Therapeutic Guidelines Australia

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INTRODUCTION

Therapeutic Guidelines Limited (TGL) is an independent, not-for-profit enterprise that focuses on the writing, publication, and sale of prescribing guidelines for health professionals. This article presents the major initiatives of TGL, its goals and organizational structure, and publishing process.

HISTORY

TGL had its genesis in the late 1970s, when a group of enthusiastic individuals joined forces to improve prescribing in an Australian public hospital.

At that time, Melbourne hospitals were experiencing an upsurge in the isolation of antibiotic-resistant organisms. There was concern among health professionals that this was the result of the inappropriate use of antibiotics. A multidisciplinary group from the major Melbourne hospitals responded to the problem by developing an agreed position on what constituted appropriate and cost-effective therapy for a range of common conditions. In 1979, the first edition of *Antibiotic Guidelines* was launched.

In 1985, the Therapeutics Committee of the Victorian Medical Postgraduate Foundation (VMPF-TC) was established to take responsibility for the distribution, promotion, and evaluation of the *Antibiotic Guidelines*, which at that time was the only guideline booklet available.

In 1986, in recognition of the importance of appropriate drug use, a ministerial advisory committee, the Victorian Drug Usage Advisory Committee (VDUAC) was established. The VDUAC believed the availability of independent information regarding drug therapy was integral to informed decision making by prescribers. In light of the increasing acceptance and use of the *Antibiotic Guidelines*, the Committee resolved to build on this concept and to produce additional prescribing guideline booklets.

In conjunction with this expansion, a number of innovative educational marketing and outreach projects were undertaken. The result was increased implementation of the Guidelines in both hospital and community practice.

By 1996, the Guidelines were firmly entrenched and growing rapidly. The VDUAC was responsible for the production of the manuscripts, and the VMPF-TC for publication, distribution, promotion, and evaluation of the books. The number of titles was increased; the target group was extended to include community practice; and authorship was widened to ensure input from the most eminent Australian experts.

With the expansion, however, administration became difficult under the complex committee structure described above; therefore, in 1996 a separate entity, TGL, was established under which all Guidelines activities were consolidated.

ORGANIZATIONAL STRUCTURE

TGL is a not-for-profit company limited by guarantee. It is independent of government and the pharmaceutical industry and is funded solely through sales of its Guidelines.

It is governed by a board of nine directors, four of whom are nominated by organizations that reflect the genesis of the company: the Victorian Medical Postgraduate Foundation; the Victorian Drug Usage Advisory Committee; The Royal Australian College of General Practitioners; and the Commonwealth Department of Health and Ageing.

The current directors of TGL are medically and pharmaceutically qualified professionals working in the areas of health education, medicine, and pharmacy. They are:

- Professor D. Birkett (Clinical Pharmacology), South Australia
- Dr. J.S. Dowden (Medical Publishing), Australian Capital Territory

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- Dr. J.E. Marley (General Practice), New South Wales
- Dr. M.L. Mashford (Clinical Pharmacology), Victoria
- Associate Professor F.W. May (Pharmacy), South Australia
- Dr. J.G. Primrose (International Medicinal Drug Policy) Australian Capital Territory
- Professor J.W.G. Tiller (Postgraduate Medical Education), Victoria

The organization employs the equivalent of approximately ten full-time staff members, including the Chief Executive Officer, Mrs. Mary Hemming, B Pharm., Grad Dip Epi Biostat.

Staff are employed in the areas of production (both print and electronic), information technology, marketing, sales and administration, and evaluation. To supplement the expertise and skills within the organization, consultants in finance, law, and marketing are utilized.

The Board appoints expert writing groups as ad hoc committees, who work with editors to develop content for the titles. Each writing group is chaired by a Director.

MISSION

TGL's mission statement is promoting quality use of medicines through the preparation, publication, and sale of independent, authoritative, up-to-date, problem-orientated information.

OBJECTIVES

The key objectives of TGL are:

- To encourage the use of Therapeutic Guidelines by health professionals to assist them in making therapeutic decisions to facilitate optimum healthcare.
- To encourage the use of Therapeutic Guidelines internationally through licensing agreements with appropriate organizations.
- To preserve the integrity of the organization through strict policies for Directors, staff, and members of the writing groups, on issues such as conflict of interest.
- To maintain financial independence.
- To establish strategic alliances with other organizations to further the objectives of the organization.
- To increase the range of products, e.g., information for consumers.
- To allocate funds for research and development.

CURRENT INITIATIVES

Guideline Development

The core activity of TGL is the writing, publication, and sale of Therapeutic Guidelines. These are published as a series of pocket-sized books, and also in electronic formats suitable for both stand-alone and networked computers. All titles are regularly updated in iterative cycles, thus allowing for shifts with evidence, response to feedback, and increased input over time.

