient care service within that organization.

Prescribing activities:[2]

- *Select*: When pharmacotherapy is necessary, and after review of an individual patient's history, medical status, presenting symptoms, and current drug regimen, the clinician chooses the best drug regimen among available therapeutic options.
- *Initiate*: After selecting the best drug therapy for an individual patient, the clinician determines the most appropriate initial dose and dosage schedule and writes an order or prescription.
- *Monitor*: Once drug therapy is initiated, the clinician evaluates response, adverse effects, therapeutic outcomes, and adherence to determine if the drug, dose, or dosage schedule can be continued or needs to be modified.
- *Continue*: After monitoring the current drug therapy for a patient, the clinician renews or continues the same drug, dose, and dosage schedule.
- *Modify*: After monitoring a patient's drug therapy, the clinician makes an adjustment in dose and/or dosage schedule, or adds, discontinues, or changes drug therapy.
- *Administer*: Regardless of who initiates a patient's drug therapy, the clinician gives the drug directly to the patient, including all routes of administration.

CURRENT PHARMACY PRACTICE ENVIRONMENT

As the volume and potency of prescription medications have increased, the nation's attention has become focused on the staggering human and economic cost of medication errors. Drug-related morbidity and mortality in the United States has a vast economic impact on the healthcare system. The nation was stunned in 1999 when the Institute of Medicine (IOM) issued a report that concluded that medical errors account for between 44,000 and 98,000 deaths annually.[3] The IOM report noted that "[b]ecause

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DOI: 10.1081/E-ECP 120006316

of the immense variety and complexity of medication now available, it is impossible for nurses or doctors to keep up with all of the information required for safe medication use. The pharmacist has become an essential resource in modern hospital practice."[4]

Critical to understanding how to reduce the rate of medication errors is understanding what, how, and when drug-related problems arise.[5] Approximately 39% of medication errors occur in the prescribing phase.[6] Another 50% occur during order transcription and drug administration, and 11% occur during dispensing. The single proximal cause of medication errors (22%) is a lack of complete knowledge about drugs during the prescribing, order transcription, and drug administration stages. The direct presence and involvement of pharmacists during these stages can reduce medication errors as much as 66%.[7]

The traditional system of providing patient care—wherein physicians initiate drug therapy, pharmacists dispense medications, and nurses administer medications—is often run in a disjointed fashion. This results in potentially avoidable adverse drug events that contribute to poor patient outcomes and increased medical costs.[8] Efforts aimed at modifying the current processes of care to enhance efficiency of workflow, improve patient outcomes, and reduce medication errors are needed.

Pharmaceutical care has become the philosophy of pharmacy practice in recent years, as well as a mission or purpose for the profession. However, another term that has come into use to simultaneously describe pharmaceutical care and the system for the medication use process—CDTM. As the healthcare system grows in complexity, pharmaceutical care becomes increasingly important. It becomes more and more necessary for pharmacists, physicians, and other health professionals to work together in collaboration to assure safe use of medication. CDTM is an innovative approach in which pharmaceutical care services can be provided by a pharmacist in a supportive healthcare environment after a process of credentialing, privileging, and approval of a Collaborative Practice Agreement.

In a system utilizing CDTM, the American Society of Hospital Pharmacists (ASHP) supports the activities of a pharmacist that may include, but are not limited to: 1) initiating, modifying, and monitoring a patient's drug therapy; 2) ordering and performing laboratory and related tests; 3) assessing patient response to therapy; 4) counseling and educating a patient on medications; and 5) administering medications.[9] The American College of Clinical Pharmacists (ACCP) advocates the role of qualified pharmacists as capable collaborative drug therapy managers. Further, ACCP supports the pharmacists' role in CDTM to improve patient outcomes and increase efficiencies in the healthcare system. ACCP's core requirements for CDTM are:[2]

- A collaborative practice environment.
- Access to patients.
- Access to medical records.
- Knowledge, skills, and ability.[10]
- Documentation of activities.
- Compensation for these activities.[11]

CDTM is an interdisciplinary approach wherein pharmacists are integrated into the medical team to solve patient and medication-related problems and to share the responsibility for outcomes. A collaborative practice maximizes physician training and expertise in diagnosis, as well as the pharmacist training and expertise in drug therapy management. As of June 2002, in 38 states and in the federal government,[12] pharmacists share prescriptive authority with other healthcare professionals.[13] Pharmacists will find themselves in new legal and ethical positions as a result of these expanded prescribing roles.[14]

In most successful examples, pharmacists and physicians enter into a collaborative practice agreement. There is a specific Scope of Practice for the pharmacist in which, physicians diagnose and make initial treatment decisions, then authorize the pharmacist to continue, select, initiate, monitor, modify, or discontinue medications as necessary to achieve established therapy goals and favorable patient outcomes. While such pharmaceutical care goals can be provided through conventional pharmacy approaches, when legally feasible, CDTM agreements make provision of care simpler, more efficient, and more convenient than through traditional means. In addition, the literature is now rich with data proving that every dollar invested in clinical pharmacy services returns financial rewards and reduces patient mortality.[15]

Some examples of tasks associated with the provision of pharmaceutical care through CDTM have been published.[16] Many of these tasks are necessary to help patients use their medication optimally, but may be prohibited for pharmacists to perform independently by some state pharmacy statutes and regulations. CDTM may also be prohibited in some current practice sites of traditional pharmacy because they lack some core requirements from the list given above.[17] Note that we are discussing a fundamental change in the medication use *system*.

Next, we discuss the writing of a Collaborative Practice Agreement. This discussion assumes that core requirements for CDTM have been met or exceeded. Legal requirement may differ from state to state and from one practice environment to another. Credentialing re-

quirements might also be very different depending on the environment of care and the tasks the pharmacist wishes to perform. To confirm that all core requirements are met, most health systems require "privileging" or approval by a health system committee. During this process a healthcare organization, having reviewed an individual healthcare provider's credentials[10] and performance and found them satisfactory, authorizes that individual to perform a specific scope of patient care service within the organization. Credentialing and privileging are processes fundamental to CDTM.

Even though many pharmacists possess all of the core requirements, the widespread implementation of CDTM has not yet occurred. Although progress is being made in many environments, integrated health systems are among the fastest moving. Perhaps this is because these systems are rapidly incorporating the factors that support pharmaceutical care. Five enabling factors have been identified as features of a system or infrastructure that would likely facilitate CDTM or pharmaceutical care:

- Presence of an integrated electronic medical records system.
- Availability of an automated dispensing system for ambulatory care prescriptions.
- Pharmacist participation on multidisciplinary care teams.
- Support from medical staff.
- Support from senior management.

These trends in ambulatory care pharmacy have been studied by two surveys of the ASHP Managed Care and Ambulatory Care Pharmacy in Integrated Health Systems.[18,19]

COLLABORATIVE PRACTICE AGREEMENTS

The document describing the specific routine and non-routine professional duties to be performed (the boundaries of practice) and the general areas of responsibility for each pharmacist practitioner is called a Scope of Practice. When this scope of practice has concurrence by the physician(s) or other collaborating practitioners in the patient care/program area in which the pharmacist functions, it is called a Collaborative Practice Agreement (CPA). The health system will generally have written policies to address all aspects of scope of practice issues for pharmacists including medication prescribing authority, quality assurance, and peer review. In addition, a process of credentialing and privileging will be outlined in policy, and CPAs will be reviewed at predetermined frequencies by appropriate boards, individuals, and committees.[20,21] An example of a CPA for primary care pharmacists is shown in Fig. 1.

TYPES OF COLLABORATIVE PRACTICE AGREEMENTS

CPAs can be written as process specific, or disease-state specific, or both. Process documents describe the routine duties of the pharmacist in global terms; e.g., write prescriptions, order laboratory tests needed to monitor medication, order certain radiological tests, take medication histories, record information in the medical record, order consults, etc. Disease specific CPAs give examples of the specific patient populations the pharmacist will see, and may include protocols for patient management. These CPAs may describe comprehensive, interim-care, and unscheduled or acute-care practice models.

Provision of *longitudinal comprehensive pharmaceutical care* using CPAs involves evaluation of patients' drug-related problems during an ongoing relationship with other care providers. One example of a pharmacist's role in CDTM programs focuses on identification of drug-related problems in the comprehensive review of a patient's medical record and by interviews with the patient. This review can be conducted when the patient is admitted to a general inpatient facility or is in an outpatient, primary-care clinic. In this model, the pharmacist uses a problem-based approach to determine the presence of medication-therapy problems and composes a problem list considering and incorporating disease state, adverse effects, cost, and compliance issues. The pharmacist then establishes treatment goals, monitoring parameters, and plans patient follow-up. Documentation in the medical chart of these actions is a critical component of any CDTM model. Interventions using this comprehensive model have been described.[22]

Interim care is defined as frequent care for specified patient populations and close patient monitoring between visits to the primary provider. Interim care models follow a similar process for delivering care as do comprehensive pharmaceutical care models, but on a disease-state specific basis. Many examples of this exist in the CDTM model. Examples of interim-care CDTM models include: anticoagulation/heparin clinics and clinics to treat asthma, seizures, pain, hypertension, diabetes, HIV, dyslipidemia, congestive heart failure, and other chronic-disease conditions.

Pharmacists working within *unscheduled acute care* or *urgent care models* handle patient issues that require immediate attention between scheduled visits. Some

SCOPE OF PRACTICE

Clinical Pharmacy Specialist

PHARMACIST: _____

I am educationally competent and physically capable of performing the activities that I have requested. Where indicated below, it is fully understood that my scope is defined by approved protocols/procedures.

Signature of Applicant Date

RECOMMEND APPROVAL/DISAPPROVAL

Chief, Pharmacy Service Date

Reviewed by Credentialing Subcommittee on _____ APPROVED/DISAPPROVED

RECOMMEND APPROVAL/DISAPPROVAL

Chief of Staff Date

RECOMMEND APPROVAL/DISAPPROVAL

Medical Center Director Date

Granted on: _____

To be reviewed on or before: _____

References:
VHA Directive 10-95-019 - General Guideline for Furnishing Medication Prescribing Authority for Clinical Nurse Specialists, Nurse Practitioners, Clinical Pharmacy Specialists and Physician Assistants, dated March 3, 1995
VHA Directive 96-034 – Scope of Practice for Clinical Pharmacy Specialists, dated May 7, 1996

Fig. 1 Example of a CPA for primary care pharmacists.

C

1. PURPOSE:

To identify scope of practice privileges for the clinical pharmacy specialist (CPS) at the VA Medical Center, and to define criteria for the qualifications for these privileges. The CPS will be qualified and authorized to perform specific clinical duties to assure high quality health care and appropriate pharmaceutical care is provided to the veterans.

2. POLICY:

Scope of practice guidelines for CPS shall be delineated in writing and will follow established protocols.

3. QUALIFICATIONS:

The CPS is trained in clinical pharmacy, clinical pharmacokinetics and clinical pharmacology. He/she is a Masters or Pharm. D. graduate, has completed an accredited pharmacy residency, is a specialty board certified pharmacist, or has equivalent education, training and experience functioning as a clinical pharmacist.

4. KEY FUNCTIONS:

- Conduct comprehensive appraisals of patients' health status by taking health histories, drug histories and performing physical examinations necessary to assess drug therapy
- Document relevant findings of a patients' health status in the patients' medical record
- Evaluate drug therapy through direct patient care involvement, with clinical assessment, subjective and objective findings relating to patient's responses to drug therapy and communicating and documenting those findings and recommendations to appropriate individuals and in appropriate records (i.e., patient's medical record)
- Develop, document and execute therapeutic plans utilizing the most effective, least toxic, and most economical medication treatments as per national or VA guidelines or VISN protocol or established local protocol
- Provide ongoing primary care for chronic stable or minor acute health problems as delineated in protocols/procedures
- Provide patient and health care professional education and medication information
- Evaluate and document patients' and caregivers ability to understand medication instructions and provide oral and written counseling on their medications
- Refer patients by consult to specialty clinics, order appropriate laboratory tests and other diagnostic studies necessary to monitor and support the patient's drug therapy
- Perform venipuncture or finger sticks for the purpose of withdrawing blood for clinical laboratory test
- Prescribe medications, including initiation, continuation, discontinuation, and altering therapy, based upon established formulary or protocols
- Conduct and coordinate research drug investigations and research under FDA guidelines and regulations and approval by appropriate local officials

Fig. 1 Example of a CPA for primary care pharmacists (*Continued*).

- Analyze laboratory and diagnostic test data so as to modify drug therapy and dosing as necessary.
- Perform physical measurement necessary to assure the patients responses to drug therapy
- Implement protocols approved by the Pharmacy and Therapeutics Committee or other Medical Center Committees regarding drug therapy
- Assist in the management of medical emergencies, adverse drug reactions, and acute and chronic disease states
- Administer medication according to pre-established protocol when requested by physicians
- Identify and take specific corrective action for drug-induced problems
- Serve as clinical managers of drug and drug-related programs in clinics and wards in conjunction with the attending physician

5. FURNISHING MEDICATIONS AND SUPPLIES:

A. The ability to prescribe non-controlled medications has been outlined in the General Guideline for Furnishing Medication Prescribing Authority for Clinical Nurse Specialists, Nurse Practitioners, Clinical Pharmacy Specialists and Physician Assistants in VHA Directive 10-95-019. CPS will initiate, continue, modify and monitor medication therapy as outlined in approved treatment protocols listed below or in policies and procedures of the Medical Center. The CPS will prescribe all drugs except narcotics.

B. Equipment and non-medication supplies issued by Pharmacy and Prosthetics/Materials Management Services may be ordered without co-signature of a physician.

6. SUPERVISION:

A collegial relationship with mutual consultation and referral exists with the physicians and the CPS. Consultation with the physician or referring practitioner is outlined and co-signature is required for practice outside approved procedures/protocols. The CPS will provide patient care as a Non-Physician Clinician (NPC). A physician is available at all times by telephone or in person for consultation. Periodic chart and peer reviews, and annual evaluations provide ongoing medication use evaluation. The CPS prescribing practices are included in the medication use evaluation process.

7. CLINICAL CONDITIONS:

The following is a list of clinical conditions that the CPS at the VA Medical Center would commonly be referred for evaluation and management. The most recent version of the protocols listed will be the working copy of the CPS protocols.

VISN 21 Protocol

	Requested		**Approved**		**Approved with Supervision**	
	No	Yes	No	Yes	No	Yes
Anticoagulation Clinic	☐	☐	☐	☐	☐	☐
Medication Renewal Clinic	☐	☐	☐	☐	☐	☐

Fig. 1 Example of a CPA for primary care pharmacists (*Continued*).

VHA Treatment Guidelines Pharmacologic Management of:
http://www.dppm.med.va.gov/PBM/menu.htm

	Requested		Approved		Approved with Supervision	
	Yes	No	Yes	No	Yes	No
Chronic Heart Failure	☐	☐	☐	☐	☐	☐
Chronic Obstructive Pulmonary Disease	☐	☐	☐	☐	☐	☐
Depression	☐	☐	☐	☐	☐	☐
Type 2 Diabetes Mellitus	☐	☐	☐	☐	☐	☐
Gastroesophageal Reflux Disease	☐	☐	☐	☐	☐	☐
H. pylori in PUD and Dyspepsia	☐	☐	☐	☐	☐	☐
Hyperlipidemia	☐	☐	☐	☐	☐	☐
Hypertension	☐	☐	☐	☐	☐	☐

VHA Clinical Practice Guidelines for the Management of:
http://www.va.gov/HEALTH/clinical.htm

	Requested		Approved		Approved with Supervision	
	Yes	No	Yes	No	Yes	No
COPD/Asthma	☐	☐	☐	☐	☐	☐
Major Depressive Disorder	☐	☐	☐	☐	☐	☐
Diabetes Mellitus	☐	☐	☐	☐	☐	☐

Other National Guidelines

	Requested		Approved		Approved with Supervision	
	Yes	No	Yes	No	Yes	No
HIV/AIDS Antiretroviral Therapy	☐	☐	☐	☐	☐	☐

Other Clinical Conditions (specify):

	Requested		Approved		Approved with Supervision	
	Yes	No	Yes	No	Yes	No
_____	☐	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐	☐

Fig. 1 Example of a CPA for primary care pharmacists (*Continued*).

patients may be new with no previously scheduled appointment. With this approach, pharmacists solve specific, urgent-care needs. Comprehensive evaluations, drug-therapy reviews, and extensive suggestions for treatment-plan modifications are not routine activities associated with this model, as pharmacists may not have an opportunity to perform follow-up with these patients. Examples of acute-care CDTM models include:

1. Refill/triage clinics.
2. Code teams.
3. Operating room protocols.
4. Polypharmacy consults.
5. Renal function drug dosing program.
6. Parenteral to oral route switch programs.

CONCLUSION

Pharmacists are assuming new roles in the healthcare system. Pharmacists with roles as direct patient care providers with expertise in identifying, resolving, and preventing drug-related problems are providing pharmaceutical care through CDTM. Essential components for the provision of CDTM have been identified. As examples and models of pharmacists' contributions in CDTM programs continue to grow, new proactive models will allow pharmacists to become key members of a system to decrease medication errors and their related costs.

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College of Psychiatric and Neurologic Pharmacists

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INTRODUCTION

The College of Psychiatric and Neurologic Pharmacists (CPNP) was founded on March 24, 1998 when the network of pharmacists formerly known as the Conference of Psychiatric and Neurologic Pharmacists became an official professional society.

The formation of CPNP was the culmination of efforts of many pharmacists practicing in the psychiatry and neurology specialties over the past 30 years. But serious discussion for a formal professional society began at a strategic planning meeting in Austin, Texas, in October 1994. Forty neuropsychiatric pharmacists held a post-CE-program planning conference that would eventually give birth to CPNP. In the summer of 1997, a smaller group of these pharmacists drafted a constitution and bylaws that were eventually approved by the founding membership. A call was issued for founding members in the fall of 1997, which generated 60 additional members. Eventually, 116 founding members joined ranks to create the College of Psychiatric and Neurologic Pharmacists. These members then ratified the constitution and bylaws and nominated candidates for offices. The first officers were sworn in at the First Annual Meeting of the College in Orlando, Florida, April 23–26, 1998. They were President: Gary M. Levin (Albany, New York), president-elect: Alex A. Cardoni (Storrs, Connecticut), Treasurer: James E. Wilson (Omaha, Nebraska), Secretary: Cherry W. Jackson (Charleston, South Carolina), Director-at-Large: Lawrence J. Cohen (Oklahoma City, Oklahoma), and Director-at-Large: Sally K. Guthrie (Ann Arbor, Michigan).

ORGANIZATIONAL STRUCTURE AND GOVERNANCE

The CPNP constitution and bylaws provide for the structure and governance of the organization. Membership consists of Active Members, Founding Members, and Corporate Members.

Active Members are dues-paying members who are interested in advancing the specialty of psychiatric or neurologic pharmacy.

Founding Members include original members instrumental in creating CPNP who have paid Founding Member dues.

Corporate Members consist of corporations and members of corporations who are interested in supporting the goals and objectives of CPNP.

The officers of CPNP are president, immediate past-president, president-elect, secretary, and treasurer. The president-elect is elected by the general membership for a one-year term and ascends successively to the office of president. The president ascends to the office of immediate past-president. The secretary and treasurer are elected on alternate years for a two-year term of office.

The president chairs the Board of Directors and presides at all meetings of the Board as well as general membership meetings. The president appoints all chairs and members of committees and is an ex-officio member of each committee.

The immediate past-president presides at meetings in the absence of the president and the president-elect.

The president-elect executes the duties of the president in the president's absence and is vice-chair of the Board of Directors.

The secretary records minutes of all meetings, maintains the membership roll, receives and prepares all correspondence, and approves all membership applications.

The treasurer serves as the custodian of all funds, receives and keeps account of all monies received as dues or from other sources, and disburses monies at the discretion of the Board of Directors.

The Board of Directors of CPNP is composed of the elected officers and two Directors-at-Large elected by the membership. The Board represents the organization as the official voice of all members. The Board has charge of property and authority to control and manage the affairs and funds of the organization, and also to supervise all publications and to select editors for publications. The Board makes ultimate decisions regarding actions of

committees and officers on professional and administrative matters.

CPNP committees function in an advisory capacity to the Board of Directors, developing and implementing programs and policies authorized by the Board in the major areas of interest to which it is assigned.

The following are standing committees of CPNP: Communication and Information—responsible for publishing the CPNP Newsletter and maintaining the web site cpnp.org; Community Resource—acts as a liaison to extramural groups and organizations on issues relating to psychiatry and neurology; Program—responsible for planning the annual meeting as well as other continuing education programs; and Membership—responsible for the recruitment and retention of members of CPNP.

CPNP officers since its founding are summarized: 1998—President: Gary Levin; president-elect: Alex Cardoni; Secretary: Cherry Jackson; and Treasurer: James Wilson. 1999—President: Alex Cardoni; president-elect: Roger Sommi; Immediate Past-President: Gary Levin; Secretary: Cherry Jackson; and Treasurer: James Wilson; and 2000—President: Roger Sommi; president-elect: Cherry Jackson; Immediate Past-President: Alex Cardoni; Secretary: Judith Curtis; and Treasurer: James Wilson. The following members were elected as Directors-at-Large: 1998–2000—Lawrence Cohen; 1998–2001—Sally Guthrie; and 2000–2002—Charles Caley.

MEMBERSHIP

As of fall 2000, the College of Psychiatric and Neurologic Pharmacists has a membership of approximately 300 individuals. In a survey of CPNP membership conducted in 1999, the following profile emerged:

- 60% between ages of 31–50.
- 52% female.
- 45% based in hospitals.
- 57% in practice less than 10 years.
- 50% with psych/neuro specialty residency training.
- 20% with fellowship training.
- 70% working in psychiatric pharmacy; 10% in neurologic pharmacy.
- 55% board certified in psychiatric pharmacy.

MISSION

The mission of the College of Psychiatric and Neurologic Pharmacists is to advance neuropsychiatric pharmacy practice, education, and research and to optimize the health of individuals affected by psychiatric and neurologic disorders.

Objectives include the following:

- Facilitate dissemination of information regarding psychotherapeutic pharmacotherapy, patient care, and community support.
- Endorse the Psychiatric Pharmacy Certification Exam process and support programs for the preparation of candidates for the exam.
- Facilitate programming in the areas of psychiatric and neurologic pharmacy at national meetings and with organizations that support our interests.
- Improve patient care.
- Promote research in patient care.

CURRENT MAJOR INITIATIVES

The Board of Directors has identified several priority initiatives in 2000:

- Further develop and refine "cpnp.org" web site.
- Retain the services of a management consultant to assume responsibility for routine administrative operations of the organization.
- Implement and facilitate a board recertification process for board certified psychiatric pharmacists by working with existing professional organizations.
- Initiate strategic planning for the organization that will set goals and objectives and a budget for the next several years.
- Stimulate development of pharmaceutical care psychiatric and neurologic clinical services by establishing a competitive "visiting expert" grant program.
- Stimulate development and growth of regional affiliates to facilitate attainment of CPNP goals and objectives.

MAJOR MEETINGS

CPNP holds its annual meeting in the spring, usually late March or early April. The site of the meeting changes to include East Coast, mid-America, and West Coast. The meeting is 2–2 1/2 days in length and includes sessions which focus on contemporary clinical and research topics in psychiatric and neurologic pharmacy. A poster session allows for presentation of research and clinical practice activities of members.

CPNP members also traditionally participate in the annual NCDEU meeting sponsored by the National Institutes of Mental Health. This meeting is held in the spring as well, usually in late May or early June. The location has been (with few exceptions) in Boca Raton, Florida. Cutting-edge programming characterizes this meeting, with presentations from leading NIH researchers as well as others in the United States and abroad. A poster session also facilitates reporting of research findings.

Regional programming for CPNP members and other psychiatric and neurologic pharmacists is provided by local "chapters" of CPNP throughout the country. Annual pharmacotherapy updates are held in the Northeast region (fall), Georgia-Southeast (winter), Midwest region (fall), Texas (fall), Arizona-Southwest (winter), and in Montana-Northwest (spring). These sessions bring high-quality programming to members and nonmembers who may not be able to attend the annual meeting.

Commission to Implement Change in Pharmacy Education, AACP

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INTRODUCTION

In July, 1989, Dr. William A. Miller, President of the American Association of Colleges of Pharmacy (AACP), appointed the Commission to Implement Change in Pharmacy Education to consider, debate, and offer recommendations on a series of issues pivotal to the further development of pharmacy education in the United States.

DISCUSSION

Members of the Commission included C. Douglas Hepler, Ph.D.; Mary Anne Koda-Kimble, Pharm.D.; David A. Knapp, Ph.D.; Kenneth W. Miller, Ph.D.; Milap C. Nahata, Pharm.D.; Charles O. Rutledge, Ph.D.; William E. Smith, Ph.D.; John H. Vandel; Victor A. Yanchick, Ph.D.; Charles A. Walton, Ph.D.; and Harold H. Wolf, Ph.D. (Chairman). Richard P. Penna, Pharm.D. artfully crafted the discussions of the Commission into documents.

Key questions to be addressed by the Commission included: What is the mission of pharmacy practice that should serve as the basis for pharmaceutical education? What types of pharmacy manpower are needed to fulfill this mission? What should be the curricular emphasis in an entry-level pharmacy practice degree? What should be the length of the curriculum and title of the degree? When should differentiation occur in the continuum of pharmaceutical education and training, and what are the roles of postgraduate educational experiences? What are the needs of the pharmacy enterprise for pharmaceutical scientists and clinical scientists, and what are appropriate models for such training? What changes in accreditation standards should be made by the American Council on Pharmaceutical Education to facilitate the broad implementation of such reforms?

The Commission met 13 times over a 3-year period and produced a series of position papers containing policy statements for AACP as well as recommendations for actions directly impacting pharmacy education that were to be implemented at individual schools or colleges.

Initially, the Commission examined the purpose of pharmaceutical education in contemporary society. To do this, it developed working statements for the mission of the profession of pharmacy and for pharmacy practice.[1] In crafting the former, the Commission offered the view that "The pharmacy profession is a major part of a system that discovers, develops, produces, and distributes drug entities and drug products. It creates, and disseminates knowledge related to drug entities, drug products, and drug distribution systems. The major outputs of the profession are pharmaceutical care, knowledge, drug entities and drug products. The primary personnel in the profession that produce these outputs are practitioners, educators, researchers, and those involved with the manufacture and distribution of drug products (p. 375)."

In designing a working mission statement for pharmacy practice, the Commission expressed its belief that "... the mission of such practice is to render pharmaceutical care with the view that such care focuses pharmacists' attitudes, behaviors, commitments, concerns, ethics, functions, knowledge, responsibilities, and skills on the provision of rational drug therapy. The goal of such therapy being outcomes which improve the quality of patients' lives (p. 376)."

While the Commission clearly recognized that the mission of pharmaceutical education certainly derives from the mission of the profession and thus must be consistent with the mission of pharmacy practice, it also recognized that the enterprise of pharmacy education is responsible for fulfilling that portion of the profession's mission that relates to research and education. Thus, the Commission described the mission of pharmaceutical education, in part, as follows:

> Pharmaceutical education is responsible for preparing students to enter into the practice of pharmacy and to

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DOI: 10.1081/E-ECP 120006188

function as professionals and informed citizens in a changing health care system. It does this by maintaining a dynamic, challenging, and comprehensive curriculum. It is also responsible for generating and disseminating new knowledge about drugs and about pharmaceutical care systems.

Pharmaceutical education inculcates students with the values necessary to serve society as caring, ethical, learning professionals and enlightened citizens. It provides students with scientific fundamentals and fosters attitudes necessary to adapt their careers to changes in health care over a lifetime. It also encourages students prior to and after graduation to take active roles in shaping policies, practices, and future directions of the profession.

Pharmaceutical education promotes advances in pharmaceutical care by fostering postgraduate residencies and fellowships in the clinical sciences and differentiated areas of pharmacy practice. It provides structured postgraduate education and training through which practitioners maintain their competence and acquire new competencies to serve the changing needs of society.

Pharmaceutical education is responsible to the profession and to society for generating new knowledge about drugs, drug products, drug therapy, and drug use through the conduct of basic and applied research. It promotes the pharmaceutical sciences by fostering graduate education and research within its schools and colleges. Pharmaceutical education is responsible for both professional education and graduate education for research. The latter focuses on preparing students to discover new knowledge, primarily by use of the scientific method. The goal is to prepare scholars to perform independent, creative research that addresses important questions related to the discovery and use of drugs.

Pharmaceutical education continually evaluates its mission, objectives, goals, and outcomes and determines and implements necessary changes in the nature and scope of education and research performed within the purview of pharmaceutical education (p. 376).

Perhaps the most substantive portion of the Commission's work resides in its second position paper (Background Paper II) which dealt with issues of entry level, curricular outcomes, curricular content, and educational process.[2] In considering what is "entry level," the Commission embraced the view that while a system of pharmaceutical care requires the participation of both generalists and specialists, students prepared at the entry level are general practitioners who coordinate and render pharmaceutical care. And they must be able to do this at a level commensurate with the evolving mission of pharmacy practice (see above).

Based on this assumption, the Commission outlined the major practice functions that comprise pharmaceutical care as rendered at the entry level and offered recommendations for the educational outcomes and competencies that are necessary to perform pharmaceutical care functions.

The practice functions identified were:

- Participate in the drug use, decision-making process.
- Select the appropriate dosage form, formulation, administration, and delivery system of specific drug entities.
- Select the drug product source of supply.
- Determine the dose and dosage schedule.
- Prepare medication for patient use.
- Provide drug products to patients.
- Counsel patients.
- Monitor patients to maximize compliance.
- Monitor patients' progress with regard to therapeutic objectives.
- Monitor patients to prevent adverse drug reactions and drug interactions.

Several general outcomes and competencies were described that underlie the education of a professional person and citizen. These included:

- Thinking abilities involving scientific comprehension and critical thinking.
- Communication abilities involving communication competence and aesthetic sensitivity.
- Facility with values and ethical principles involving professional ethics.
- Personal awareness and social responsibility involving contextual competence and professional identity.
- Self-learning abilities and habits involving adaptive competence, scholarly concern for improvement, and motivation for continued learning.
- Social interaction and citizenship including effective, interpersonal, and intergroup behaviors as well as leadership competence.

Additional professional outcomes and competencies were identified as essential to perform the functions that support practice. These included the broad skills necessary to solve problems and make decisions; manage; learn; communicate, teach, and collaborate; and participate in policy formulation and professional governance.

The Commission than proceeded to describe a core curriculum to serve as a guide for pharmacy faculty at individual schools and colleges to design the content of a specific curriculum felt likely to engender the competencies and outcomes necessary to render pharmaceutical care.

A major portion of the Commission's efforts in the area of curriculum was devoted to recommendations relating to the educational process. Particular suggestions were offered to assist faculty in teaching problem solving, fundamental information, communication skills, and practice skills.

Certainly the most controversial issues examined by the Commission were those contained in its position paper dealing with the standards of educational quality necessary for the entry-level curriculum, the length of that curriculum, and the title of the ensuing degree.[3] The Commission concluded that AACP must advocate the outcomes, competencies, content, and processes contained in Background Paper II before the American Council on Pharmaceutical Education (ACPE) for incorporation into the revised entry-level program accreditation standards that the Council was then developing. It emphasized that this should be done for all programs, including existing Pharm.D. offerings. The Commission went on to say that at least one additional year of professional education (beyond the 5-year entry-level programs commonly in place) was needed to accomplish the educational objectives previously described, and thus, proposed that AACP endorse an entry-level program that is at the doctoral level, is at least four professional, academic years in length, and follows preprofessional instruction of sufficient quality and length (2-year minimum) to prepare applicants for doctoral level education. Finally, the Commission proposed that AACP support the doctor of pharmacy (Pharm.D.) degree as the sole degree for entry into pharmacy practice and offered several recommendations to overcome the barriers that could impede the process of implementing such needed changes in pharmaceutical education.

The balance of the Commission's efforts related to discussions surrounding faculty scholarship, graduate education, fellowships, and postgraduate professional education.[4] Particular attention was focused on issues of fostering scholarship, assessing graduate programs, preparing clinical scholars, developing mid-career residencies, and considering the role of distance learning in sustaining up-to-date competence. Numerous recommendations were advanced, with the intent that these profound responsibilities of the enterprise of pharmaceutical education receive the attention necessary to catalyze required change.

The Commission was reappointed in 1995 by AACP President Mary Anne Koda-Kimble to analyze and assess how a range of rapid and extensive changes in health care delivery, education, and research might alter its original observations and recommendations. The Commission met twice, reaffirmed the contemporary value of its original views, and, in 1996, encouraged all schools and colleges of pharmacy to accelerate their plans for curricular reform based on recommendations made in its previous reports.[5]

While history will judge the overall impact of the Commission's work, there is little doubt that the effort was a catalyst for major change in pharmaceutical education.[6] Subsequent to the release of the Commission's reports and adoption of most of its recommendations by AACP in 1992, major, nationwide energies were, and continue to be, directed toward changes both in curricular structure based on educational outcomes as well as in the process of teaching within the curriculum. Moreover, there occurred a substantial increase in the number of schools offering the Pharm.D. as the sole professional degree. At the time the Commission's recommendations were adopted, 19% of pharmacy schools offered the Pharm.D as the sole professional degree. As of fall 1995, 37% of schools were admitting students into all Pharm.D. programs. In fall 1996, that percentage increased to over 50%. Finally, as a result of the Accreditation Standards and Guidelines for the Professional Program in Pharmacy Leading to the Doctor of Pharmacy Degree adopted June 14, 1997 by the American Council on Pharmaceutical Education,[7] all schools of pharmacy will only admit students into a Pharm.D. program by 2002. Thus, an issue that had been hotly debated within and outside of AACP for some 42 years is finally resolved.

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Computer Software for Clinical Pharmacy Services

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INTRODUCTION

The decision-making process for purchasing computer software for use by pharmacists used to be a lot simpler. A small task force was formed with the goal of formulating a recommendation of the most functional software solution for any individual pharmacy department, outpatient pharmacy, or community pharmacy. A few site visits would take place, perhaps, and a budget would be drawn up for acquisition cost, training requirements, and ongoing/monthly update costs. The decision to purchase would be made, and then development of the necessary interfaces would begin (usually as an afterthought). The development of these interfaces would often consist of an employee looking at the screen of one system while typing those data into a second system.

The pendulum has now swung to another extreme where integration is a primary consideration for purchase decisions. Mainframe computers, which were nearly pronounced dead, are now being looked at favorably as the repository for a data warehouse that contains all necessary clinical information. The data repository concept is providing the thrust to move organizations into a future driven by an information-rich environment. Unfortunately, health system pharmacy departments are often mandated departmental solutions that are functionally inferior to their stand-alone systems, but are sold as globally integrated within the healthcare institution. Some of these systems are so terrible that pharmacists operate manually all day and then hire clerks to input transactions that occurred during the day in an after-hours session.

SYSTEM OVERVIEW

The decision to purchase pharmacy departmental software includes additional vendor-related factors that must be considered. There is a growing trend among many of the larger vendors to minimize the importance of functionality based on the opinion that many of the software systems are beginning to look and act alike. If this is indeed true, it is potentially more important to focus on the ability of the different vendors to implement their applications. The common conception that larger vendors provide better products and services must also be reconsidered. With a larger customer base comes less customization and specialization for the individual customer. While larger companies do have increased financial stability, the ability of a smaller company to tailor a product to a customer's specific usage cannot be overstated. Finally, we have seen from direct experience that many of the vendors in today's market have more than enough clients to get them through the coming year. Decision makers within health systems must recognize this fact and plan accordingly. Agree upon a timetable suitable for your system yet feasible for your vendor. And most importantly, recognize that the vendor's responsibility is to design and install the system, as well as to train your personnel. It is your responsibility to implement the system and put it to use as best applies to your health system.[1]

Today, the purchase of information technology solutions for pharmacy confronts decision makers with a vast array of decisional factors to consider. Some of these include:

- Identification of the core competency of vendors being considered.
- Comparison of the largest installation and installed user base of vendors.
- Comparison of budgetary constraints and prices of various solutions.
- Careful consideration of operating system platforms that are supported.
- Level of Transmission Control Protocol/Internet Protocol (TCP/IP) and Health Level 7 (HL7) support.
- System interfaces that include admission discharge transfer (ADT), pharmacy charges, automation, labs, etc.

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DOI: 10.1081/E-ECP 120006318

- Identification of value-added features and enhancements that discriminate one choice from other solutions.
- Vendor ability to personalize the solution for a health system's specific needs.
- Determination of quality assurance and safety features.
- Satisfaction that security features are adequate and responsive to the organizational structure.
- Identification of the frequency of significant system upgrades.
- Determination of the assistance available for data migration and the system rollout planning.
- Strategic and tactical consideration for how the pharmacy software solution matches up with the clinical information systems, Internet solutions, health resource planning, access management, decision support, home care, managed care, and infrastructure applications.

These considerations are primarily enterprise-wide in scope. With integration being of primary importance to healthcare in general, it is still necessary to obtain best-of-class software solutions for specific pharmacy activities. Recommendations that will help select appropriate applications and technologies that are backed by reliable implementation, support, and services will be the focus of the remainder of this chapter. Refer to Tables 1 and 2 (used with permission from *ComputerTalk*) as you read this chapter. These figures contain an extensive evaluation of the current information systems market.