The intention of the Guidelines is to provide prescribers with clear, practical, succinct, and up-to-date therapeutic information for a range of diseases. For experienced prescribers, the recommendations provide a valuable "second opinion" against which they can compare their own prescribing. For those less experienced, the recommendations form an acceptable basis for the management of patients. For other health professionals such as pharmacists and nurses, Therapeutic Guidelines provide information to support their contribution to the pharmaceutical care of their patients.

Basis of Recommendations

The Guidelines are derived from the best available scientific evidence, but the experience, insight and opinions of Australian experts are an essential element of the writing process, with the final text reflecting independent and expert interpretation.

Because the Guidelines cover all common disorders and not just those for which there is a body of evidence, there are many instances where trial data are not available, where published data fail to answer questions relevant to prescribers, or where research findings may not be relevant to local practice. To resolve gaps in the evidence, recommendations for reasonable therapy are developed, with criteria such as a drug's adverse effect profile, long-term safety data, and cost being taken into consideration.

Review and Endorsement

Critical steps in the development of the manuscripts are an extensive external review process, reconciliation of text with that of other relevant therapeutic guidelines, and endorsement by national or peak bodies such as The Royal Australian College of General Practitioners and the National Prescribing Service.

Postpublication Evaluation

The evaluation unit liaises with a network of approximately 250 users (general practitioners, specialists, pharmacists, and students) to actively solicit feedback on the various texts. Participants in the network are provided with all titles free-of-charge, and staff visit these users regularly to discuss and record comments.

Before any new edition is commenced, accrued feedback on the previous edition is collated and passed on to the writing group for consideration in the revision of the text.

MAJOR DIRECTIONS

International

Internationally, TGL has been active. A model for an international publishing agreement has been established that is working extremely well. A Japanese not-for-profit organization (comprising doctors and pharmacists) is licensed to translate and modify the texts to suit the Japanese market. The translated books are printed and sold in Japan, with a royalty returning to TGL. Similar licenses are in place with groups in China, Spain, and Russia.

Electronic

The impact of written clinical guidelines is limited by their accessibility at the time of decision making. Therefore, the long-term goal of TGL is to optimize clinical practice by integrating Therapeutic Guidelines into decision support systems, free of commercial bias, so they can assist health practitioners at the time of consultation.

As an initial step toward this goal, all current titles were converted into electronic versions suitable for both stand-alone computers networks. The next step was the aggregation and integration of all ten Therapeutic Guidelines to produce a single comprehensive prescribing resource.

Alternate modes of delivery of the information are now being investigated. For mobile prescribers in institutional settings, the use of handheld computers is being explored. For prescribers in office settings, information embedded in prescribing software is being developed.

Research

Research is an integral part of the organization and the major focus of TGL research is on improving access to the Guidelines at the point of clinical decision making and increasing integration of the Guidelines with other information sources, prescribing modules, and patient databases.

TGL is an industry partner in a major research project, which provides one postdoctoral and two doctoral scholarships to further develop and optimize the production of electronic Therapeutic Guidelines, including the integration of Therapeutic Guidelines with prescribing, dispensing, and medical record management software.

GUIDELINES AVAILABLE

The series includes ten titles in the Therapeutic Guidelines series and one Management Guidelines title:

- Therapeutic Guidelines: Analgesic, Version 4
- Therapeutic Guidelines: Antibiotic, Version 11
- Therapeutic Guidelines: Cardiovascular, Version 3
- Therapeutic Guidelines: Dermatology, Version 1
- Therapeutic Guidelines: Endocrinology, Version 2
- Therapeutic Guidelines: Gastrointestinal, Version 3
- Therapeutic Guidelines: Neurology, Version 2
- Therapeutic Guidelines: Palliative Care, Version 1
- Therapeutic Guidelines: Psychotropic, Version 4
- Therapeutic Guidelines: Respiratory, Version 2
- Management Guidelines: People with Developmental and Intellectual Disabilities

The Guidelines are extensively used in public teaching hospitals, general practice, community pharmacies, government instrumentalities, and medical and pharmacy schools.

ADDITIONAL READINGS

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http://www.tg.com.au.

Therapeutic Interchange

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INTRODUCTION

In the 1980s, hospital pharmacies were important revenue generators for the institution. However, the impact of managed care coupled with reductions in public programs has significantly changed how budgets of pharmacy departments are viewed. Today, pharmacy has moved from being a revenue generator to a cost center for hospitals, and pharmacy expenses have increasingly become the focus of cost reduction strategies. In general, medication costs represent only 4–8% of total hospital expenses. However, this percentage is increasing due to the influx of more costly medications, increased acuity of hospitalized patients, and the increasing number of medications derived from technology.