THE HARDWARE ARRAY

Decision-makers now have an interesting array of hardware options with which to manage the data processing for pharmacy operations. Client/server architecture is still the dominant means of configuration, but Application Service Providers (ASPs) are expected to be utilized more as both information technology (IT) professionals and corporate executives begin to understand what these services offer. As pharmacists have moved from the central pharmacy into satellite pharmacies, home care, and other modalities that demand a mobile solution, other hardware must be considered for a total solution. Initially, pharmacists employed the use of notebook computers that operated offline for data storage and retrieval. These devices were limited because they did not provide real-time access to the health system's information system. Then, progressive hospitals began to develop the necessary infrastructure and to connect these devices wirelessly. More recently, however, enough resources have been developed in the PDA (personal digital assistant) market to have this platform considered fully in any purchase decision. PalmPilots and other compatible devices now comprise over 80 percent of the PDA market. Wireless versions using a variety of bandwidths and frequencies are making it possible to provide connectivity to devices that easily fit within the shirt pocket, lab coat pocket, and purse. As memory increases in these PDA devices, it is now possible to have complete medication references as well as network access, a bar-code scanner, a pager, a digital voice recorder, and a cellular telephone combined into a single device.

One must also consider the functional specifications of workstation hardware. While we're waiting for the perfectly integrated system to be realized, it will be necessary to consider terminal emulation as a first step in communicating with diverse systems. Previously, "dumb" terminals, which consisted of a keyboard and monitor connected to a server, dominated the workstations used in most pharmacies. Now a combination of terminal emulation running on microcomputers and Internet thin client workstations are beginning to proliferate. With the use of terminal emulation it is possible to have three or more patient sessions running on a taskbar of a Microsoft Windows workstations and, through multitasking, access Internet-based and information applications simultaneously. Due to the volume of data that must be transmitted, some functions still tend to run better offline during peak network congestion times in an organization. As bandwidth increases, this problem may diminish.

The importance of integration between systems is quite high. Historically, pharmacy departments purchased point-to-point interfaces at a cost of $1500 to $15,000 each. Interfaces are now more popular and often are more cost-effective for an organization. So important is the functioning of these interfaces that many pharmacists wear pagers that alert them when an interface has gone down. This occurs automatically as pages are sent from the information technology systems as problems are identified. Another interface consideration is the ability to remotely address problems such as these. Programs that allow system access and control from any computer in the world are becoming normal. Of course, firewall protection from unwanted intruders is necessary in all aspects of data management, including remote access.

Telecommuting presents unique opportunities and challenges for the health system and the pharmacy department, especially. As the pharmacist shortage continues, with one pharmacy chain reportedly building enough stores to hire every pharmacy school graduate for the next ten years, new approaches to practice must be explored. Telecommuting will be one response to this shortage, bringing the work to the worker. When work can be brought to the worker instead of bringing workers to the

Table 1 Entry-level prices for products and services

See page		Retail Pharmacy Mgmt.	Chain Central Mgmt.	Automated Dispensing/ Robotic Systems	HME/ Diabetes Type II Billing	E-Prescriptions	POS	Pharmaceutical Care	Self-Care/ Nutritional
65	Allwin Data	-	-	-	c/p[1]	-	-	-	-
65	AppDC	-	-	-	-	-	-	-	-
7	ateb, Inc.	-	-	-	-	c/p	-	-	-
39	Cam Commerce Solutions	-	-	-	-	-	$8,157[3]	-	-
8	CarePoint, Inc.	$9,500[S]	c/p	c/p	inc.	c/p	$3,500[S]	inc.	-
9	ComCoTec	c/p	c/p	c/p	inc.	inc.	c/p	inc.	c/p
10	DAA Enterprises	$4,995	-	-	-	-	-	inc.	-
53	Delphi	$9,000[S]	-	-	-	-	-	$2,000[S]	-
65	Digital Simplistics	$6,950	-	-	-	-	-	-	-
40	D.P. Hamacher	-	-	-	-	-	-	-	-
58	Etreby Computer	$3,995[S]	-	-	inc.	inc.	$3,000[S]	$4,995[S]	-
60	First DataBank	-	-	-	-	-	-	-	-
41	Freedom Data Systems	$8,000	$14,000[7]	-	-	-	$13,500	-	-
65	GVP Medicare Billing	-	-	-	$149	-	-	-	-
13	HBS, Inc.	$7,995	$140,000[S]	c/p	-	inc.	$11,000[8]	-	$50/mo.
14	HCC	$2,995[S]	$7,500[S]	$1,500[S]	inc.	u/d	$3,995[S]	$2,995[S]	$50/mo.
15	Innovation Associates	-	-	$40,000	-	-	-	-	-
19	Interactive Systems	$9,995	c/p	c/p	[10]	c/p	$5,700[10]	[10]	-
66	The JAG Group	-	-	-	-	-	-	-	c/p
22	jASCorp	$5,995	c/p	-	-	-	c/p	$4,995	c/p
66	Liberty Computer	c/p	c/p	c/p	-	-	c/p	-	-
23	McKessonHBOC	$11,995[-1]	$29,995[11]	c/p	-	inc.	$13,995[11]	-	-
61	Micromedex	-	-	-	-	-	-	-	-
66	OmniSYS	$995[S]	-	-	[12]	-	-	-	-
67	OPUS Core Corporation	$3,000[S]	$6,500[S]	$3,500[S]	$1.25/cl.	$.25/trx.	$5,500[S]	-	$40/mo.
25	pc I	$4,000[S]	-	i/f inc.	inc.	inc.	$13,500[-/S]	$5,000[S]	-
26	PDX-NHIN	$10,500[S]	$50,000[S]	i/f inc.	-	inc.	c/p	$5,995[S]	-
62	Pharmex	-	-	-	-	-	-	-	-
28	QS/1 Data Systems	$8,000[S]	$12,000[S]	c/p	$2,500[S]	inc.[14]	$6,000[S]	inc.[14]	inc.[14]
55	RNA	$9,995[S]	-	$4,500[S]	inc.	$9,000[S15]	inc.[IF]	inc.	-
56	Rescol Systems Group	inc.	c/p	c/p	c/p[13]	-	inc.	inc.	-
30	Retail Mgmt. Products	-	-	-	-	-	-	-	-
46	RMS	-	$10,000[18]	-	-	-	$6,500	-	-
67	Rx-Net-Inc.	-	-	-	-	-	-	-	-
36	RX30	c/p	c/p	c/p	c/p	c/p	c/p	c/p	c/p
33	SRS	$8,200[20]	$12,950[20]	-	inc.	-	-	-	-
67	ScripMaster	$9,000	c/p	-	-	-	$20,000	-	$400/yr.
31	ScriptPro	-	-	c/p	-	-	-	-	-
32	Smart Solutions	-	-	-	-	-	-	-	-
68	SymRx	-	-	-	-	$60-75/mo.	-	inc.	inc.
34	TechRx	c/p	c/p	c/p	-	c/p	c/p	-	-
68	TMT	-	-	-	-	-	-	-	-
64	Two Point Conversions	-	-	-	-	-	-	-	-
68	Voice-Tech	-	-	-	-	-	-	-	-

Table 1 Entry-level prices for products and services *(Continued)*

Central Processing/Fill	Compounding Software	IVR	Workflow Mgmt.	Assisted Living	Long Term Care	Outpatient Hospital	HMO Pharmacy	Mail Order	Other
-	-	-	-	-	-	-	-	-	-
-	$1,975[2]	-	-	-	-	-	-	-	-
c/p	-	c/p	c/p	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-
c/p	inc.	c/p	c/p	inc.	$3,000[S]	$9,500[S]	-	-	-
c/p	inc.	c/p	inc.	c/p	c/p	c/p	c/p	c/p	4
-	-	-	-	-	$500[S]	-	-	$1,295[S]	-
-	inc.	-	-	-	$10,000[S5]	-	-	-	-
-	-	-	-	-	inc.	-	-	-	-
-	-	-	-	-	-	-	-	-	c/p
-	-	-	-	inc.	$5,995[S5]	$3,995[S]	$6,995[S]	$6,995[S]	-
-	-	-	-	-	-	-	-	-	c/p[5]
-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-
$300,000[S]	-	$2,995[S]	inc.	inc.	$7,500[S]	inc.	-	$75K-275k	-
inc.[9]	inc.	$6,995[H/S]	-	-	inc.	inc.	inc.	inc.	9
$40,000	-	-	$10,000[S]	-	-	$40,000	$40,000	$40,000	-
c/p	-	$5,995[10]	c/p	-	$5,000[10]	c/p	c/p	-	-
c/p	inc.	c/p	c/p	c/p	-	c/p	-	-	-
c/p	-	-	-	-	-	c/p	c/p	c/p	-
-	inc.	$2,400[11]	c/p	-	$5,995[11]	inc.	-	inc.	-
-	-	-	-	-	-	-	-	-	c/p[6]
-	inc.	-	-	-	-	-	-	-	-
-	$500[S]	$2,000[S]	-	$1,500[S]	$2,500[S]	$5,500[S]	-	$3,500[S]	-
-	inc.	i/f inc.	-	inc.	$500[S]	inc.	inc.	inc.	-
c/p	-	$150[S]	c/p	-	$1,800[S]	-	-	-	-
-	-	-	-	-	-	-	-	-	c/p[13]
$12,000[14]	inc.	$1,500[S]	inc.	$3,000[S]	$12,000[S]	inc.[11]	inc.[14]	inc.[14]	-
$7,500[S]	inc.	-	inc.	inc.	inc.	inc.	inc.	inc.	-
inc.	$260[15]	-	c/p	inc.	$885[15]	-	inc.	inc.	-
-	-	-	-	-	-	-	-	-	17
-	-	-	-	-	-	-	-	-	c/p[19]
c/p	c/p	c/p	-	c/p	c/p	c/p	c/p	c/p	-
$17,900[20]	-	-	-	$1,200[S]	-	Inc.	-	-	20
-	-	c/p	-	-	-	-	-	c/p	-
c/p	-	-	c/p	-	-	c/p	c/p	c/p	-
-	-	$3,500	$1,500	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-
c/p	-	c/p	c/p	c/p	c/p	c/p	c/p	c/p	-
-	-	$4,700	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	c/p[21]
-	-	$4,400[22]	-	-	-	-	-	-	-

Footnotes

1 Price based on transactions.
2 Includes software and support.
3 Price includes training.
4 System includes automatic online split billing.
5 Price includes assisted living.
6 Clinical drug information.
7 POS system for chain central management.
8 $11-12,000 —1 lane; $14-15,000 — 2 lane system.
9 Central fill is under development "other" includes Dr. Fax, for $1,295
10 HME is through OmniSYS CareCLAIM; POS price is per register, plus server. Pharm. Care through The jASCorp. IVR price is for four-line system. LTC is additional to retail system.
11 Discounts available to McKessonHBOC customers.
12 No charge for software, but there is a transaction charge.
13 Software-driven warning labels.
14 Included in retail and LTC systems. Central-processing/fill price reflects a host/remote only.
15 Price includes setup as Internet host.
16 Price represents monthly charge that includes license and support fees for software. Company charges on per-claim basis for HME and third-party claims submissions. All categories represent long-term-care pharmacy-management applications
17 Barcode scanning and verification systems, $399 to $1,495.
18 POS-host system.
19 Pricing service.
20 Price includes conversion, training, scanner, and laser report program. Chain-central management and central-processing/fill systems are scheduled for release 1Q/2001. "Other" price is $1,400 for major-medical accounts receivable.
21 Data conversion and database-management services.
22 $4,400 is for retail system; $7,500 for hospital/mailorder.

LEGEND

S = software only
H/S = hardware and software
i/f = interface
c/p = call for pricing
inc. = included in price of pharmacy-management system unless otherwise noted.
u/d = under development

Table 2 Installed base and functionality offered

See page		Segments Served						Functionality		
		Installed Base	Independents	Chains	Outpatient Hospitals	Mail Order	HMO Pharmacy	Retail Pharmacy Mgmt.	Chain Central Mgmt.	Auto. Dispensing/ Robotic Systems
65	Allwin Data	8,500[1]	•	•	•	•	•	-	-	-
65	AppDC	68	•	•	•	•	•	-	-	-
7	ateb, Inc.	10,000+[2]	•	•	•	•	•	-	-	-
39	Cam Commerce Solutions	200	•	•	•	-	-	-	•[3]	-
8	CarePoint, Inc.	110	•	•	•	•	•	•	•	i/f
9	ComCoTec	1,700	•	•	•	•	•	•	•	i/f
10	DAA Enterprises	475	•	-	•	•	-	•	-	-
53	Delphi	38[4]	•	•	•	-	-	•	-	i/f
65	Digital Simplistics	250	•	-	•	-	-	•	-	i/f
40	D.P. Hamacher	n/a[5]	•	•	-	-	-	-	-	-
5	Eatonform	300+[6]	•	-	-	-	-	-	-	-
58	Etreby Computer	1,336	•	-	•	•	•	•	-	-
60	First DataBank	n/a[7]	•	•	•	•	•	-	-	-
41	Freedom Data Systems	363	•	•	•	-	-	•	•[8]	i/f
65	GVP Medicare Billing	n/s	•	•	•	-	-	-	-	-
13	HBS, Inc.	1,000+[9]	•	•	•	•	•	•	•	i/f
14	HCC	3,000+	•	•	•	•	•	•	•	i/f
15	Innovation Associates	140+[10]	•	•	-	-	-	-	-	•
19	Interactive Systems	687[11]	•	-	•	-	•	•	•	i/f
66	The JAG Group	1,800	•	•	•	•	•	-	-	-
22	JASCorp	352	•	•	•	-	-	•	•	-
66	Liberty Computer	n/s	•	•	•	•	-	•	•	i/f
23	McKessonHBOC	2,900	•	•	•	•	-	•	•	i/f
61	Micromedex	n/a[12]	•	•	•	•	•	-	-	-
66	OmniSYS, Inc.	320[13]	•	•	-	-	-	•	-	i/f
67	OPUS Core Corporation	n/s	•	•	•	•	•	•	•	i/f
25	pc I	378[14]	•	•	•	•	-	•	-	i/f
26	PDX-NHIN	9,000	•	•	-	u/d	-	•	•	i/f
62	Pharmex	n/a[15]	•	•	•	•	•	-	-	-
28	QS/1 Data Systems	8,182	•	•	•	•	•	•	•	i/f
55	RNA	495	•	•	•	•	•	•	•	i/f
56	Rescot Systems Group	315[16]	•	•	•	-	-	-	•	i/f
30	Retail Mgmt. Products	3,000[17]	•	•	•	•	•	-	-	-
46	RMS	n/s[18]	•	•	•	-	-	-	•	-
67	Rx-Net-Inc.	n/a[19]	•	•	•	-	-	-	-	-
36	Rx30	1,850	•	•	•	•	•	•	•	i/f
33	SRS	140[20]	•	•	•	-	-	•	•	-
67	ScripMaster	350	•	•	-	•	-	•	•	i/f
31	ScriptPro	2,000[21]	•	•	•	•	•	-	-	•
32	Smart Solutions	4,000	•	•	•	•	•	-	-	-
68	SymRx	1,800[22]	•	•	-	-	-	-	-	-
34	TechRx	n/s[23]	•	•	•	•	•	•	•	i/f
68	TMT	430	•	•	•	•	•	-	-	-
64	Two Point Conversions	n/a[24]	•	•	•	-	-	-	-	-
68	Voice-Tech	n/s	•	•	•	•	-	-	-	-

Table 2 Installed base and functionality offered (*Continued*)

Functionality

HME/Diabetes Type II Billing	E-Prescriptions	POS	Pharmaceutical Care	Self-Care/Nutritional	Central Processing/Fill	Compounding	IVR	Workflow Mgmt.	Assisted Living	Long Term Care
•	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	•	-	-	-	-
-	•	-	-	-	•	•	•	•	-	-
-	-	•	-	-	-	-	-	-	-	-
•	•	i/f	-	-	•	•	i/f	•	•	•
•	•	i/f	•	•	•	•	i/f	•	•	•
-	-	i/f	•	-	-	-	-	-	•	•
-	-	-	•	-	-	•	-	-	•	•
•	•	i/f	-	-	-	-	i/f	-	-	•
-	-	-	-	-	-	-	-	-	-	-
•	•	-	-	-	-	-	-	-	•	•
•	•	i/f	•	-	-	-	-	-	•	•
-	-	•	-	-	-	-	-	-	•	•
•	•	i/f	•	•	•	•	i/f	•	•	•
•	u/d	•	•	•	u/d	•	i/f	-	•	•
-	-	-	-	-	•	-	-	•	-	-
•	•	•	•	•	•	•	i/f	•	•	•
-	-	-	•	-	-	-	-	-	-	-
-	-	i/f	•	•	•	•	i/f	•	•	•
-	-	•	-	-	-	•	-	-	-	-
•	•	•	•	•	•	•	i/f	i/f	-	•
-	-	-	-	-	-	-	-	-	-	-
•	•	i/f	•	•	-	-	•	•	•	•
•	•	-	•	•	-	-	i/f	•	•	•
•	•	i/f	•	-	•	•	i/f	•	-	•
•	•	•	•	•	•	•	i/f	•	•	•
•	•	i/f	•	-	•	•	-	•	•	•
-	-	•	-	-	-	-	-	-	-	-
•	•	-	-	-	-	-	i/f	•	-	-
-	•	-	-	-	-	-	•	•	-	-
-	•	•	-	-	•	-	i/f	•	•	•
-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-

Footnotes

1 Internet-based Medicare billing and CMN documentation-management system. Markets served also include infusion pharmacy.
2 IVR system designed to handle electronic prescriptions and interface with central-processing and central-fill systems.
3 Chain central management for POS system.
4 Installations represent primarily large, long-term-care providers. Also serve correctional institutions.
5 Database for front-store systems.
6 Medication-compliance system.
7 Clinical drug data.
8 Chain central management for POS system.
9 Also systems to LTC market and offers ASP service.
10 Also have installations at military locations.
11 Systems also installed in clinics, correctional institutions, and long-term-care facilities.
12 Clinical drug data.
13 Also serve HME pharmacy market, with billing service that has 8,422 clients.
14 Also have systems installed in veterinary practices.
15 Products use by Dept. of Defense/VA as well. Company sells software-driven warning labels.
16 Company is dedicated soley to the long-term-care market. Installation figure represent 6,684 users serving in excess of 1 million LTC beds. All functionality offered is for long-term-care pharmacy. Chain installations represent long-term-care chain providers.
17 Represents installations of barcode scanning for data entry and verification.
18 Company specializes in POS systems. Chain central management is for POS system.
19 Customized pricing service for retail pharmacy.
20 Chain central management system will be released Nov. 2001.
21 Installed base also includes military installations.
22 Web design and management for retail pharmacy. Installations represent CornerDrugstore.com sites.
23 A core product is an ASP service.
24 Data conversion and database-management services.

LEGEND

i/f = interface
n/a = not applicable
n/s = not specified
u/d = under development

work, new and unique hardware challenges will be presented. Bandwidth to the home represents one of the greatest challenges for telecommuting. Services such as DSL and cable modems offer potential solutions to this bandwidth problem. Productivity gains as high as 30 percent are reported as an incentive for investigation of this area.