Since the late 1990s, considerable literature has been published on methods to manage drug expenditures in the hospital setting. The method that is recognized as being the most effective is a well-managed drug formulary system. Institutions with well-managed formulary systems demonstrate significant decreases in medication costs per patient day compared with institutions without these systems.[1] The formulary system, as defined by the "ASHP Statement on the Formulary System," is a method for evaluating and selecting suitable drug products for the formulary of an organized health care setting.[2] Formulary management is a process employing various techniques to monitor the therapeutic, economic, and clinical outcomes of medication use in the organization.

Therapeutic interchange is the cornerstone of an effective formulary system. Therapeutic interchange is defined as the exchange of one therapeutic equivalent therapy for another with the intent of improving patient outcomes.[2] Reductions in medication expenditures resulting from therapeutic interchange programs are realized by the reduction in the number of medications routinely stocked and, in most instances, contractual-based reductions in drug costs. The primary intent of this article is to provide an overview of the therapeutic interchange process.

In this article, the following definitions are used:

- *Drug Formulary System*: An ongoing process whereby a health care organization, through its physicians, pharmacists, and other health care professionals, establishes policies on the use of drug products and therapies, and identifies drug products and therapies that are the most medically appropriate and cost effective to best serve the health interests of a given population.[3]
- *Drug Formulary*: A continually updated list of medications and related information, representing the clinical judgment of physicians, pharmacists, and other experts in the diagnosis and/or treatment of disease and promotion of health.[3]
- *Therapeutic Substitution*: The act of dispensing a therapeutic alternative for the drug product prescribed without prior authorization of the physician. This is a controversial procedure.[3]
- *Therapeutic Interchange*: The authorized exchange of therapeutic alternatives in accordance with previously established and approved written guidelines or protocols within a formulary system.[3]
- *Generic Substitution*: The substitution of drug products that contain the same active ingredients and are chemically identical in strength, concentration, dosage form, and route of administration to the drug product prescribed.[3]
- *Pharmacy and Therapeutics (P&T) Committee*: An advisory committee that is responsible for developing, managing, updating, and administering the drug formulary system.[3] This committee should be composed of a variety of health care providers such as physicians, pharmacists, nurses, microbiologists, administrators, discharge planning, quality assurance, and risk managers.

HISTORY OF THE FORMULARY SYSTEM

In the United States, most health care systems establish formularies based on the recommendations of the

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Pharmacy and Therapeutics (P&T) Committee. The first guidelines describing a formulary system were published jointly in the early 1930s by the *Journal of the American Medical Association* and the *Journal of the American Pharmaceutical Association*.[4] In 1965, the Joint Commission on Accreditation of Hospitals (JCAHO) mandated that hospitals develop formularies.[5] In 1959, efforts by the American Society of Hospital Pharmacists (ASHP) and the American Hospital Association (AHA) were directed at providing a description of the role of the P&T Committee. Based on the recommendations of the two organizations, the P&T Committee was established as the major committee within the health care organization for determining which medications should be routinely used in the hospital. Data from the American Medical Association (AMA) suggest that 90% of hospitals have some type of formulary.[6] Historically, P&T Committees have determined which medications were selected to the formulary based on the safety, efficacy, and acquisition cost of the medications.

The function of the P&T Committee has evolved secondary to greater pressures caused by managed care, costly medications, and expedited Food and Drug Administration (FDA) review processes. Modern P&T Committees must consider the cost of therapy instead of simplistically evaluating solely the acquisition cost of the medication when deciding formulary status. Until recently, cost effectiveness information was not a routine component of data submitted to the FDA during the drug approval process. In addition, shorter FDA evaluations of new drugs mandate that hospitals, through P&T Committees, constantly review information regarding clinical outcomes, medication errors, and adverse drug effects long after the medication has been approved for use.

THERAPEUTIC INTERCHANGE PROCESS

The term *therapeutic interchange* is often used interchangeably with *therapeutic substitution*. There are important differences between the two methods of formulary management; therefore, the terms should not be used in this manner. Based on the list of definitions previously presented, the major difference between these methods of formulary management is whether the prescribing physician has given approval of the interchange of one medication for another or received notification that the interchange occurred. In an effective therapeutic interchange system, physicians are informed before the alternative medication is dispensed and administered. A great deal of controversy surrounds therapeutic interchange and substitution in the outpatient setting. The Public Advocate for the City of New York contended that the use of formularies and therapeutic interchange in ambulatory care settings resulted in inappropriate, or less appropriate, drug therapy.[7] Furthermore, this inappropriateness in drug therapy occurs in great part because financial considerations—much more than clinical considerations—drive formulary decisions in managed care organizations.[7] In a published comparison evaluating the utilization of ambulatory services for patients in a health maintenance organization (HMO), the use of formularies and therapeutic interchange was found to increase the utilization of health care resources.[8] Proponents of formularies and therapeutic interchange in the outpatient settings argue that these criticisms are unfounded. The Academy of Managed Care Pharmacy (AMCP) states that a well-developed and maintained medication formulary decreases patients costs and improves patient care.[9]

In the inpatient setting, therapeutic interchange has been accepted by a number of medical and pharmacy organizations. These organizations include the AMA American Society of Health-Systems Pharmacists, and the American College of Physicians.[2] These organizations support therapeutic interchange within the established guidelines of a formulary system to meet the therapeutic and institutional goals for the ultimate benefit of patient care.