POINT-OF-CARE SOFTWARE

If one asks the question, "What is my computer supposed to be doing when I'm providing pharmaceutical care?" the answer will not only describe the appropriate hardware or device that matches the needs of the professional providing the care, but should also describe the optimal software that will support the provision of pharmaceutical care. We define the point-of-care as the place where a pharmacist provides pharmaceutical care to a patient or assists a colleague (pharmacist, physician, or nurse) in the provision of care. Many kinds of software available on the market today focus solely on transaction processing, with minimal decision support available through prospective drug utilization review (DUR) modules.

Because the clinical environment demands real-time or near-real-time decisions, a different kind of computer support is required. Pharmacy is like other healthcare disciplines in that we face the problem of having large volumes of information but a lack of information services that are able to translate this information into better outcomes for patients.[2] A clinical practitioner requiring decision support wants this support to be presented in a succinct manner that facilitates a timely response to the problems routinely encountered in his or her practice. Specific characteristics of successful decision-support systems include the provision of patient-specific recommendations, delivery of measurable time savings, and seamless integration into the daily work activities of the clinical setting.[3] Documentation should occur as a by-product of the interactions between clinical practitioners and their patients or clients. Access to patient records should not only be provided instantaneously through electronic means, but the ability to customize the information provided into a format desired by the individual practitioner should be allowed. When pharmacokinetic calculations are required, known demographic values such as body weight or serum creatinine levels should be prepopulated into calculation variables.

Clinicians will often desire to examine historical data or use relevant references, or primary or secondary literature sources. The software design should include these aspects at a minimum. When prospective drug utilization review flags are presented, false positive warnings should be minimal to prevent practitioners from getting in the habit of simply ignoring them. System oversight for monitoring the potential of medication error should occur throughout the process, beginning with point-of-prescribing through point-of-administration. Bar codes and other technologies will be needed to facilitate this process.

DOCUMENTATION

It has been said, "If you didn't document it, you didn't do it." In the litigious environment in which we live, documentation is paramount to professional survival. Without documentation, reimbursement can be challenged. Personnel reductions are almost assured without documentation to demonstrate the impact of clinical services. Without documentation, unnecessary redundancies and events will be exacerbated.

Ideally, documentation should occur as a natural by-product of rendering care to patients. In these times where the integration of care (care management) is being sought, the ability of clinical software to access and populate a clinical data repository is a key evaluation criterion. Increasingly, integration with clinical practice protocols is facilitating more effective and more comprehensive delivery of care. A major question is, "Will the patient and the profession of pharmacy be best served by accessing, on a read/write basis, an electronic medical record that is seen by all other disciplines, or should pharmacists to continue to have a pharmacy-specific software solution?"

It may be mission critical to the profession for pharmacists to gain or maintain read/write privileges where all pharmaceutical care contributions can be viewed by all caregivers. Additionally, pharmacists will need to be able to access diagnosis, laboratory, and other charted information such as demographics on a common medical record. Thus, at a minimum, it will be necessary for all pharmacy software to be able to be integrated into the electronic medical records as they emerge.

Orthopedics has recognized the importance of measuring outcomes in terms of quality-adjusted life-years instead of length of implant survival.[2] Similarly, pharmacy must implement software documentation solutions that facilitate outcomes monitoring beyond cost savings. Software is needed with the ability to calculate, in a cost-benefit analysis, the clinical impact of pharmacist interventions as they affect therapeutic, financial, and humanistic outcomes. The current array of products could be better integrated into documentation software to facilitate tabulation of these data. With the power of the Internet to manipulate data in a dynamic database, it would even be possible for hospitals to compare their outcomes on a local, regional, or national basis. Furthermore, the database could

be utilized to gain new insights into additional interventions that could be implemented by clinical personnel.

SPECIFIC CLINICAL SOFTWARE ATTRIBUTES

Distribution software has had many years to evolve and improve. Software that supports the provision of pharmaceutical care is still maturing. The provision of pharmaceutical care is a process. Whether this provision occurs in a community, health system, long-term care facility, or other pharmacy practice setting, there is a process that underlies each practice. The practice of pharmaceutical care begins with the appraisal of the patient. Based on the findings of that appraisal, the pharmacist will perform one or several interventions. Having documented an intervention, the pharmacist will then need to evaluate the outcomes of these interventions. Once the desired outcomes have been achieved and documented, a suitable follow-up and monitoring schedule should be established.

Software that supports this process to the highest degree should be sought, identified, evaluated, purchased, and through user feedback, enhanced continually. The best-of-class clinical software available helps pharmacists assure that an efficient, comprehensive, and cost-effective rendering of pharmaceutical care is provided. Excellent pharmaceutical care software will be evidence-based in all aspects of support, including practice protocols and decision support tools. Due to the importance of financial outcomes, multiple aspects of care provision would be covered by these applications, including medications, nondrug therapies, steps for prevention, lifestyle issues, and alternative medicine. The software would also include suggested outcomes to be measured and appropriate scheduling considerations.

Ideally, clinical software should help prompt practitioners through the provision of the care process. Automatic to-do lists will assure consistency in care provision. Integration with all other aspects of the management and distribution side of pharmacy practice must be assured so that the coordination of care within a pharmacy operation is assured. Prospective drug utilization review assets and succinct decision-support resources should be internalized within the software to minimize the necessity of using multiple applications for every problem-solving exercise. Again, measurement of the potential impact for pharmaceutical care interventions should be done as a by-product of rendering care. This means that as a pharmacist uses clinical software the application deductively calculates potential calamities that were averted and dollar savings that were attained.

Thus far we have only focused on patient care clinical software. An increasingly important alternative focus would include population-based patient management. Some health systems call this care management, and it is largely a nursing-involved activity. Because pharmacists use automation to a greater degree than other healthcare disciplines, it is possible to generate a clinical data repository revolving around drug-related problems in a timelier manner than is possible with a total system approach. Data mining of this repository can yield significant management information resources on both a strategic and tactical level. Selection of clinical software should never ignore this population-based aspect of data analysis. Although pharmacist involvement in this area is currently not as widespread as it could be, there are many opportunities available for expansion.

ASSOCIATED PERFORMANCE-ENHANCEMENT TOOLS

There are several complementary computer applications that deserve mention. Part of the difficulty associated with the increased documentation necessary from pharmacy can be alleviated, in part, through the use of continuous speech recognition applications. This chapter was authored using a speech recognition program, which allowed the authors to speak at 160 words per minute with about 99 percent accuracy. It recognizes medical vocabulary and will allow the user, after only a five-minute training session, to speak directly into any Windows-based program.

Other applications that should be considered for integration involve access to tertiary literature sources directly from the clinical application. The purpose of information is to reduce uncertainty. The ability for the pharmacist to access and validate decisions based on evidence found in the literature is an important skill and a necessary requirement for clinical software support. This kind of support can be provided in palm-top form, from network resources, and as intranet applications.

A movement is underway in medicine and nursing that will allow a concept known as just-in-time continuing education to become mainstream. When pharmacists need to access reference information while solving a clinical problem, it is appropriate that this activity be accredited as continuing education. When pharmacists accumulate one hour of this continuing education activity, a posttest would be offered at a convenient time. A score of 75 percent would result in 0.1 CEUs being awarded. Currently, WebMD is providing credit to physicians who use its Web site to keep up with current issues in medicine. Pharmacists will be the focus of a similar effort if funding permits.

SECURITY, PRIVACY, AND CONFIDENTIALITY

Even though patients distrust the implications surrounding their medical records being available electronically, the benefits for this movement should outweigh the potential risks. There are currently 14 layers of technology to help ensure privacy, security, and confidentiality of the medical records of patients. Encryption, user tracking, biometric authentication, and other measures make it possible, beyond a reasonable certainty, to give patients the assurance necessary for them to sign an informed consent document allowing their records to be online. The basis for moving forward in this effort will be founded on the trust relationship between individual practitioners and individual patients.

Research based on widespread use of electronic medical records in three British hospitals has demonstrated that these records can be practical while ensuring patient privacy. The first step taken was to develop an access control list to identify which individual caregivers are responsible for a patient, and therefore, can access his/her records. The system also documents all occasions when a record is accessed, whether or not information in it was modified. As not all caregivers will be acknowledged as providing care to a particular patient, certain users are given override privileges that allow them to access records when the system is not aware that they are, indeed, providing care to this patient. The user is warned that his actions are being documented when this override procedure is used. The ability to collate enterprise-wide clinical data has posed a problem in this system. When caregivers want to gather data on a specific condition, they are only able to gather information on those patients under their care. This is an acknowledged limitation of this current system. It is important to note that in the five years this system has been in use, no patients have requested a report of all accesses of their record.[4] Again, trust in caregivers translates into trust for the electronic medical record.

RECOMMENDATIONS

There is an old joke about a man, who, upon approaching the gates of heaven, sees that the people in heaven are singing and playing harps, and the people in hell are playing golf and tennis, and watching sports events. Because he doesn't sing very well or play a harp, he decides to opt for hell. Upon arriving, he finds himself enveloped by fiery brimstone and demons that are poking him with their pitchforks. He sees the devil walking by and asks where all the golfing and tennis went? The devil replies, "Oh, you must have seen our demo." One of the first recommendations we make is, during an evaluation of a piece of software, stop allowing the salesperson to show you the "power path" way their software can solve all of your problems. Each salesperson knows the best set of circumstances to show off all of the unique features available from an application.

We recommend, instead, that you build a matrix whereby you will place competing systems in rows on the matrix and place all of the features and benefits offered by each system in the columns of the matrix. Next, devise a rating system where 3 would equal excellent, 2 would equal moderately available, 1 would equal minimally available, and 0 would equal missing. A simple priority system can help weight each feature by a priority to the pharmacy operation. A calculation using feature score and feature weight would help create a selection of the most powerful application, with the greatest score identifying the most suitable system from those compared. Subjective assessments of user-friendliness, screen designs, and number of keystrokes necessary to perform the most common tasks can be similarly evaluated.

In clinical applications, the best recommendation for testing available applications would be to use a case-based methodology. We recommend that five or six complicated cases, which would represent a cross section of the patient population served by the pharmacy, be used to test the application. In this way, the clinician will see how the application performs throughout an entire care process and avoid the power path demonstration. In this information age, selecting clinical software is an extremely important task. The explosion of capabilities offered by the Internet can make the selection process both exciting and confusing. A careful analysis of options will usually be rewarded by better results, but wary buyers need to prepare themselves to revisit the marketplace more frequently than they might have in the past to identify innovative alternatives.

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Credentialing in Pharmacy

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INTRODUCTION

Pharmacist credentialing has become a topic of important discussions in the profession of pharmacy in recent years. These discussions, inherently complex, have sometimes been further complicated by the lack of a common lexicon. The situation is understandable. Many different words are used to describe the process by which pharmacists are educated, trained, licensed, and otherwise recognized for their competence and achievements. Many different organizations—public and private—are involved in assessing pharmacists' knowledge and skills, granting credentials, and accrediting programs and institutions.

Purpose of This Paper

The purpose of this paper is to create a common frame of reference and understanding for discussions concerning pharmacist credentialing. It begins with definitions of several terms that are essential to any discussion of credentialing. This is followed by a short section highlighting the importance of credentialing to pharmacists. The next three sections, which form the body of the paper, discuss in detail the three types of credentials that pharmacists may earn:

- Credentials needed to prepare for practice (i.e., academic degrees).
- Credentials needed to enter practice (i.e., licensure) and to update professional knowledge and skills (i.e., relicensure) under state law.
- Credentials that pharmacists voluntarily earn to document their specialized or advanced knowledge and skills (i.e., postgraduate degrees, certificates, certification).

Each of these sections contains, as applicable, information about the credential awarded, the training site, whether the credential is voluntary or mandatory, the credentialing body, and the agency that accredits the program. Particular attention is given to pharmacist certification programs, an area that has engendered much of the current interest in pharmacist credentialing.

The paper also includes a brief section on credentialing of pharmacy supportive personnel. It concludes with two appendices. Appendix A contains a comprehensive glossary of key terms relating to pharmacist credentialing. Appendix B is an alphabetical list of organizations involved in pharmacist credentialing and program accreditation. The list contains names, addresses, and uniform resource locators (URLs).

Council on Credentialing in Pharmacy

"Credentialing in Pharmacy" has been created by the Council on Credentialing in Pharmacy (CCP), a coalition of 11 national pharmacy organizations founded in 1999 to provide leadership, standards, public information, and coordination for professional voluntary credentialing programs in pharmacy. Founding members of the CCP include the following organizations:

- Academy of Managed Care Pharmacy.
- American Association of Colleges of Pharmacy.
- American College of Apothecaries.
- American College of Clinical Pharmacy.
- American Council on Pharmaceutical Education.
- American Pharmaceutical Association.
- American Society of Consultant Pharmacists.
- American Society of Health-System Pharmacists.
- Board of Pharmaceutical Specialties.
- Commission for Certification in Geriatric Pharmacy.
- Pharmacy Technician Certification Board.

SIX ESSENTIAL DEFINITIONS

Discussions of credentialing are often complicated by a lack of common understanding of key terms and the contexts in which they are used. To clarify these misunder-

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006319

standings, one must first distinguish between processes (e.g., credentialing) and titles (a credential). Distinctions must also be made between processes that focus on individuals (e.g., credentialing and certification) and those that focus on organizations (accreditation). Finally, it is essential to understand that for practicing pharmacists, some credentials are required (e.g., an academic degree or a state license), while others are earned voluntarily (e.g., certification).

Beyond these distinctions, it is also necessary to understand the definitions of the words that commonly come up in discussions of credentialing and to be able to distinguish the sometimes subtle differences among them. A comprehensive glossary of such words and their definitions appears in Appendix A. The following definitions are provided here, because an understanding of these terms is a prerequisite to any meaningful discussion of credentialing in pharmacy.

- A *credential* is documented evidence of a pharmacist's qualifications. Pharmacist credentials include diplomas, licenses, certificates, and certifications. These credentials are reflected in a variety of abbreviations that pharmacists place after their names (e.g., Pharm.D. for "doctor of pharmacy," an earned academic degree; R.Ph. for "registered pharmacist," which indicates state licensure; and acronyms such as BCNSP for "Board-Certified Nutrition Support Pharmacist," which indicates that an individual has demonstrated advanced knowledge or skill in a specialized area of pharmacy).
- *Credentialing* is the process by which an organization or institution obtains, verifies, and assesses a pharmacist's qualifications to provide patient care services.
- *Accreditation* is the process by which a private association, organization, or government agency, after initial and periodic evaluations, grants recognition to an organization that has met certain established criteria.
- A *certificate* is a document issued to a pharmacist upon successful completion of the predetermined level of performance of a certificate training program or of a pharmacy residency or fellowship.
- A *statement of continuing education credit* is a document issued to a pharmacist upon participation in an accredited continuing education program.
- *Certification* is a voluntary process by which a nongovernmental agency or an association grants recognition to a pharmacist who has met certain predetermined qualifications specified by that organization. This formal recognition is granted to designate to the public that this pharmacist has attained the requisite level of knowledge, skill, or experience in a well-defined, often specialized, area of the total discipline. Certification usually requires initial assessment and periodic reassessments of the individual's qualifications.

IMPORTANCE OF CREDENTIALS IN PHARMACY

"Credential" and "credentialing," like the words "creed" and "credence," derive from the Latin verb *credere*, which means "to trust," "to entrust," or "to believe." A pharmacist's credentials are indicators that he or she holds the qualifications needed to practice the profession of pharmacy and is therefore worthy of the trust of patients, of other health care professionals, and of society as a whole.

In the profession of pharmacy, the interest in credentials has been catalyzed in recent years by several factors. First among them is the pace of change and the increasing complexity of health care. A second factor is the pharmacist's expanding clinical role. Interest in credentialing has likewise been stimulated by the growing trend toward specialization in pharmacy practice and by the need to document the pharmacist's ability to provide specialty care.

Another contributing factor has been the need to help ensure lifelong competence in a rapidly changing, technologically complex field. The need to provide a means of standardization of practice has also had a role. Such a motivation was key, for example, to the development of the Federal Credentialing Program, which is creating a national database of health professionals that will include pharmacists.

Finally, economic realities enter the picture. Pharmacists who are providing cognitive services or specialized care need to be reimbursed for the services they provide. Payers rightfully demand validation that pharmacists are qualified to provide such services. Credentials, and in many cases, more specifically, certification, can help provide the documentation that Medicare and Medicaid, managed care organizations, and other third-party payers require of pharmacists today and in the future.

OVERVIEW OF CREDENTIALING IN PHARMACY

Pharmacist credentials may be divided into three fundamental types:

- The first type—college and university degrees—is awarded to mark the successful completion of a pharmacist's academic training and education.

- The second type—licensure and relicensure—is an indication that the pharmacist has met minimum requirements set by the state in which he or she intends to practice.
- The third type of credential—which may include advanced degrees and certificates—is awarded to pharmacy practitioners who have completed programs of various types that are intended to develop and enhance their knowledge and skills, or who have successfully documented an advanced level of knowledge and skill through an assessment process.

These three paths to pharmacist credentialing are illustrated in Fig. 1. The sections that follow provide information on each of the credentials offered in pharmacy, the credentialing or accreditation body involved, whether the credential is mandatory or voluntary, and other related information.

Preparing for the Pharmacy Profession

- *Credential earned*: Bachelor of Science degree in Pharmacy; Doctor of Pharmacy degree.
- *Credential awarded by*: School or college of pharmacy.
- *Accreditation body for professional programs in pharmacy*: American Council on Pharmaceutical Education (ACPE). The U.S. Department of Education has recognized the ACPE accreditation of the professional degree program in pharmacy.

Until July 1, 2000, an individual who wished to become a pharmacist could enroll in a program of study that would lead to one of two degrees: a bachelor of science degree in pharmacy (B.S.Pharm. or Pharm.B.S.) or a doctor of pharmacy (Pharm.D.) degree.

As of 1998, two-thirds of all students studying in professional programs in pharmacy were enrolled in Pharm.D. programs. The Pharm.D. degree became the sole degree accredited by ACPE for pharmacists' entry into practice in the United States, as of July 1, 2000, with the institution of new ACPE professional program accreditation standards. Pharm.D. programs typically take six years to complete and generally involve two years of preprofessional coursework and four years of professional education. A few programs

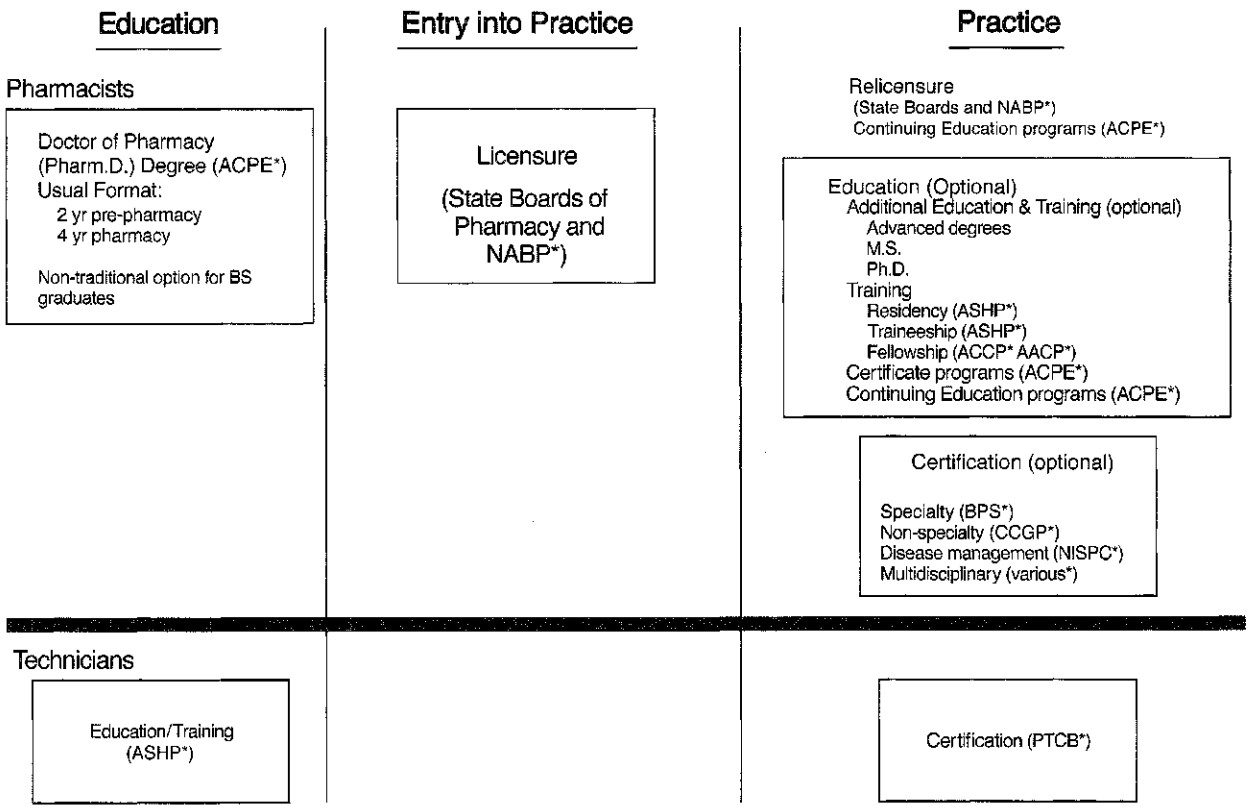

Fig. 1 U.S. pharmacy credentials and oversight bodies. (*Oversight bodies are described in text.)

offer the professional education over three years of full-time education.

B.S. level pharmacists who have been in the workforce may also return to a college or school of pharmacy to earn the Pharm.D. degree. These programs, which are tailored to the individual's background and experience, may follow "nontraditional" pathways; however, they must produce the same educational outcomes as does the entry-level Pharm.D. degree.

State boards of pharmacy require a Pharm.D. or B.S. degree from a program approved by the boards (almost always an ACPE-accredited program) for a candidate to be eligible to take the state licensing examination. A listing of accredited professional programs offered by colleges and schools of pharmacy is published annually by the ACPE, and is available on the ACPE web site (www.acpe-accredit.org).

Entering Practice and Updating Professional Knowledge and Skills

- *Credentials earned*: Licensure as registered pharmacist (R.Ph.); relicensure.
- *Credential awarded by*: State board of pharmacy.
- *Licensure process overseen by*: State regulatory authorities.

Before a graduate of a school or college of pharmacy can practice pharmacy in the United States, he or she must become licensed. The licensure process is regulated at the state level by the boards of pharmacy.

Candidates for licensure in all states but California must pass the North American Pharmacist Licensure Examination™ (NAPLEX®), a computer-adaptive, competency-based examination that assesses the candidate's ability to apply knowledge gained in pharmacy school to real-life practice situations. California administers a unique examination process. Most states also require candidates to take a state-specific pharmacy law examination. Currently, 36 states use the Multistate Pharmacy Jurisprudence Examination™ (MPJE™), a computer-adaptive assessment that tailors each examination to address the pharmacy law and regulations of the state in which the candidate is seeking licensure.

Both the NAPLEX and the MPJE are developed by the National Association of Boards of Pharmacy (NABP) for use by the boards of pharmacy as part of their assessment of competence to practice pharmacy. Development of these examinations is directly related to NABP's mission, which is to assist its member boards and jurisdictions in developing, implementing, and enforcing uniform standards for the purpose of protecting the public health. The NAPLEX and MPJE examinations are administered by appointment, daily, throughout the year, at a system of test centers located in all 50 states.

In addition to the NAPLEX and MPJE, some states require a laboratory examination or an oral examination before licensure is conferred. All state boards also require that candidates complete an internship before being licensed. The internship may be completed during the candidate's academic training or after graduation, depending upon state requirements.

State licensure is an indication that the individual has attained the basic degree of competence necessary to ensure the public health and welfare will be reasonably well protected. The names of individuals who have received a license may use the abbreviation "R.Ph." (for "registered pharmacist") after their names.

Nearly all state boards of pharmacy also require that registered pharmacists complete a certain number of continuing education units (CEUs) before they can renew their licenses. The CEUs must be earned through participation in a continuing education (CE) program whose provider has been approved by the American Council on Pharmaceutical Education (ACPE). The symbol used by the American Council on Pharmaceutical Education to designate that the continuing education provider is approved is  .

Note that ACPE approves providers of continuing education, not individual CE programs. CEUs may be secured by attending educational seminars, teleconferences, and meetings; reading journal articles; or completing traditional home study courses or computer-based education programs. Receipt of a satisfactory score on an assessment that is created by and submitted to the CE provider is sometimes required as a documentation of completion of a CE program. ACPE publishes an annual directory of approved providers of continuing pharmaceutical education, which is available on the ACPE web site (www.acpe-accredit.org).

Licensure and relicensure are mandatory for pharmacists who wish to continue to practice their profession.

In their regulatory role, state boards of pharmacy are ultimately responsible to the state legislature.

Developing and Enhancing Knowledge and Skills

Pharmacy practitioners who wish to broaden and deepen their knowledge and skills may participate in a variety of

postgraduate education and training opportunities. They include the following:

Academic postgraduate education and training

Pharmacists who wish to pursue a certain field of study in depth may enroll in postgraduate master's or doctor of philosophy (Ph.D.) programs. Common fields of study for master's candidates include business administration, clinical pharmacy, and public health. Common fields for Ph.D. studies include pharmacology, pharmaceutics, pharmacy practice, and social and administrative sciences.

Residencies

- *Credential earned*: Residency certificate.
- *Credential awarded by*: Residency training program.
- *Program accreditation*: The American Society of Health-System Pharmacists (ASHP). (independently or in collaboration with other pharmacy organizations).

ASHP is the chief accreditation body for pharmacy practice and specialty residency programs in pharmacy. A total of 505 programs nationwide now hold ASHP accreditation. ASHP also partners with other organizations, including the Academy of Managed Care Pharmacy, the American College of Clinical Pharmacy, the American Pharmaceutical Association, and the American Society of Consultant Pharmacists, in accrediting residency programs.

The majority of pharmacists who pursue residency training do so in the area of pharmacy practice. These residencies sometimes focus on a particular practice setting, such as ambulatory care. Pharmacists may also pursue specialty training in a certain topic (e.g., pharmacokinetics), in the care of a specific patient population (e.g., pediatrics), or in a specific disease area (e.g., oncology).

Residency programs last one to two years. The typical training site is a practice setting such as an academic health center, a community pharmacy, a managed care organization, a skilled nursing facility, or a home health care agency.

The Health Care Financing Administration (HCFA), an agency of the federal government, recognizes residency accreditation bodies within the health professions.

Fellowships[a]

- *Credential earned*: Fellowship certificate.
- *Credential awarded by*: Fellowship training program.
- *Program accreditation*: No official accreditation body.

A fellowship is an individualized postgraduate program that prepares the participant to become an independent researcher. Fellowship programs, like residencies, usually last one to two years. The programs are developed by colleges of pharmacy, academic health centers, colleges and universities, and pharmaceutical manufacturers.

There is no official accreditation body for fellowship programs; however, the American Association of Colleges of Pharmacy and American College of Clinical Pharmacy have issued guidelines that are followed by many fellowship program directors.

Certificate Training Programs

- *Credential earned*: Certificate of Completion.
- *Credential awarded by*: Educational institutions and companies, pharmacy organizations, and others.
- *Provider accreditation*: American Council on Pharmaceutical Education.

A certificate training program is a structured and systematic postgraduate continuing education experience for pharmacists that is generally smaller in magnitude and shorter in duration than degree programs. Certificate programs are designed to instill, expand, or enhance practice competencies through the systematic acquisition of specified knowledge, skills, attitudes, and behaviors. The focus of certificate programs is relatively narrow; for example, the American Pharmaceutical Association offers programs in such areas as asthma, diabetes, immunization delivery, and management of dyslipidemias.

Certificate training programs are offered by national and state pharmacy organizations and by schools and colleges of pharmacy and other educational groups. The programs are often held in conjunction with a major educational meeting of an organization. The American Council on Pharmaceutical Education (ACPE) approves providers of such programs. The symbol used by the ACPE to designate that a certificate training program is provided by an accredited provider is 

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[a]Several pharmacy organizations, including the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, and the American Pharmaceutical Association, award the honorary title of "Fellow" to selected members as a means of publicly recognizing their contributions to the profession. A Fellow of ASHP, for example, may write "FASHP" for "Fellow of the American Society of Health-System Pharmacists," after his or her name. The two uses of the word "fellow"—one denoting an individual participating in a postgraduate training program and the other denoting receipt of an honorary title—should be clearly distinguished.

Traineeships

Traineeships, in contrast to certificate training programs, are defined as intensive, individualized, structured postgraduate programs intended to provide the participant with the knowledge and skills needed to provide a high level of care to patients with various chronic diseases and conditions. Traineeships are generally of longer duration (about five days) and involve smaller groups of trainees than certificate training programs do. Some are offered on a competitive basis, with a corporate sponsor or other organization underwriting participants' costs. Pharmacy organizations currently offering traineeships include the American College of Apothecaries, the American Society of Consultant Pharmacists, and the American Society of Health-System Pharmacists' Research and Education Foundation.

Certification

Certification is a credential granted to pharmacists and other health professionals who have demonstrated a level of competence in a specific and relatively narrow area of practice that exceeds the minimum requirements for licensure. Certification is granted on the basis of successful completion of rigorously developed eligibility criteria that include a written examination and, in some cases, an experiential component. The certification process is undertaken and overseen by a nongovernmental body.

The development of a certification program includes the following steps:

- *Role delineation.* The first step is to define the area in which certification is to be offered. This is done through a process called role delineation or "task analysis." An expert panel of individuals in the proposed subject area develops a survey instrument to assess how practitioners working in the area rate the importance, frequency, and criticality of specific activities in that practice. The instrument is then sent to a sample of pharmacists who are practicing in that field.
- *Development of content outline.* On the basis of responses to the survey, a content outline for the certification program is developed.
- *Preparation of examination.* The written examination component of the certification program is developed on the basis of the content outline.
- *Other activities.* Appropriate measures are taken to ensure that security and confidentially of the testing process are maintained, that the examination and eligibility criteria are appropriate, and that the knowledge and skills of those who are certified do, in fact, reflect competence.

A professional testing company typically assists in the development of the role delineation and the examination to ensure that the examination meets professional standards of psychometric soundness and legal defensibility.

Certifying agencies for pharmacists only

Three groups—the Board of Pharmaceutical Specialties, the Commission for Certification in Geriatric Pharmacy, and the National Institute for Standards in Pharmacist Credentialing—offer certification to pharmacists.

Board of Pharmaceutical Specialties (BPS). Established in 1976 by the American Pharmaceutical Association, BPS is the only agency that offers certification at the specialty level in pharmacy. It certifies pharmacists in five specialties: nuclear pharmacy, nutrition support pharmacy, oncology pharmacy, pharmacotherapy, and psychiatric pharmacy. As of June 2002, nearly 3500 pharmacists held BPS certification, distributed across the five specialties as follows:

Nuclear Pharmacy—471
Nutrition Support Pharmacy—425
Oncology Pharmacy—288
Pharmacotherapy—1843
Psychiatric Pharmacy—387

Pharmacists who wish to retain BPS certification must be recertified every seven years.

The recognition of each specialty is the result of a collaborative process between the Board and one or more pharmacy organizations, which develop a petition to support and justify recognition of the specialty. This petition must meet written criteria established by the BPS.

The BPS is directed by a nine-member board that includes six pharmacists, two health professionals who are not pharmacists, and one public/consumer member. A specialty council of six specialist members and three pharmacists not in the specialty direct the certification process for each specialty.

BPS examinations are administered with the assistance of an educational testing firm, resulting in a process that is psychometrically sound and legally defensible. Each of the five specialties has its own eligibility criteria, examination specifications, and recertification processes. All

five examinations are given on a single day once a year in approximately 25 sites in the United States and elsewhere.

In 1997, BPS introduced a method designed to recognize focused areas within pharmacy specialties. A designation of "Added Qualifications" denotes that an individual has demonstrated an enhanced level of training and experience in one segment of a BPS-recognized specialty. Added qualifications are conferred on the basis of a portfolio review to qualified individuals who already hold BPS certification. The first added qualification to receive BPS approval was infectious diseases, within the pharmacotherapy specialty.

Commission for Certification in Geriatric Pharmacy (CCGP). In 1997, the American Society of Consultant Pharmacists (ASCP) Board of Directors voted to create the CCGP to oversee a certification program in geriatric pharmacy practice. CCGP is a nonprofit corporation that is autonomous from ASCP. It has its own governing Board of Commissioners. The CCGP Board of Commissioners includes five pharmacist members, one physician member, one payer/employer member, one public/consumer member, and one liaison member from the ASCP Board of Directors.

Pharmacists who meet CCGP's requirements are entitled to use the designation Certified Geriatric Pharmacist, or CGP. As of June 2002, approximately 800 pharmacists have earned the CGP credential. Pharmacists who wish to retain their CGP credential must recertify every five years by successfully completing a written examination.

CCGP contracts with a professional testing firm to assist in conducting the role delineation or task analysis and in developing and administering the examination. The resulting process is psychometrically sound and legally defensible; it also meets nationally recognized standards. The CGP certification exams are administered twice a year at multiple locations in the United States, Canada, and Australia. CCGP publishes a candidate handbook that includes the content outline for the examination, eligibility criteria for taking the examination, and the policies and procedures of the certification program.

National Institute for Standards in Pharmacist Credentialing (NISPC). The NISPC was founded in 1998 by the American Pharmaceutical Association, the National Association of Boards of Pharmacy (NABP), the National Association of Chain Drug Stores, and the National Community Pharmacists Association. The purpose of NISPC is to "promote the value and encourage the adoption of National Association of Boards of Pharmacy disease-specific examinations as the consistent and objective means of documenting the ability of pharmacists to provide disease state management services."

NISPC offers certification in the management of diabetes, asthma, dyslipidemia, and anticoagulation therapy. At the time of its founding, the organization's immediate objective was to design a process that would document the competence of pharmacists providing care for patients with these disease states. The NISPC credential was first recognized in the state of Mississippi, where it was used to enable pharmacists to qualify for Medicaid reimbursement as part of a pilot project in that state. The NABP developed the competency assessment examinations and oversees their administration. As of June 2002, 1340 pharmacists hold NISPC certification: 771 in diabetes, 314 in asthma, 120 in dyslipidemia, and 135 in anticoagulation therapy.

The NISPC tests are administered nationally as computerized examinations and are available throughout the year.

Multidisciplinary certification programs

Some certification programs are available to professionals from many health disciplines, including pharmacists. Areas in which such certification programs are available include diabetes education, anticoagulation therapy, pain management, and asthma education. Some of these programs are still in the early stages of development. Several of these providers are listed in Appendix B; however, the information is not intended to be exhaustive.

PHARMACY SUPPORTIVE PERSONNEL

A pharmacy technician is an individual who assists in pharmacy activities that do not require the professional judgment of a pharmacist. For example, pharmacy technicians may accept orders from patients, prepare labels, enter drug information into the pharmacy's computer system, and retrieve medications from inventory. As pharmacists assume an increasing number of clinical roles, pharmacy technicians are taking more and more responsibility for distributive functions in pharmacies in all settings.

The exact functions and responsibilities of pharmacy technicians are defined by state laws and regulations and are also determined by the willingness of pharmacists to delegate the nonjudgmental activities of their practice. Pharmacy technicians always work under the supervision of a licensed pharmacist.

The education and training, certification, and continuing education of pharmacy technicians are similar in some ways to those of pharmacists.

Education and Training

Most pharmacy technicians today have been trained on the job, either formally or informally. As the responsibilities of pharmacy technicians grow, however, more and more individuals are enrolling in formal training programs. These programs are generally affiliated with a community college, a four-year college, a hospital, or another health care organization. Graduates of these programs may be awarded an associate's degree or a certificate of completion.

ASHP is the accreditation body for pharmacy technician training programs. Sixty programs were accredited as of 1999.

Regulation

State boards of pharmacy oversee the registration of pharmacy technicians. Practices differ substantially from state to state.

Certification

The Pharmacy Technician Certification Board (PTCB) was established in 1995 as a national voluntary certification program for pharmacy technicians. Its founders were the American Pharmaceutical Association, the American Society of Health-System Pharmacists, the Illinois Council of Health-System Pharmacists, and the Michigan Pharmacists Association.

In collaboration with testing experts, the PTCB developed a national examination, the Pharmacy Technician Certification Examination (PTCE). The examination is designed to assess the candidate's knowledge and skill base for activities that are most commonly performed by a pharmacy technician, as determined by a national task analysis.

The Board administers the PTCE three times a year at more than 120 sites across the nation. A technician who passes the PTCE is designated as a Certified Pharmacy Technician (CPhT). As of June 2002, more than 100,000 pharmacy technicians have earned PTCB certification.

Pharmacy technicians must renew their certification every two years. To qualify for recertification, they must participate in at least 20 hr of pharmacy-related continuing education that includes an hour of pharmacy law.

APPENDIX A

Glossary

These definitions have been developed by a variety of organizations involved in credentialing and are generally accepted by those in the pharmacist credentialing arena.

Accreditation: The process whereby an association or agency grants public recognition to an organization that meets certain established qualifications or standards, as determined through initial and periodic evaluations.

Certificate Training Program: A structured, systematic postgraduate education and continuing education experience for pharmacists that is generally smaller in magnitude and shorter in duration than a degree program. Certificate programs are designed to instill, expand, or enhance practice competencies through the systematic acquisition of specific knowledge, skills, attitudes, and performance behaviors.