In general, there are three mechanisms by which therapeutic interchange can occur.[10] The first mechanism consists of a system whereby pharmacists independently substitute medications on the basis of their

Table 1 Therapeutic interchanges at SJHA

Low molecular weight heparins
Extended spectrum penicillins
First-generation cephalosporins
Second-generation cephalosporins
Third-generation cephalosporins
Proton pump inhibitors
H^2 blockers
5HT3 inhibitors
Fluroquinolones
Oxazolidinones/streptagramins
Parenteral amino acids
Sedative hypnotics
Enteral feedings
Insulins
IV immunoglobulins
Narcotic analgesics
Multivitamins

own professional judgment, without the consent of the prescribing physician. This mechanism is highly discouraged by the majority of professional organizations and is considered illegal in several states. The second mechanism is the most commonly accepted. In this mechanism, medications are automatically interchanged with prior physician approval based on established institutional protocols. These protocols are established through the hospital's P&T Committee or through HMO policies. In most instances, this mechanism relies on the institution's computer system to activate the therapeutic interchange. The last mechanism involves obtaining physician approval prior to each therapeutic interchange. Although effective in some situations, this mechanism can be time consuming for pharmacists, physicians, nurses, and patients.

A survey published in 1992 by the American Society of Health-Systems Pharmacists suggested that only 61% of the hospitals participating in the survey had well-controlled formulary systems.[11] Of these hospitals, 69% had formulary systems based on the concepts of therapeutic interchange. Common medication classes involved in therapeutic interchanges were antimicrobials, antacids, and multivitamins. The medication class of antimicrobials is particularly suitable for therapeutic interchange. Antimicrobials represent a pharmacologic class with multiple therapeutic redundancies.[2] This pharmacologic class represents approximately 10–40% of a typical hospital's drug expenditures.[2]

Saint Joseph's Hospital of Atlanta (SJHA) is a 348-bed, tertiary care, nonprofit hospital that specializes in interventional cardiology, oncology, cardiac surgery, vascular surgery, orthopedics, and neurology. The hospital currently has a drug budget of approximately $10 million. Therapeutic interchange has been used extensively to manage the pharmacy drug budget. It is estimated that a well-managed formulary system based on therapeutic interchange avoids $800,000 to $1 million annually based on medication acquisition costs. Table 1 contains a listing of therapeutic interchanges by medication class.

One of the most recent medication classes reviewed for potential therapeutic interchange was the fluroquinolone antibiotics. A listing of the procedures involved in the process is provided in Table 2. This listing should serve as a guide for implementing a therapeutic interchange. Other guidelines have also been published.[12,13]

Table 2 Guidelines for implementing a therapeutic interchange program

Step 1: Identify the feasibility of a therapeutic interchange based on medication class usage trends, patient outcomes, clinical trial data, medication error trends/potential, adverse reaction information, cost benefits, or resistance patterns.

Step 2: Determine the purpose of the therapeutic interchange. If after determining that two agents are therapeutically equivalent, cost savings can become an important factor of the therapeutic interchange.

Step 3: Obtain support for the therapeutic interchange from the P&T Committee, Antibiotic Subcommittee, and any medical staff sections that would be involved in the therapeutic interchange.

Step 4: Communicate the proposed therapeutic interchange to members of the medical and hospital staffs. In general, input should be obtained from members of the laboratory, nursing staff, administration, risk management, key physician groups, and quality improvement staffs.

Step 5: Once approved, advertise the therapeutic interchange to the medical, nursing, administrative, and pharmacy staffs. Communication can be in the form of medical staff newsletters, pharmacy newsletters, mailings, inservices, and posters.

Step 6: Implement the interchange. Physicians are generally more accepting of therapeutic interchange programs if they know that nonformulary medications can be obtained if indicated. At SJHA, a nonformulary medication will not be interchanged if "brand necessary" or "do not substitute" is designated by the physician on the medication order.

Step 7: Monitor the program for positive or negative impacts. This is perhaps the most important aspect of developing a therapeutic interchange program. Feedback regarding the program should be continuously obtained from members of the medical, nursing, discharge planning, and laboratory staffs and, in some instances, from patients. Be prepared to modify the program, if necessary.