Certified: Adjective that is used to describe an individual who holds certification and that is incorporated into the name of the credential awarded that individual. For example, someone who has earned BPS certification in oncology is a "Board-Certified Oncology Pharmacist."

Certificate: A certificate is a document issued to a pharmacist upon successful completion of the predetermined level of performance of a certificate training program or of a pharmacy residency or fellowship. See also "statement of continuing education credit."

Certification: The voluntary process by which a nongovernmental agency or association formally grants recognition to a pharmacist who has met certain predetermined qualifications specified by that organization. This recognition designates to the public that the holder has attained the requisite level of knowledge, skill, or experience in a well-defined, often specialized, area of the total discipline. Certification entails assessment, including testing, an evaluation of the candidate's education and experience, or both. Periodic recertification is usually required to retain the credential.

Clinical privileges: Authorization to provide a specific range of patient care services. *See* also Privileging.

Competence: The ability to perform one's duties accurately, make correct judgments, and interact appropriately with patients and with colleagues. Professional competence is characterized by good problem-solving and decision-making abilities, a strong knowledge base, and the ability to apply knowledge and experience to diverse patient-care situations.

Competency: A distinct skill, ability, or attitude that is essential to the practice of a profession. Individual competencies for pharmacists include, for example, mastery of aseptic technique and achievement of a thought process that enables one to identify therapeutic duplications. Pharmacists must master a variety of competencies in order to gain competence in a profession.

Continuing education: Organized learning experiences and activities in which pharmacists engage after they have completed their entry-level academic education and training. These experiences are designed to promote the continuous development of the skills, attitudes, and knowledge needed to maintain proficiency, provide quality service or products, respond to patient needs, and keep abreast of change.

Credential: Documented evidence of professional qualifications. For pharmacists, academic degrees, state licensure, and Board certification are all examples of credentials.

Credentialing: 1) The process by which an organization or institution obtains, verifies, and assesses a pharmacist's qualifications to provide patient care services; 2) The process of granting a credential (a designation that indicates qualifications in a subject or an area.)

Fellowship: A directed, highly individualized postgraduate program designed to prepare a pharmacist to become an independent researcher.

License: A credential issued by a state or federal body that indicates that the holder is in compliance with minimum mandatory governmental requirements necessary to practice in a particular profession or occupation.

Licensure: The process of granting a license.

Pharmacy technician: An individual who, under the supervision of a licensed pharmacist, assists in pharmacy activities not requiring the professional judgment of the pharmacist.

Privileging: The process by which a health care organization, having reviewed an individual health care provider's credentials and performance and found them satisfactory, authorizes that individual to perform a specific scope of patient care services within that organization.

Residency: An organized, directed, postgraduate training program in a defined area of pharmacy practice.

Registered: Adjective used to describe a pharmacist who has met state requirements for licensure and whose name has been entered on a state registry of practitioners who are licensed to practice in that jurisdiction.

Scope of practice: The boundaries within which a health professional may practice. For pharmacists, the scope of practice is generally established by the board or agency that regulates the profession in a given state or organization.

Statement of continuing education credit: A document issued to a pharmacist upon completion of a continuing education program provided by an organization approved by the American Council on Pharmaceutical Education.

Traineeship: A short, intensive, clinical, and didactic postgraduate educational program intended to provide the pharmacist with knowledge and skills needed to provide a high level of care to patients with specific diseases or conditions.

APPENDIX B

Referenced Pharmacy Organizations and Certification Bodies

Pharmacy organizations

Academy of Managed Care Pharmacy (AMCP)
100 North Pitt Street, Suite 400; Alexandria, Virginia 22314; (800) 827-2627
www.amcp.org

American Association of Colleges of Pharmacy (AACP)
1426 Prince Street; Alexandria, Virginia 22314-2841; (703) 836-8982
www.aacp.org

American College of Apothecaries (ACA)
P.O. Box 341266; Memphis, Tennessee 38184; (901) 383-8119
www.acaresourcecenter.org

American College of Clinical Pharmacy (ACCP)
3101 Broadway, Suite 380; Kansas City, Missouri 64111; (816) 531-2177
www.accp.com

American Council on Pharmaceutical Education (ACPE)
20 North Clark Street, Suite 2500; Chicago, Illinois 60610; (312) 664-3575
www.acpe-accredit.org

American Pharmaceutical Association (APhA)
2215 Constitution Avenue, NW; Washington, D.C. 20037-2985; (202) 628-4410
www.aphanet.org

American Society of Consultant Pharmacists (ASCP)
1321 Duke Street; Alexandria, Virginia 22314-3563; (703) 739-1300
www.ascp.com

American Society of Health-System Pharmacists (ASHP)
7272 Wisconsin Avenue; Bethesda, Maryland 20814; (301) 657-3000
www.ashp.org

National Association of Boards of Pharmacy (NABP)
700 Busse Highway; Park Ridge, Illinois 60068; (847) 698-6227
www.nabp.net

National Association of Chain Drug Stores (NACDS)
413 N. Lee Street, P.O. Box 1417-D49; Alexandria, Virginia 22313-1480; (703) 549-3001
www.nacds.org

National Community Pharmacists Association (NCPA)
205 Daingerfield Road; Alexandria, Virginia 22314; (703) 683-8200
www.ncpanet.org

Certification bodies for pharmacists or pharmacy technicians (may be multidisciplinary)

Anticoagulation Forum
88 East Newton Street, E-113; Boston, Massachusetts 02118-2395; (617) 638-7265
www.acforum.org

Board of Pharmaceutical Specialties (BPS)
2215 Constitution Avenue, NW; Washington, D.C. 20037-2985; (202) 429-7591
www.bpsweb.org

Council on Certification in Geriatric Pharmacy (CCGP)
1321 Duke Street; Alexandria, Virginia 22314-3563; (703) 535-3038
www.ccgp.org

National Asthma Educator Certification Board
American Lung Association
1740 Broadway; New York, New York 10019-4374; (212) 315-8865
www.lungusa.org

National Certification Board for Diabetes Educators (NCBDE)
330 East Algonquin Road, Suite 4; Arlington Heights, Illinois 60005; (847) 228-9795
www.nbcde.org

National Institute for Standards in Pharmacist Credentialing (NISPC)
P.O. Box 1910; Alexandria, Virginia 22313-1910; (703) 299-8790
www.nispcnet.org

Pharmacy Technician Certification Board (PTCB)
2215 Constitution Avenue, NW; Washington, D.C. 20037-2985; (202) 429-7576
www.ptcb.org

PROFESSIONAL DEVELOPMENT

Critical Care Pharmacy Practice

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INTRODUCTION

Pharmacists have been practicing in critical care since the 1970s when the new breed of clinical pharmacists were expanding the horizons of care to include more than dispensing services. These early practitioners recognized, as we do today, that critically ill patients are treated with a large number of different drugs that have significant alterations in their pharmacokinetics and pharmacodynamics, and great potential for drug misadventure.

Today, a growing number of pharmacists practice exclusively in critical care settings. They are recognized members of the critical care team, along with the intensivist, nurses, dietitians, respiratory therapists, and others. The exact number of critical care pharmacists is not known, but more than 450 pharmacists are members of the Society of Critical Care Medicine (SCCM). This number may only represent a fraction of the total number because many other pharmacists work in critical care satellites and provide a broad range of pharmaceutical care services.

HISTORY OF CRITICAL CARE PHARMACY

The 1985 textbook, *Practice of Critical Care Pharmacy* was the gateway for many young practitioners. This book contained chapters written by many of the groundbreaking practitioners in critical care.[1] These chapters detailed the roles these and other influential critical care practitioners had developed and served as a primer for practice in various intensive care units (ICU). These clinicians deserve recognition for this and other contributions to the development of critical care pharmacy practice in a variety of practice settings: Dave Angaran, MS (cardiovascular); Deborah Armstrong, PharmD (pediatric); Joyce Comer, PharmD (medical); Gary Cupit,PharmD (pediatric and neonatal); Joseph Dasta, MS (surgical); Robert Elenbaas, PharmD (emergency medicine); Thomas Majerus, PharmD (trauma); and Christine Quandt, PharmD (neurosurgical). These same practitioners fostered the expansion of the specialty through pharmacy residency and fellowship training programs.

The need for ongoing education in a rapidly evolving specialty led these practitioners to the SCCM, an organization whose membership includes critical care practitioners from every discipline. As the number of pharmacist members grew, a section was formed within SCCM in 1989, and its membership has expanded progressively. Although the pharmacy organizations, the American College of Clinical Pharmacy (ACCP) and American Society of Health-Systems Pharmacists (ASHP) have sections or interest groups devoted to critical care, the SCCM has been a focal point for the organizational activity of many of these pharmacists. Many critical care pharmacists have made significant contributions to these national organizations through service on the governing boards and committees.

Bart Chernow, MD, a member of SCCM, was very influential in the initiation of the Clinical Pharmacy and Pharmacology Section of SCCM. His textbook on critical care pharmacology included a chapter entitled, "The Role of the Pharmacist in Caring for the Critically Ill Patient."[2] This was a vehicle to introduce the benefits of the pharmacist as a member of the critical care team to critical care physicians. Critical care physicians have been strong advocates for the role of the critical care pharmacist, were essential champions for the early practitioners, and continue to be today. The SCCM recognizes the critical care pharmacist as an essential member of the multidisciplinary ICU team.[3] These guidelines recommend that pharmacists provide pharmaceutical care through monitoring of dosing, adverse drug reactions, drug interactions, and education to create cost-optimized regimens. In addition, the guidelines also recognize the important role of critical care pharmacists in the care of the most complex patients treated in tertiary care centers. The SCCM also includes a permanent position for a critical care pharmacist on its governing council.

Additional recognition of the importance of the critical care pharmacist has been the selection of numerous pharmacists as fellows of the American College of Critical Care Medicine (ACCM). This designation is awarded to critical care practitioners who have demonstrated a high level of practice, research, education, and service to SCCM and their local organizations.

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006226

Pharmacists have contributed to our understanding of the needs of the critically ill patient through descriptive reports characterizing patterns of drug utilization. In surgical and trauma patients, an average total of 7.6 and 9.1 medications per patient were reported, respectively.[4,5] These data reaffirm reports that a growing number of medications are used in ICU patients, from an average of 4.2 to 7 ± 4.6 drugs per patient in general ICUs.[6,7] In 1988, the pharmacoeconomic impact of the large number of medications used in surgical ICU patients was significant, averaging 13.6% of total hospital charges.[8]

Hazards of these complex drug therapy regimens are becoming well documented. Concern with medication errors is a frequent topic in the medical and lay literature.[9] A general adult ICU reported that a medication error was made in more than 50% of the patients, but the overall error rate was low, detected in 2.2% of the doses dispensed or administered.[10] However, this unit reported a generous 1:1 nurse-to-patient ratio and relied on a retrospective medical record review to detect errors. Current staffing patterns with 1:2 or 1:3 nurse-to-patient ratios are becoming more common and may adversely affect error frequency. Higher rates have been detected in other studies, due to differences in the definition of an error and the method of detection. New therapies and technologies may increase the risk of critical errors.[11] The ability of the pharmacist to reduce medication errors and adverse drug events has been reported.[12] Pharmacists participating on physician rounds on a part-time basis were shown to decrease all adverse drug events and, in particular, to decrease preventable adverse drug events by 66%.[12] The pharmacist primarily detected prescribing errors such as incomplete orders, incorrect doses or frequency, and therapy duplication; however, the pharmacist also avoided inappropriate drug selection. Alternative therapies were recommended that were safer (avoided a drug interaction or allergy) or less expensive. Participation of a pharmacist in the medication ordering process in a teaching hospital appears to be essential to avoid prescribing errors.

Pharmacists have used avoidance of medication errors to justify expanding services. A pediatric critical care satellite was opened to reduce the rate of errors from a total of 17.4% in an intensive care nursery and 38% in a pediatric ICU.[13] A large number of the errors (86.5%) occurred with medications possessing a high potential for serious adverse consequences.

Avoidance of medication administration errors is another potential contribution of critical care pharmacists. A multicenter analysis of medication errors from five ICUs revealed that medication errors occurred most commonly with vasoactive agents and sedative-analgesics.[14] Incorrect infusion rate was the most common error. The overall error rate was 3.3% (187 of 5744 observations), which is lower than previously reported. The majority of the errors caused no harm, but some required additional patient monitoring or intervention. Other errors were related to omission of doses or administration at an incorrect time. Critical care pharmacists observed these medication errors during their routine daily activities. The presence of these trained specialists may have influenced the number and type of errors. The process in this report differs from prior observational studies where a trained observer recorded medication administration practices and recorded errors. However, calculation of infusion rates was identified as an area for potential quality improvement.

CURRENT PRACTICE

Pharmacists have developed specialty practices in every facet of critical care and emergency medicine. These include burn, cardiac care, cardiovascular surgery, medical, neurological, neurosurgical, renal, respiratory, surgical, trauma, and pediatric and neonatal critical care. Pediatric specialty units in the same areas may also have pharmacists dedicated to those units. Descriptive reports of their contributions to these units have been published.[15–23]

Although many of these practitioners work for larger hospitals or have academic appointments, there is a growing number of pharmacists focusing on critical care patients in smaller hospitals. In 1989, a survey of hospitals with >100 beds demonstrated that 34% of medium-size hospitals had pharmacy satellites, as did 61% of large hospitals.[24] The majority (76%) of pharmacists who staffed these satellites held BS degrees. However, one-third of the pharmacists spent more than 50% of their day providing clinical services. Hopefully, this level of pharmacist involvement has been maintained or has grown since the early 1990s. Although not a complete measure, the number of critical care pharmacists who are members of SCCM has grown progressively from approximately 80 in the early 1990s to the current number of more than 450 pharmacist members. It is hoped that this reflects a larger number of specialty practitioners in critical care.

The majority (63.2%), of critically ill patients are cared for in hospitals without full-time or consultative intensivists.[25] Patients are more likely to be cared for by their primary physician or a single or multiple consultants (pulmonary or cardiology), although hospitalists are becoming more available to care for ICU patients (internal medicine specialists who care for hospitalized patients full-time). An intensivist is a physician who is board

certified in critical care but may have received their initial medical training in medicine, surgery, anesthesia, or pediatrics. Board certification is achieved through the subspecialty organizations after completion of a written examination. The SCCM model of critical care is that of an intensivist-led multidisciplinary team. An organized critical care team has been a predictor of improved patient care.[26] Despite the apparent benefit of the intensivist-led team, workforce projections predict a significant manpower shortfall by 2020, due to a relatively constant supply but an increasing demand for critical care services.[25] Critical care pharmacists may have increasing opportunities to affect the care of these patients as a result of this imbalance.

RESEARCH IN CRITICAL CARE

There are many challenges to performing research in a critically ill patient. Informed consent may be difficult to obtain if there is a narrow window for therapy initiation. The ICU population may have numerous other injuries or organ dysfunction that would disqualify the patient. Finally, an adequate number of patients may be difficult to recruit. As a result, animal research models have been used by critical care pharmacists to develop the framework for clinical trials and control the large number of patient variables present in a critically ill patient.

Numerous avenues exist for critical care research. Critical care pharmacists have contributed to the understanding of pharmacotherapy of multiple disease states and organ systems. Evaluation of pharmacokinetics and pharmacodynamics in the critically ill patient has facilitated the design of therapeutic regimens in these complicated patients. For example, the variations in hepatic metabolic rate following head trauma or hemorrhagic shock have been characterized.[27,28] However, much additional research is needed to further characterize the impact of changes in organ function on pharmacokinetics in this complex and heterogeneous population.

Clinical case reports of unusual treatments or response to therapy have presented a plethora of questions that remain to be answered. Case series and descriptions of experience with treatment protocols or the impact of pharmacist interventions are useful contributions to the literature. Evaluation of economics and outcomes has been an important area of research in critical care. The critically ill patient patient typically receives a large number of different and often expensive medications, and is monitored with expensive devices. Pharmacists have characterized various aspects of the cost of care, although comprehensive pharmacoeconomic outcome research is difficult to accomplish in complex patients where numerous factors can influence outcome, but is essential to the integration of novel therapies and improved utilization of existing agents.

Critical care pharmacists have also been active in the area of collaborative disease-state management and quality improvement projects, and have documented the impact of these on patient outcome. Pharmacists often take a leadership role in these efforts. Examples of the impact of these programs include reductions in the use of laboratory tests,[29,30] cost saving through improved antibiotic utilization,[18] improved utilization of sedative and neuromuscular blocking agents,[31–33] improved monitoring of sedation, and avoidance of adverse drug events.[12]

Training in critical care research is available through fellowships cosponsored by the pharmaceutical industry through organizations such as SCCM and ACCP, as well as through a number of clinical training centers.

KNOWLEDGE BASE

Although critical care is considered a specialty area, there is a challenge to define the body of knowledge encompassed by this field. Critical care patients as a whole are a very heterogeneous group. As a result, many institutions provide care for a more homogenous group of patients in geographically distinct units. Whether these patients are in

Table 1 Important components of critical care pharmacist knowledge base for adult and pediatric patients

Pharmacokinetic alterations in the critically ill
Analgesia, sedation, neuromuscular blockade
Cardiovascular pathology and therapeutics
Endocrine pathology and therapeutics
Gastrointestinal pathology and therapeutics
Hemodynamic monitoring/manipulation
Hepatic pathology and therapeutics
Hematologic pathology and therapeutics
Infection control/antimicrobial therapy
Inflammatory injury/multiple organ system dysfunction
Neurological pathology and therapeutics
Nutritional support
Patient/ventilator interface
Psychiatric therapeutics
Renal pathology and therapeutics
Respiratory pathology and therapeutics
Resuscitation therapeutics
Shock and related problems
Thrombosis/hemostasis and therapeutics
Toxicologic therapeutics

a specialty unit or a general ICU, the critical care practitioner must focus on a variety of complex patient problems and therapeutic areas (Table 1).

Understanding the potential pharmacokinetic changes experienced by critically ill patients is essential for the optimal dosing and monitoring of drug therapy in the critically ill patient.[34] Altered organ blood flow, dysfunction of drug-eliminating organs, and changes in fluid compartment volumes often dictate the need for individualized approaches to drug dosing.[35–38] Pharmacists are ideally trained to provide comprehensive therapeutic drug monitoring and optimize expenditures for serum drug concentrations.[29]

Universal concern with the comfort of the patient requires knowledge of analgesics and sedatives. Guidelines have been published to guide the optimal use of these agents.[39] These therapies must be prescribed in a manner that does not adversely affect the respiratory status of the patient and, in many cases, is used to facilitate adequate ventilation of patients with acute lung injury. An understanding of lung injury and mechanical ventilation is essential. Use of pharmacologic agents to induce paralysis may be an essential part of this care for some patients.[40] Prevention of common adverse events such as stress-related gastrointestinal bleeding and deep venous thrombosis requires knowledge of the gastrointestinal and coagulation systems and therapeutics. Nutrition support consultation is also provided by critical care pharmacists in many settings. Critically ill patients may be highly catabolic and optimal provision of macro- and micronutrients may enhance their recovery. Proper application of immune-enhancing nutrients has added complexity to the nutritional support of critically ill patients.

Critically ill patients are at high risk for a variety of nosocomial infections. Knowledge of infection control techniques, as well as proper use of prophylactic and empiric antibiotics, is an important component of critical care pharmacy practice. Inappropriate antibiotic use can lead to antimicrobial resistance and outbreaks of nosocomial infection that are difficult to treat with conventional therapies. Critical care pharmacists work with infection control staff and infectious disease pharmacists to optimize the use of antimicrobial therapies.

The hemodynamic stability of patients is another universal concern for critical care pharmacists. Patients with cardiac diseases or postcardiac surgery are obvious candidates for inotropic and vasoactive therapy (vasopressors and vasodilators). However, patients of all ages with severe injury, sepsis, or the systemic inflammatory response syndrome require vigorous resuscitation with fluids and vasoactive agents. Guidelines have been written to guide the management of these challenging patients.[41] Understanding the cardiovascular system and therapeutics is another fundamental portion of a critical care pharmacists' knowledge base. In addition, expertise in the resuscitation of patients experiencing an acute cardiac or respiratory event is an important skill and knowledge set. Pharmacist knowledge of the current guidelines and participation in cardiopulmonary resuscitation teams is a clinical pharmacy service shown to be associated with reduced hospital mortality.[42,43]

Disease-specific therapies and other fundamental components of the knowledge-base required to practice as a critical care specialist is outlined in the ASHP requirements for critical care residency training.[44] In addition to direct patient care, the critical care resident should receive training or experience in drug information and drug policy development, practice management, and participate in the management of drug distribution systems in the critical care setting.

There are currently 21 critical care residencies listed in the ACCP *2001 Guide to Residencies and Fellowships.* Eight of these residencies are accredited by the ASHP. In addition, 11 critical care fellowships are available.[45]

IMPACT OF CRITICAL CARE PHARMACISTS

Critical care pharmacists have demonstrated numerous contributions to the cost-effective care of ICU patients. Pharmacist initiated interventions in a 1200-bed teaching hospital were demonstrated to lower the drug costs by 41% compared with a control group (mean $73.75 vs. $43.40; $p < 0.001$).[46] Approximately, fifty percent of the 259 patients were in critical care units. The majority (79%) of the interventions over the 30-day trial period were aimed at improving the quality of care, whereas the remaining 21% were to provide equivalent care at a lower cost. There was no impact on length of stay or readmission rates, but there was a trend toward lower hospital mortality in the intervention group.

Similarly, a multidisciplinary performance improvement team that included a pharmacist established a series of patient care protocols and tested the impact on the costs of care and outcome.[30] Protocols were developed that eliminated many standing orders for laboratory tests, electrocardiograms, and chest x-ray films. Other protocols were directed toward the use of sedatives, analgesics, neuromuscular blocking agents, and ventilator weaning. The outcome and costs from a baseline evaluation of 72 patients were compared with 85 patients in the follow-up phase. Application of the guidelines reduced costs for laboratory tests by 65%, and the number of chest x-rays were reduced by 56%. The cost of neuromuscular block-

ers was reduced by 75%. In addition, the length of ICU stay and duration of mechanical ventilation were reduced. There was no change in mortality. If these results can be extrapolated to a larger population and maintained, significant economic and outcome benefits could be realized. Another publication from this same group focused on the impact of guidelines for the use of analgesics, sedatives, and neuromuscular blocking agents in the same population.[47] The pharmacist was involved in protocol development, education and implementation, and ongoing intervention when practice did not meet guidelines. A reduction of direct drug costs, ventilator time, and length of stay were accomplished by using the protocol. Pharmacists have demonstrated similar results using sedation protocols elsewhere.[48]

Others have shown a positive impact of critical care pharmacists. A clinical pharmacist working part-time (daily rounds, average 10 hours per week) in a medical ICU over 8 weeks demonstrated a net benefit of $101 per day, considering cost avoidance, cost savings, increased drug costs, and the pharmacist's salary.[49] Although the medical ICU was unable to increase staffing levels to maintain this service, they redistributed pharmacist and technician workloads to perpetuate the clinical activities. Similarly, a clinical pharmacist with 50% teaching responsibility was assigned to participate in daily work rounds with the (medical-surgical patients) critical care team for 13 weeks.[50] A cost saving using drug costs only (no personnel costs) was $69.11 per patient day. Inclusion of personnel costs, for an average of 3 hours per day, did not negate the cost benefit. High-cost drugs were targeted, so it may be difficult to maintain this level of cost savings once the prescribing habits are modified or as protocols are implemented.

ONGOING CHALLENGES

A focal point for critical care pharmacists and hospitals with critical care units is a position paper on critical care pharmacy services jointly developed and published by ACCP and SCCM.[51] This paper identifies and describes the fundamental, desirable, and optimal activities that define the scope of practice of the critical care pharmacist (Table 2). Fundamental activities are deemed vital to the safe provision of pharmaceutical care to the critically ill patient. The fundamental responsibilities of critical care pharmacists include a full-time commitment to critical care patients, evaluation of all drug therapy, identification of adverse events, individualized drug dosing, provision of drug information, documentation of activities, and participation in quality improvement activity. At a higher level of practice, the desirable activities additionally include critical care-specific pharmacotherapeutic services. Additional desirable activities may include rounding with a critical care team, review of medication histories, participation in resuscitation events, student and resident education, protocol development, participation in research, and outcome analysis. At the highest level, the optimal activities of a critical care pharmacy specialist include provision of education to families, pharmacists, and physicians, development of research protocols, new pharmacy services, and publication of the results of these programs. A single pharmacist cannot provide all these services, but rather should function within a team to meet these goals.

A similar model is used to present the recommended levels of service and personnel from a pharmacy department and hospital perspective.[51] Fundamental service includes the use of patient profiles, provision of "ready to administer" medications and parenterals, and adequate quality improvement programs. Desirable pharmacy services include computerized information management systems and an ICU satellite. Optimal pharmacy department services include a 24-hour satellite, physician order entry, and continuous availability of pharmaceutical care services. This document challenges practitioners and institutions to measure their progress and strive for the deli-

Table 2 Selected critical care pharmacist activities

Fundamental
Dedicated ICU pharmacist providing pharmaceutical care
Order evaluation and intervention
Adverse drug event and medication error management and prevention
Documentation of impact
Medication use policy implementation and support
Desirable
Rounding with the critical care team
Medication history review
Resuscitation response
Education of pharmacy students and residents
Implements and evaluates drug therapy protocols or pathways
Participates in clinical research
Optimal
Formal and informal education of the critical care team
Advanced cardiac life support education
Residency or fellowship development
Conducts research and presents and publishes findings

(From Ref. [51].)

very of optimal pharmaceutical care services to critically ill patients.

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INTRODUCTION

The object was to identify and describe the scope of practice that characterizes the critical care pharmacist and critical care pharmacy services. Specifically the goals were to define the level of clinical practice and specialized skills characterizing the critical care pharmacist as clinician, educator, researcher, and manager; and to recommend fundamental, desirable, and optimal pharmacy services and personnel requirements for the provision of pharmaceutical care to critically ill patients. Hospitals having comprehensive resources as well as those with more limited resources were considered.

Consensus of critical care pharmacists from institutions of various sizes providing critical care services within several types of pharmacy practice models was obtained, including community-based and academic practice settings. Existing guidelines and literature describing pharmacy practice and drug use processes were reviewed and adapted for the critical care setting.

By combining the strengths and expertise of critical care pharmacy specialist with existing supporting literature, these recommendations define the level of clinical practice and specialized skills that characterize the critical care pharmacist as clinician, educator, researcher, and administrator. Recommendations include fundamental, desirable, and optimal pharmacy services as well as personnel requirements or the provision of pharmaceutical care to critically ill patients.

HISTORICAL BACKGROUND

The discipline of critical care pharmacy practice evolved since the mid-1970s to become an essential component of the multidisciplinary team in the intensive care unit (ICU).[1–3] In the early 1970s, there were a few practitioners in critical care who were members of surgical or trauma services and cardiac arrest teams. During the next decade, pharmacy services expanded to various ICU settings (both adult and pediatric), the operating room, and the emergency department. In these settings, pharmacists established clinical practices consisting of therapeutic drug monitoring, nutrition support, and participation in patient care rounds. Pharmacists also developed efficient and safe drug delivery systems with the evolution of critical care pharmacy satellites and other innovative programs.

In the 1980s, critical care pharmacists designed specialized training programs and increased participation in critical care organizations. The number of critical care residencies and fellowships doubled between the early 1980s and the late 1990s. Standards for critical care residency were developed,[4] and directories of residencies and fellowships were published.[5,6] Several professional pharmacy organizations formed specialty groups consisting of critical care pharmacists. These include the American College of Clinical Pharmacy (ACCP), American Society of Health-System Pharmacists, and the Operating Room Satellite Pharmacy Association. In 1989, the Clinical Pharmacy and Pharmacology Section was formed within the Society of Critical Care Medicine, the largest international, multidisciplinary, multispecialty critical care organization. This recognition acknowledged that pharmacists are necessary and valuable members of the physician-led multidisciplinary team.

The Society of Critical Care Medicine Guidelines for Critical Care Services and Personnel deem that pharmacists are essential for the delivery of quality care to critically ill patients. These guidelines recommend that a pharmacist monitor drug regimens for dosing, adverse reactions, drug–drug interactions, and cost optimization for all hospitals providing critical care services.[1] The guidelines also advocate that a specialized, decentralized pharmacist provide expertise in nutrition support, cardiorespiratory resuscitation, and clinical research in academic medical centers providing comprehensive critical care.[1]

Since the early 1990s, clinical pharmacy became increasingly specialized and developed specialty board certification.[7] The growth of critical care pharmacy practice paralleled this development. Pharmacists assumed in-

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DOI: 10.1081/E-ECP 120006407

creased responsibility for monitoring patient outcomes as well as supervising drug distribution services.[3]

Pharmacists have demonstrated a role in the management of drug costs and reductions in morbidity and mortality.[2,3,6–19] Clinical pharmacy services such as clinical research, provision of drug information, drug admission histories, and participation on a cardiopulmonary resuscitation (CPR) team have been associated with reduced mortality.[11] Prospective, controlled trials demonstrated that when pharmacists assume responsibility for pharmacotherapy as part of a multidisciplinary health care team, significant reductions in adverse drug events (ADEs) and length of stay are realized.[12–16] Many of these findings have been documented in specialized critical care populations.[14–20] The ACCP estimates that a benefit of $16.70 is realized for every $1.00 invested in clinical pharmacy programs.[17] A landmark study involving critical care pharmacists confirmed that pharmacist rounding in the ICU with the multidisciplinary team reduces preventable ADEs and associated costs caused primarily by prescribing errors.[16] Pharmacist intervention during prescribing decreased the rate of preventable ADEs by 66% from 10.4 to 3.5/1000 patient-days ($p < 0.001$). Pharmacist involvement was categorized as drug order clarification (45%), provision of drug information (25%), and recommendations for alternative therapy (12%). Based on an estimated cost of $4685/preventable ADE, the annualized financial impact in the unit studied would be $270,000 (1995 dollars).

Despite the growing evidence supporting the critical care pharmacist's contribution to patient care, many ICUs have not taken full advantage of this vital resource.[18] A description of pharmacy services and pharmacist activities in a critical care setting will assist practitioners and administrators in establishing or advancing these specialized pharmacy services. This article may be used to educate other health care providers, administrators, and developers of health care policy on the role of pharmacists and pharmacy services in the care of the critically ill. Furthermore, the application of the elements in this article will allow researchers to further document the effect of critical care pharmacy services on improving patient outcomes.

PURPOSE

This article identifies and describes the scope of pharmacy practice of the critical care pharmacist and critical care pharmacy services. Specifically, the aims of the Task Force on Critical Care Pharmacy Services were:

1. To define the level of clinical practice and specialized skills characterizing the critical care pharmacist as clinician, educator, researcher, and manager.
2. To recommend levels of service and personnel requirements for the provision of pharmaceutical care to critically ill patients. The levels will be defined as fundamental, desirable, or optimal.

METHODS

The Task Force on Critical Care Pharmacy Services consisted of members from the Clinical Pharmacy and Pharmacology Section of the Society of Critical Care Medicine and the Critical Care Practice and Research Network of the ACCP. Members of the task force were from institutions of various sizes and they provide critical care services within a variety of pharmacy practice models. Practitioners from both community-based and academic practice settings were included.

The formulation of these recommendations, including discussion and development of consensus, took place between October 1997 and September 1999. Task force members were charged with developing graded parameters within six domains: clinical activities, drug distribution, education, research, documentation, and administration. This article was organized into pharmacist activities and pharmacy services. Drafts were reviewed and evaluated by all members of the task force, and a consensus was reached. When differences in opinion were expressed, they were resolved using a modified Delphi method.[21] The document was reviewed externally by three established leaders in critical care pharmacy and by 18 pharmacy and hospital administrators for appropriateness of categorization of pharmacy activities and services. The article was further reviewed by select members and the governance of both the Clinical Pharmacy and Pharmacology Section of the Society of Critical Care Medicine and the Critical Care Practice and Research Network of the ACCP. Before organizational endorsement, the article underwent internal review by both the Council of the Society of Critical Care Medicine and the Board of Regents of the ACCP.

Existing guidelines and literature for pharmacy practice and drug use processes were reviewed and adapted for the critical care setting.[7,22–24] The needs of hospitals with comprehensive resources as well as those with more limited resources were considered. The task force created three gradations of pharmacist responsibilities and departmental services as fundamental, desirable, and optimal. Classification of the elements into each category was the result of the consensus process. For the purposes of this article, the following definitions were used. Fundamental activities are vital to the safe provision of pharmaceutical

care to the critically ill patient. Desirable activities include fundamental activities and critical care-specific pharmacotherapeutic services. Optimal activities encompass the range of fundamental to desirable services and, additionally, reflect an integrated, specialized, and dedicated model of critical care that aims to optimize pharmacotherapeutic outcomes through the highest level of teaching, research, and pharmacotherapy practice. Fundamental services should not be interpreted as an acceptable minimum level of service. Each institution and practitioner continually should strive for the highest level of service possible.

A single pharmacist cannot perform all the fundamental activities on all patients every day. Rather, these critical care pharmacy activities will require varying levels of involvement from multiple pharmacists and trained technicians acting as a team, along with support from pharmacy and hospital administrators, and other personnel. The exact allocation of labor and the pharmacist-to-patient ratio will vary by institution and depend on the level of care, the acuity of patients, and the degree of specialization of the institution.

"The pharmacist," as used herein, refers to the team of licensed pharmacy practitioners with specialized training or practice experience focusing on the unique characteristics and needs of critically ill patients. Although various practice models exist, the pharmacist practices within the framework of a multidisciplinary team. In collaboration with other members of the patient care team, pharmacists share the responsibility for patient care outcomes, not just by providing basic dispensing functions and drug information services, but by solving patient- and drug-related problems and by making decisions regarding drug prescribing, monitoring, and drug regimen adjustments.[25] The pharmacist's practice may integrate varying elements of patient care, teaching, and research activities, depending on the nature of the institution and the pharmacist's training.

The task force recognizes the varied educational backgrounds of practicing critical care pharmacists. Having the qualifications and competence necessary to provide pharmaceutical care in the ICU is essential and may be achieved by a variety of means including advanced degrees, residencies, fellowships or other specialized practice experiences.

The term pharmacy and hospital services refers to departmental and institutional/organizational components of the infrastructure that support the pharmacist's activities. They consist of systems, operations, and personnel who facilitate and support the provision of patient care, teaching, and research to optimize safe and effective pharmaceutical care of the critically ill.

This article is not intended to be a standard of practice; however, we envision that it will serve as a guideline for hospitals of varying resources to optimize the delivery of pharmaceutical care to the critically ill. It is expected that these recommendations will continue to be reviewed at intervals of approximately 5 years as critical care pharmacy services, clinical pharmacy, and critical care medicine evolve.

CRITICAL CARE PHARMACIST ACTIVITIES

Fundamental Activities

1. The pharmacist's time is dedicated to critical care patients, with few commitments outside the ICU area.
2. The pharmacist prospectively evaluates all drug therapy for appropriate indications, dosage, drug interactions, and drug allergies; monitors the patient's pharmacotherapeutic regimen for effectiveness and ADEs; and intervenes as needed.
3. In conjunction with the clinical dietitian, the pharmacist evaluates all orders for parenteral nutrition and recommends modifications as indicated to optimize the nutritional regimen.
4. The pharmacist identifies ADEs and assists in their management and prevention, and develops process improvements to reduce drug errors and preventable ADEs.
5. The pharmacist uses the medical record as one means to communicate with other health care professionals and to document specific pharmacotherapeutic recommendations.
6. The pharmacist provides pharmacokinetic monitoring when a targeted drug is prescribed.
7. The pharmacist provides drug information and intravenous compatibility information to the ICU team and uses the regional poison information center when indicated.
8. The pharmacist maintains current tertiary drug references.
9. The pharmacist provides drug therapy-related education to ICU team members.
10. The pharmacist participates in reporting ADEs to institutional committees and to the Food and Drug Administration's MedWatch program.
11. The pharmacist documents clinical activities that include, but are not limited to, disease state management, general pharmacotherapeutic monitoring, pharmacokinetic monitoring, ADEs, education, and other patient care activities.
12. The pharmacist acts as a liaison between pharmacy, nursing, and the medical staff to educate health professionals regarding current drug-

related procedures, policies, guidelines, and pathways.
13. The pharmacist contributes to the hospital newsletters and drug monographs on issues related to drug use in the ICU.
14. The pharmacist implements and maintains departmental policies and procedures related to safe and effective use of drugs in the ICU.
15. The pharmacist collaborates with nursing, medical staff, and hospital administration to prepare the ICU for the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) survey and responds to any deficiencies identified.
16. The pharmacist provides consultation to hospital committees, such as Pharmacy and Therapeutics, when critical care pharmacotherapy issues are discussed.
17. The pharmacist identifies how drug costs may be minimized through appropriate use of drugs in the ICU and through implementation of cost-containment measures.
18. The pharmacist participates in quality assurance programs to enhance pharmaceutical care.