CONCLUSION

When used appropriately, therapeutic interchange has proven to be an extremely effective method of medication cost management. An active and well-organized P&T Committee is essential to the success of any therapeutic interchange program. As the focus on the costs involved with medication therapy in health care organizations increases, P&T Committees will have to become even more creative in methods used to promote, evaluate, and monitor the effects of therapeutic interchange. The evaluation of quality of life issues, pharmacoeconomics,

clinical outcomes, and humanistic/behavioral outcomes will become increasingly important.[51]

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Therapeutic Interchange, Guidelines (ACCP)

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INTRODUCTION

Therapeutic interchange involves the dispensing of chemically different drugs that are considered to be therapeutically equivalent. Therapeutically equivalent drugs are chemically dissimilar but produce essentially the same therapeutic outcome and have similar toxicity profiles. Usually these drugs are within the same pharmacologic class. They frequently differ in chemistry, mechanism of action, and pharmacokinetic properties, and may possess different adverse reaction, toxicity, and drug interaction profiles.

Interest in therapeutic interchange has risen as a result of two primary influences: rapid expansion in numbers of drugs within the same therapeutic class, and the need to contain medication and health care costs while maintaining rational drug therapy. Therapeutic interchange policies grant pharmacists the authority to interchange one drug for another without prior consent from a physician, according to procedures outlined in a specific policy.

The policies are usually developed and guided by an advisory group such as the Pharmacy and Therapeutics Committee. This committee is composed of physicians, pharmacists, and other health professionals who combine their expertise, knowledge, and experience to recommend policies to the medical staff and administration of an organization on matters related to the therapeutic use of drugs. Among other duties, the committee 1) serves in an advisory capacity to the medical staff and administration in all matters pertaining to the use of drugs, including therapeutic interchange; 2) establishes programs and procedures that help ensure cost-effective drug therapy; 3) establishes or plans suitable educational programs for the professional staff on matters related to drug use; 4) participates in quality assurance activities; and 5) initiates or directs drug use evaluation programs and reviews their results.[1–7] Thus, a successful therapeutic interchange policy is directly related to the effectiveness of the Pharmacy and Therapeutics Committee in performing its functions.

The concept of therapeutic interchange has aroused much controversy and debate. Several definitions or interpretations exist, which have fueled this debate and resulted in considerable confusion.

Concerns associated with responsibility, liability, communication, and monitoring influence an organization's statement on therapeutic interchange. This publication presents the American College of Clinical Pharmacy's (ACCP's) definition of and position on therapeutic interchange. It also reviews and discusses current views on therapeutic interchange held by the American College of Physicians (ACP), the American Medical Association (AMA), the American Society of Hospital Pharmacists (ASHP), the American Pharmaceutical Association (APhA), the American Association of Colleges of Pharmacy (AACP), the Generic Pharmaceutical Industry Association (GPIA), and the Pharmaceutical Manufacturers Association (PMA).

OTHER ORGANIZATIONS' VIEWS ON THERAPEUTIC INTERCHANGE

Organizations representing the medical, pharmacy, and drug manufacturing communities have position statements or policies regarding therapeutic interchange. These statements differ in their definitions and support of the concept. For example, the ACP published a position paper in which therapeutic interchange in institutional and ambulatory settings is supported when a functioning Pharmacy and Therapeutics Committee and formulary system are in place.[8] In addition, the ACP recommends that "immediate prior consent" be obtained from the authorized prescriber with "appropriate documentation of the substitution in a timely and proper manner." Although this document supports therapeutic interchange, the requirement of "immediate prior consent from the authorized prescriber" may defeat the purpose. If a pharmacist is required to call the physician to gain per-

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mission to interchange medications, the physician can either give or withhold permission, or provide a new prescription order (verbal order). This new prescription order can override the therapeutic interchange policy and therefore negate its effectiveness.

Although it has not published a position statement or paper on the topic, the AMA does not support the use of therapeutic interchange in any setting. Their position is evident when reviewing policies 23.023, 23.033, 23.035, 23.057, and 23.060 from their current Policy Compendium.[9] These policies state firm opposition to the interchange of "(1) ... a drug product that is administered in the same route and which contains the same pharmaceutical moiety and strength, but which differs in the salt or dosage form; and (2) ... a drug product containing a different pharmaceutical moiety but which is of the same therapeutic and/or pharmacological class." At their June 1990 annual meeting, the AMA House of Delegates debated and adopted Resolution 161, which states opposition to the establishment of a system at the federal or state level for therapeutic interchange. The resolution states that this "will inevitably interfere with the ability of the patient's physician to assure that the medication prescribed is dispensed to the patient," and thus individuality of patient care can be lost.

Of note is the difference between therapeutic interchange policies endorsed by individual health care organizations, and regulations required by federal or state laws. Federal or state regulations could be misinterpreted as being blanket policies that grant pharmacists authority to interchange medications across all classes and categories. Such regulations might also inappropriately suggest that pharmacists be given the authority to override a physician's prescription without their knowledge.

Therapeutic interchange policies should not grant prescribing authority to pharmacists. Patients can be assured of getting the best care possible only when a pharmacist acts in collaboration with a physician to provide an optimal drug product.

Thus, both parties must endorse therapeutic interchange policies before such policies can be used effectively. Some states have enacted or proposed legislation that requires physicians to be involved in the development and management of therapeutic interchange guidelines, whereas other states have proposed legislation that seeks to prohibit pharmacists from enacting a unilateral interchange. The proposed or enacted legislation agrees with ACCP's definition in that physician involvement is paramount to the successful development of guidelines for therapeutic interchange, and pharmacists should not make unilateral substitution of a drug.

The ASHP supports "therapeutic interchange by pharmacists when a pharmacist and a physician interrelate on behalf of the patient."[10] They define therapeutic interchange as "the interchange of various therapeutically equivalent drug products by pharmacists under arrangements between pharmacists and authorized prescribers who have previously established and jointly agreed upon conditions for interchanges."[11] They believe that an advisory committee should develop these policies, that the policies should be reviewed and revised over time, and that prescribers should have the prerogative to override therapeutic interchange on behalf of patients. In addition, ASHP recommends that pharmacists enacting therapeutic interchange monitor affected patients to "identify and prevent any unexpected or untoward patient response."[11] Similarly, physicians should be notified when a therapeutic interchange policy has been enacted and be provided with educational materials supporting it when appropriate.

The APhA House of Delegates and the AACP support "the concept of therapeutic interchange of various drug products by pharmacists under arrangements in which pharmacists and authorized prescribers interrelate on behalf of the care of patients."[12,13] The AACP further "views initiatives to prohibit therapeutic interchange to be counterproductive and confusing because this criticism strikes at an important element of the clinical practice of pharmacy."[13] They believe that pharmacy students are adequately trained to participate in the clinical environment, and to assist in the development and process of therapeutic interchange. To this end, AACP is committed to training pharmacists who are competent to perform these activities.

The GPIA "supports the practice of therapeutic interchange in institutional or ambulatory settings where a functioning P and T committee and a formulary system are in place and where there is active consultation on behalf of the patient between physicians and pharmacists."[14] The GPIA also "supports an ongoing drug utilization evaluation process for regular review of therapeutic interchange policies and formularies, and for providing information and education to prescribers."[14]

The PMA (representing pharmaceutical manufacturers marketing brand name drugs) opposes therapeutic interchange. Its policy statement concerning drug selection states that it "supports those public policies which retain the authority and responsibility for prescription drug selection exclusively with the individual attending physician, dentist or podiatrist.... Specifically, PMA believes that inappropriate drug selection policies such as pharmaceutical or therapeutic substitution: (1) may adversely affect a patient's health, (2) raises serious legal questions, (3) may result in increased cost for medical services and (4) are highly inefficient and intrusive."[15] The policy states, however, that it "is not intended to address

the manner in which hospital pharmacy practices are implemented in an inpatient care situation. Direct physician involvement in determining the hospital formulary distinguishes such formulary practices from therapeutic and pharmaceutical substitution. Additionally, it is clear that the inpatient care environment is a highly controlled setting where patients are constantly being monitored and, consequently, is much different than the outpatient care situation."[15]

The view of many research-based pharmaceutical manufacturers is based on the economic impact therapeutic interchange may have on their organizations. Although this is an important consideration for their welfare, we believe that the manufacturers should join physicians and pharmacists in the quest to provide excellent medical care at reasonable costs, especially in light of the federal, state, and local regulations directed at achieving this goal. Such a commitment would foster a better relationship among the represented communities.

The ACCP believes that if physicians and pharmacists communicate, collaborate, and jointly agree on the purpose for and appropriate monitoring of therapeutic interchange policies, many of the opposing viewpoints outlined above can be brought together in an effort to provide state-of-the-art therapeutics and optimal patient outcomes.

ACCP GUIDELINES FOR THERAPEUTIC INTERCHANGE

The ACCP supports therapeutic interchange policies when pharmacists and physicians collaborate to develop policies designed to provide patients with the best possible care at the best overall price. These policies should result from a synergistic combination of the expertise and knowledge of pharmacists and physicians whose common goal is to ensure optimum patient care. They should not be interpreted as "bestowing prescribing authority on pharmacists." Although the policies may vary in complexity, most involve the interchange of one drug for another that is therapeutically equivalent. Thus, they should not be viewed as or become blanket policies allowing pharmacists to choose an alternative agent from an entire class or category of drugs.