Desirable Activities

1. The pharmacist regularly makes rounds as a member of the multidisciplinary critical care team (if available) to provide pharmacotherapeutic management for all ICU patients.
2. The pharmacist maintains knowledge of current primary references pertinent to critical care pharmacotherapy.
3. The pharmacist reviews a patient's drug history to determine which maintenance drugs should be continued during the acute illness.
   a. The pharmacist clarifies previously effective dosages and dosage regimens.
   b. For all suspected drug-related ICU admissions, the pharmacist assesses the patient drug history for causality and documents in the medical record any findings that will impact patient management.
4. In collaboration with the clinical dietitian, the pharmacist provides formal nutrition consultation on request and responds within 24 hours.
5. The advanced cardiac life support-certified (or pediatric advanced life support-certified) pharmacist responds to all resuscitation events in the hospital 7 days/week, 24 hours/day.
6. The pharmacist provides didactic lectures to health professional students in critical care pharmacology and therapeutics, where applicable.
7. The pharmacist participates in training pharmacy students, residents, and fellows through experiential critical care rotations, where applicable.
8. The pharmacist coordinates the development and implementation of drug therapy protocols and/or critical care pathways to maximize benefits of drug therapy.
9. The pharmacist uses a documentation program that attaches both a clinical significance and an economic value to clinical interventions.
10. The pharmacist is actively involved in critical care pharmacotherapy research by assisting in the screening and enrollment of patients and by serving as a study coordinator or contact person, where applicable.
11. The pharmacist participates in research design and data analysis, where applicable.
12. The pharmacist contributes to the pharmacy and medical literature, e.g., case reports, letters to the editor, and therapeutic, pharmacokinetic, and pharmacoeconomic reports.
13. The pharmacist is involved in nonpatient care activities including multidisciplinary committees and educational in-services.

Optimal Activities

1. The pharmacist assists physicians in discussions with patients and/or family members to help make informed decisions regarding treatment options.
2. The pharmacist provides formal accredited educational sessions, such as medical grand rounds or intensive care rounds, for medical staff, students, and residents.
3. The pharmacist participates in teaching advanced cardiac life support.
4. The pharmacist develops residencies and/or fellowships in critical care pharmacy practice.
5. The pharmacist develops and implements pharmacist and pharmacy technician training programs for personnel working in the ICU.
6. The pharmacist identifies and educates lay groups and medical personnel in the community about the role of pharmacists as part of the multidisciplinary health care team in the ICU.
7. The pharmacist independently investigates or collaborates with other critical care practitioners to evaluate the impact of guidelines and/or protocols used in the ICU for drug administration and management of common disease states.
8. The pharmacist uses pharmacoeconomic analyses to prospectively evaluate existing or new phar-

macy services and the place of new drugs in critical care pharmacotherapy.
9. The pharmacist is proactive in designing, prioritizing, and promoting new pharmacy programs and services.
10. The pharmacist secures funds for conducting research.
11. The pharmacist reports results of clinical research and pharmacoeconomic analyses to the pharmacy and medical community at regional and national meetings.
12. The pharmacist publishes in peer-reviewed pharmacy and medical literature as a result of any of the following activities:
    a. Clinical research or other original research that qualitatively and quantitatively evaluates drug therapy and the provision of pharmacy services.
    b. Investigator-initiated grants and contracts.
    c. Pharmacoeconomic and outcomes research.

PHARMACY AND HOSPITAL SERVICES

Fundamental Services

1. Drug use systems can do the following:
    a. Create and maintain patient drug profiles.
    b. Interface with patient laboratory data.
    c. Alert users to drug allergies.
    d. Alert users to maximum dosage limits.
    e. Alert users to drug–drug and drug–food/nutrient interactions.
2. If manual drug administration records are the only available drug administration document, quality assurance[1] systems are in place to verify the accuracy of this process.
3. A "ready to administer" (unit-dose) drug distribution system is available in the ICU with no more than a 24-hour supply for each patient.
4. Large- and small-volume parenteral products are prepared in the pharmacy and delivered at regularly scheduled times to the patient care area 7 days/week.
5. Pharmacy space and facilities in the ICU are assessed routinely to determine whether efficiency can be improved, where applicable.
6. Procurement, storage, inventory, and distribution of investigational drugs, where applicable, are under the supervision of a pharmacist.
7. The pharmacy department is represented on the Institutional Review Board and/or Scientific Review Board, as applicable.

Desirable Services

1. The hospital information management system is computerized, can comply with the requirements listed for drug use processes (see Fundamental Services, Item 1), and can do the following:
    a. Alert users to disease state–drug interactions.
    b. Provide intravenous admixture information (e.g., compatibility, stability, preparation).
    c. Provide online drug and poison information.
    d. Document clinical pharmacy patient care interventions.
2. Computerized drug administration records are generated. Manual records are used only in emergencies.
3. An ICU satellite pharmacy with unit-dose drug distribution and intravenous admixture capabilities is open a minimum of 40 hours/week.

Optimal Services

1. The computerized hospital information management system serving the ICU has the following additional capabilities:
    a. Direct physician drug order entry at patient bedside.
    b. Interface with bedside clinical information system.
2. An ICU satellite pharmacy with unit-dose drug distribution and intravenous admixture capabilities is open 24 hours/day, 7 days/week.
3. Pharmacotherapeutic, pharmacokinetic, and nutrition consultation are available 24 hours/day, 7 days/week.

ACKNOWLEDGMENTS

The task force acknowledges the following individuals for their review of this manuscript: Bradley A. Boucher, Pharm.D., FCCP, FCCM, BCPS, University of Tennessee, Memphis, TN; Joseph F. Dasta, M.S., FCCP, FCCM, Ohio State University, Columbus, OH; and Barbara J. Zarowitz, Pharm.D., FCCP, FCCM, BCPS, Henry Ford Health System, Bingham Farms, MI.

This position paper was developed by a task force of the Clinical Pharmacy and Pharmacology Section of the Society of Critical Care Medicine and the Critical Care Practice and Research Network of the American College of Clinical Pharmacy. It was approved by the Council of the Society of Critical Care Medicine on February 10, 2000, and the Board of Regents of the American College of Clinical Pharmacy on October 5, 1999.

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Cytochrome P450

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INTRODUCTION

The cytochrome P450 (CYP) is a major hemo (iron-containing) protein family that catalyzes drug and xenobiotic metabolism. It is present in the microsomes (tiny membrane vesicles of endoplasmic reticulum) of many different cells in the body, but it is at highest concentration in liver.[1] There are two types of microsomal enzymes in the body: those catalyzing mainly oxidations (termed the phase I enzymes) and those catalyzing conjugations (termed the phase II enzymes).[2] The CYP is the most important enzyme system catalyzing phase I metabolism reactions such as oxidation, reduction, and hydrolysis. It generally serves as a detoxification mechanism for lipophilic drugs and xenobiotics by converting them to more water-soluble compounds.[3] However, this enzyme system occasionally transforms nontoxic chemicals or drugs into toxic reactive intermediates, or procarcinogens into carcinogens. In addition, it converts hormones and steroids into more active forms.

ORIGIN AND NOMENCLATURE

In the late 1950s, it was discovered that when rat liver microsomes were treated in a certain condition, a strong absorption band occurred at approximately 450 nm wavelength in the spectrophotometer, which was very unusual for the pigments.[3] The red pigment responsible for this phenomenon was called P (for *pigment*) 450. It was later named "cytochrome P450" because it was believed to be similar to mitochondrial cytochromes.[4]

At first, it was believed that the P450 was a single protein, but soon it became apparent that it was not a single protein but comprised a number of different proteins. Each human CYP protein identified appears to be the expression of an unique gene. There are more than 1000 unique genes for CYP identified among prokaryotes and eukaryotes to date.[5] There are significantly common amino acid sequences among all CYPs in a few regions of the proteins, suggesting a common ancestry. For this reason, the CYP is referred to as a supergene family.[6,7]

Accordingly, a recommended nomenclature system has been devised based on the evolutionary relations of these enzymes.[7] According to this system, the deduced amino acid sequences from the genes are compared and divided into families, which comprise those CYPs that share at least 40% identity and designated by Arabic number after CYP (i.e., CYP1, 2, 3, etc.). These families are divided further into subfamilies, which comprise those forms that are at least 55% related by their deduced amino acid sequences, and are designated by a capital letter after the Arabic number (i.e., CYP1A, CYP2D, etc.). Each individual enzyme is designated by Arabic number after subfamily (i.e., CYP1A2, CYP3A4).

MAJOR ISOENZYMES OF CYP IN HUMAN DRUG METABOLISM

There are numerous CYPs identified in humans, animals, and plants, but currently three P450 gene families, including CYP1, CYP2, and CYP3, are responsible for most of human drug metabolism.[8] These three CYP gene families, their subfamilies, and their major substrates are illustrated in Table 1. In drug metabolism, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are important. Especially, approximately 75% of all therapeutic agents are metabolized by CYP2D6 and CYP3A4 together.[9]

INDIVIDUAL DIFFERENCES OF DRUG RESPONSE AND GENE POLYMORPHISM

It is well known that each patient may respond variably even when each patient receives the same dose of the

Encyclopedia of Clinical Pharmacy
DOI: 10.1081/E-ECP 120006216

Table 1 Major CYP enzymes, their substrates, inducers, inhibitors, and phenotype markers

Enzyme	Representative substrates	Known inducer	Inhibitor	Polymorphism	Noninvasive test marker
CYP1A2	Caffeine Theophylline	Tobacco Charcoal-broiled meat	Fluvoxamine	(Yes)[a]	Caffeine
CYP2C9	Warfarin Tobutamide	Barbiturates Rifampin	Sulfaphenazole	(Yes)[a]	Tobutamide
CYP2C19	Mephenytoin Omeprazole	Barbiturates Rifampin		Yes	(S)-Mephenytoin
CYP2D6	Metopronolol Imipramine Encainide	Barbiturates Rifampin in EMs only	Quinidine	Yes	Dextromethorphan Debrosoquine
CYP2E1	Ethanol Acetaminophen	Ethanol Isoniazid	Disulfiram	(Yes)[a]	Chlorzoxazone
CYP3A3/4	Cyclosporine Verapamil Nifedipine blockers	Phenytoin Rifampin Barbiturates	Erythromycin Verapamil Ketoconazole Grapefruit juice	(Yes)[a]	Erythromcyin Midazolam
CYP3A5	Cyclosporine	Barbiturates Rifampin	Ketoconazole Erythromycin	Yes	Erythromycin

[a]There are no conclusive evidences between genotype and phenotype, although some phenotype or genotype differences are detected in the population.

same medication. Many factors involve this inter- and intrapatient variability of drug response. The recommended dose of each therapeutic agent is determined based on clinical study results from a small number of patients who meet a narrowly defined criteria. However, the optimal daily dose in clinical practice can vary widely among patients because of factors such as age, size of the patient, gender, ethnicity, concurrent drug therapy, food intake, and the patient's own disease conditions (i.e., renal function or liver function).[10] It should be noticed that each individual patient has his or her own optimal dose of drug therapy in a specific clinical condition. Because the CYP is an important enzyme system for various drug classes, large differences in the activities of the CYP among individuals explain some of this wide variability in the dosing requirements of various drugs.[11]

Most drugs are metabolized by multiple metabolic pathways, which is necessary because this may protect the body from the toxic effects of drugs in case one metabolic pathway is shut down. However, in certain cases, single enzyme activity largely determines drug response. For example, the therapeutic effect of the drug may be correlated with the blood levels of the parent drug, and this may depend largely on the rate of metabolism of the drug catalyzed by a single CYP. Although it is not always true, there are now at least several important examples in which the relation between drug dose, blood levels, and therapeutic response in an individual patient is largely determined by the catalytic activity of single enzyme, CYP2D6. For example, patients with the poor metabolizer phenotype for CYP2D6 demonstrate significantly high area under the plasma concentration time curve for metoprolol, compared with extensive metabolizers of CYP2D6.[12] As a result, poor metabolizers generally attain therapeutic effects from these drugs at significantly reduced daily doses. If the same dose as a rapid metabolizer is given, the patients will develop severe toxicity.

The activity of CYP3A varies at least 10-fold among patients, and the activity level in a given patient appears to be related to the dosing requirements of a certain substrate metabolized by CYP3A.[13,14] It has been shown that the liver activity of CYP3A largely predicts blood levels of cyclosporine in patients receiving the drug for treatment of psoriasis;[13] that is, patients with higher CYP3A activity have lower blood levels of cyclosporine at any given daily dose of the drug.[14,15]

There are significant differences in CYP enzyme activities in the general population, which are mainly determined by genetics, although some environmental factors such as enzyme inducers or inhibitors are involved. One of the best known CYP enzyme inducer is cigarette smoking, which generally induces CYP1A2 and other CYP enzymes.[16,17] In a certain population,

there is genetically a lack of CYP genes (i.e., CYP2C19, CYP2D6), and these populations may develop significant toxicity if the standard dose of a drug with a narrow therapeutic index is given.

ROLE OF CYP IN SYSTEMIC AVAILABILITY OF DRUG

The CYP is present not only in the liver, but also in the intestine. It appears that the CYP is located mainly at the apex of the mature enterocytes, lying in a band just below the microvillous border.[18] In humans, the major enterocyte CYP appears to be the CYP3A4, which accounts for more than 70% of CYP activity in the intestine. Interestingly, CYP3A4 is located along with P-glycoprotein, a cell membrane efflux pump.[19] This may indicate that CYP3A4 along with P-glycoprotein are intended to prevent the environmental toxins, or xenobiotics such as drugs, from entering the body. The intestinal metabolism of many lipophilic drugs metabolized by CYP3A4 is estimated to be as much as one-half of the administered dose.[20] Previously, many CYP inhibitors were thought to act only on liver CYP enzymes, but it was found that they affect on both liver and intestinal CYP.[19,20] For example, ketoconazole, which is a potent inhibitor of CYP3A4, increases area under the curve of cyclosporine not only by inhibiting hepatic CYP3A4, resulting in reducing metabolism of cyclosporine, but also inhibiting intestinal CYP3A4, subsequently increasing bioavailability of cyclosporine.[21] Some food components such as grapefruit juice inhibit CYP3A in the intestine and, when oral felodipine is given with grapefruit juice, its AUC and Cmax are increased by 250% and 150%,[22] respectively. However, when intravenous felodipine is given with grapefruit juice, there is no significant difference.[22]

ROLE OF CYP IN DRUG–DRUG INTERACTION

Drug interactions constitute a major problem in chronic multiple drug therapy.[23] Although interactions affecting the pharmacodynamics of a drug can be reasonably predicted (i.e., additive effect or synergistic effect), those affecting its pharmacokinetics are difficult to predict. These might result from various contributions involving absorption, transportation, distribution, metabolism, and excretion.[23] Among these, metabolism in liver as well as intestine appears to represent the major source of drug–drug interactions. Because CYP enzymes are known to be induced or inhibited by, and involved in the oxidation of, a number of currently used drugs, they are likely to be responsible for numerous drug interactions in humans.[2] Because CYP3A4 metabolizes more than 50% of all therapeutic agents, its inhibitors and inducers have significant impact. Clinically important CYP3A4 inhibitors include ketoconazole, itraconazole, erythromycin, clarithromycin, nefazodone, ritonavir, and grapefruit juice.[23,24]

Torsades de pointes, a life-threatening ventricular arrhythmia associated with QT prolongation, can occur when these inhibitors are coadministered with terfenadine, astemizole, or cisapride because they inhibit these agents from converting the parent compound into nontoxic, pharmacologically active metabolites.[25–27] As a result, the proarrhythmic parent compound accumulates in the body, which causes toxic effects. Because of this serious drug interactions, these drugs have to be withdrawn from the market. Cyclosporine, an important immunosuppressant, has clinically been shown to be involved in multiple drug interactions.[23] Because cyclosporine is extensively metabolized in human liver and enterocytes by CYP3A4, any inducer of CYP3A4 (e.g., ripampin) should cause a decrease in cyclosporine levels, whereas any substrate or inhibitor (e.g., ketoconazole) of this CYP should elicit the opposite effect. Indeed, this has been clearly demonstrated clinically[28] as well as in an experimental model.[29]

Some drugs with multiple metabolic pathways are affected by many different inhibitors. For example, codeine is metabolized by CYP2D6 and CYP3A4, which act on different sites of action.[30] The O-demethylation of codeine is catalyzed by CYP2D6 and N-demethylation is catalyzed by CYP3A4.[31] The substrates of CYP2D6, such as thioridazine, amitriptyline, and metoprolol inhibit the O-demethylation of codeine preferentially,[30] whereas substrates of CYP3A4, such as ketoconazole, are strong inhibitors of the N-demethylation of codeine.[31]

Not all predicted drug interactions are expected to be clinically significant. For example, nifedipine and cyclosporine are both CYP3A4 substrates, but there is no clinically important drug interaction noticed.[23] To predict the drug interaction, several parameters are expected to be important. These include notably:[32] 1) relative affinity of CYP enzyme on both drugs (km); 2) dose and local concentration of each drug either in enterocytes or hepatocytes; 3) duration of concurrent therapy; and 4) CYP enzyme in the liver or intestine of the patient. The level of CYP3A is highly variable in each individual. It is possible that, in one patient with a low CYP3A level, all the cytochrome would

be saturated by the coadministered drugs, but not in another with higher CYP3A level; the consequence is that the interaction should occur in the former but not the latter.

NONINVASIVE MEASUREMENT OF CYP ACTIVITY AND PREDICTION OF DRUG RESPONSE

It would be great to measure the activity of individual CYP enzymes and predict drug response or drug interaction in individual patients because of the CYP enzymes involved in the metabolism of various therapeutic agents.[33] A reliable in vivo probe for phenotyping CYP3A4 would make it possible to identify individuals at greatest risk of toxicity due to high blood levels and inefficacy due to subtherapeutic blood levels, and to detect potentially dangerous drug–drug interactions.[34]

CYP3A is the predominant drug-metabolizing enzyme in humans. Thus, there have been considerable efforts to develop a simple, safe, and reliable phenotyping procedure for CYP3A activity; however, these efforts are largely suboptimal.[33] Among candidate probes, two procedures have shown clinical utility, intravenous midazolam clearance[35] and the erythromycin breath test (ERBT).[36,37] There is strong evidence that the clearance of midazolam provides an estimate of liver CYP3A activity.[38] However, it has a potent sedative effect, and the multiple blood sampling required for pharmacokinetic evaluation makes it inappropriate for widespread use in an outpatient setting.

The ERBT has been most widely studied[36,37] and has a significant correlation with the pharmacokinetics of the CYP3A substrate, cyclosporine.[14] The ERBT correlates with trough blood concentration of cyclosporine in patients with psoriasis[14] and with the oral clearance of cyclosporine in transplant recipients.[15] However, as a probe for CYP3A activity, the ERBT has significant limitations. Not only does it require intravenous access, which may exclude the fraction of gastrointestinal metabolism by CYP3A, but it also requires the administration of a radioactive substance, a potential safety concern.[33] In addition, ERBT fails to show a significant correlation with other known CYP3A4 substrates, such as alfentanil[39] or dapsone clearances.[40] Other markers such as dapsone, or the 6β-hydroxy cortisol urine test, have been tried with variable results.[40] Dextromethorphan shows some promise as a probe simultaneously measuring both CYP2D6 and CYP3A4 acitivity, but its urine metabolic ratios failed to predict CYP3A4 activity.[41] In the near future, genotyping information regarding individual CYP will be readily available, which may better explain individual variability of drug pharmacokinetics and pharmacodynamics.

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