The ACCP supports the following guidelines for implementing therapeutic interchange policies within health care organizations.

Guideline I

Therapeutic interchange is appropriate in institutional and ambulatory settings that have a functioning formulary system and Pharmacy and Therapeutics Committee or equivalent advisory committee.

Rationale

The success of any therapeutic interchange program is related to the effectiveness of the Pharmacy and Therapeutics Committee or its equivalent body, and the drug formulary system. This committee, representing both the pharmacy and medical staffs, must develop, implement, review, and change policies and procedures to ensure optimum patient care while containing costs. Similarly, it should recommend and assist in educating professional staff regarding current therapeutic interchange policies, the success of such policies, and any approved exceptions to them.

The Pharmacy and Therapeutics Committee should establish or assign a committee or department to monitor the effectiveness of the interchange policies. Audits or reviews should be conducted according to set policies. Criteria should be developed and used to determine when and why the therapeutic interchange policies may be ineffective (see Guideline II). The issues identified should be addressed and the professional staff notified of resulting changes to policies and procedures.

The specific types of institutional or ambulatory settings for which therapeutic interchange policies are most likely to be effective are those that have drug formularies with a functioning Pharmacy and Therapeutics Committee or its equivalent. This may include, but is not limited to, hospice settings, health maintenance organizations, community hospitals, university teaching hospitals, and ambulatory clinics affiliated with a hospital. If the policies dictate that laboratory or medical record data should be readily available to pharmacists prior to dispensing a therapeutic alternative, the setting must provide access to this information. Regardless of the setting, pharmacists and physicians must have a good working relationship and a mutual goal to provide excellent medical care while containing costs appropriately.

Guideline II

A continuous drug use evaluation process must be in place for regular review of endorsed therapeutic interchange policies and procedures.

Rationale

Drug use evaluation (DUE) reviews the types of medications prescribed within an institution. This process could identify prescription orders to which therapeutic

interchange policies apply. Once these orders are identified, the success of the policies could be further evaluated, reviewed, and reported. For example, one would have to identify whether an approved alternative agent was dispensed in place of the one originally prescribed. The DUE could also determine if appropriate patient monitoring occurred following the interchange, and whether the interchange resulted in an altered response. Results of these evaluations should be presented to the Pharmacy and Therapeutics Committee or its equivalent to determine if changes or exceptions to existing policies are indicated, or if additional educational endeavors should be made available to participating professional staff.

Guideline III

Therapeutic interchange, as defined herein, may be executed by pharmacists if the authorized prescriber is notified either verbally or in writing within a reasonable time frame, and if the pharmacists have access to medical records and appropriate laboratory or other test results as required by the therapeutic interchange policy. Exceptions to this procedure must be stated clearly in the policy.

Rationale

Therapeutic interchange policies and procedures should describe in detail the conditions and processes for interchanging medications. These should include who has authority to enact the interchange, special exceptions to a policy or procedure, criteria to be evaluated before and after the interchange occurs, and the definition of "a reasonable time frame" for notifying the physician. For example, the policy may not require that a physician be notified for interchange of certain drugs, such as multivitamins. As another example, a reasonable time frame for notification of the physician when therapeutic interchange has occurred may be defined as within 24–72 hours when the interchange involves antibiotics.

Guideline IV

The Pharmacy and Therapeutics Committee or its equivalent should ensure that professional staff are educated regarding the rationale, policies, and procedures for therapeutic interchange.

Rationale

Proper educational methods should be developed, implemented, reviewed, and revised as necessary to inform the professional staff regarding the rationale, procedures, and monitoring criteria for therapeutic interchange. These methods may include, but should not be limited to, newsletters, fliers, departmental meetings, meeting minutes, and publication of therapeutic interchange policies, such as in an organization's formulary. Physicians should be informed of the policies prospectively, and a list of active policies should be readily available to the professional staff. Concerns or problems regarding the policies should be addressed to the Pharmacy and Therapeutics Committee.

Guideline V

The therapeutic interchange policies should define a mechanism that enables authorized prescribers to disallow therapeutic interchange.

Rationale

Therapeutic interchange may not be applicable to all patients. For example, a patient's preference may play a role in a physician's decision to override a policy. An acceptable method of overriding must be made available to authorized prescribers. Ideally, it would allow one to capture information regarding decisions to override policy so that the data can be reviewed easily by an advisory committee. This could, for example, be accomplished by asking the physician to complete a brief survey or request form for disallowing therapeutic interchange. The physician would have to notify the pharmacist either in writing or verbally regarding the desire to override the existing policy.

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PROFESSIONAL DEVELOPMENT

Transplantation Pharmacy Practice

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INTRODUCTION

Transplantation of human tissues is one of the most important medical achievements of the 20th century. Transplantation began in 1902, with work of vascular surgeon Alexis Carrel, who established many of the vascular anastomosis techniques that led to effective transplantation. A century later, transplantation has become a life-saving procedure for a variety of irreversible acute and chronic diseases for which no other therapy is available. Nearly every thoracic and abdominal organ may now be successfully transplanted. In 1999, a total of 21,516 solid organ transplants were performed at centers throughout the United States, of which 16,802 were cadaveric and 4,714 were from a living donor.[1]

Increased experience and advances in surgical techniques, tissue preservation and posttransplant care have helped to improve the overall success of transplantation. In 1988, the 1-year graft survival of renal transplants using cadaver grafts was 76%, but by 1999, the 1-year cadaver graft survival rose to 89%. Results of living donors also improved from 89% to 94% for the same time period. Improvement in survival have also been achieved for other solid organ transplants with approximately 70% to 80% of grafts functioning at 1-year after transplantation.[1]

The success of any organ transplantation is due largely to control of the immune system by immunosuppressive therapy to avert rejection of the allograft. Immunosuppressive treatment strives to prevent allorecognition and subsequent destruction of the transplanted tissues. As a result, transplant recipients rely on lifelong immunosuppressive drug therapy for preventing rejection and maintaining their graft. Pharmacists, as experts on immunosuppressive drugs have a vital role in optimizing pharmacological therapy to enhance transplant outcomes and minimize drug-related complications.

OPPORTUNITIES

Since the mid 1990s, the Food and Drug Administration (FDA) has approved various potent immunosuppressive drugs for use in transplantation. Currently, there are four major classes of immunosuppressive drugs available: corticosteroids, antilymphocyte, antimetabolites, and calcineurin inhibitors (Table 1). These immunosuppressants are known to cause short-and long-term complications, including infections, cardiovascular disease, and malignancy (Table 2).[2–6] In addition, solid organ transplant recipients may have their care further complicated by preoperative conditions. The majority of patients have chronic end-stage illnesses that are inevitably fatal and necessitate their transplant. As a result, post transplantation most patients are on complex prophylactic and therapeutic multidrug regimens, leading to many drug-related complications that may compromise transplant outcomes and significantly increase the cost of transplantation.

From its inception, organ transplantation has been approached in an extraordinarily multidisciplinary manner. The transplant team has historically included surgeons, immunologists, pathologists, internists, nurses, dietitians, social workers, and spiritual representatives. With continued success of transplantation and the immunsuppression-related complications, opportunities have been created for many of the pharmacists that are now members of various transplant teams throughout the United States. As part of the team, transplant pharmacists provide direct patient care in a variety of settings, especially because they have the understanding of transplant immunology and the immunosuppressants used to preserve the graft.

Appropriately trained transplant pharmacotherapy specialists may practice in traditional clinical roles or they may fill positions outside the usual sphere of pharmacy practice. Many positions include a clinical

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Table 1 Immunosuppressive drugs

Antimetabolites	Azathioprine, mycophenolate mofetil, sirolimus
Calcineurin inhibitors	Cyclosporine, tacrolimus
Corticosteroids	Methylprednisolone, prednisolone
Monoclonal antibodies	Muromonab-CD3, basiliximab, daclizumab
Polyclonal antibodies	Antilymphocyte gamma globulin—horse Antilymphocyte gamma globulin—rabbit

practice site in addition to teaching and research opportunities.[7] These individuals may provide inpatient or ambulatory patient services. The ideal role would involve both of these areas and, in so doing, ensure continuity of care. Although the need to guarantee appropriate follow-up of treatment plans and monitoring is not unique to the field of transplantation, the vast number of specialists and subspecialists involved in the care of an organ transplant recipient provides the pharmacist with many opportunities to facilitate communications between members of the transplant and nontransplant teams. Having pharmacists coordinate the patient's pharmacotherapeutic plan when the patient is hospitalized and following discharge would increase the consistency in treatment. This would have the obvious benefit of improving patients' quality of life while reducing the cost of medical resources. The pharmacists' focus adjusts as the patients' clinical issues shift from postoperative concerns immediately following the transplant procedure to more chronic medical matters.

With the expansion of investigational immunosuppressants and clinical drug trials, many pharmaceutical drug companies working in the area of transplantation have created nontraditional roles for transplant pharmacists. Pharmacists can use their skills as researchers (clinical or basic science), educators, or medical information liaisons to assist transplant centers to achieve their ultimate goal of superior patient care.

Table 2 Possible complications of immunosuppressive drugs

Bone disease	Osteoporosis
Cardiovascular	Hyperlipidemia, hypertension
Cosmetic	Acne, sun sensitivity, hirsutism, weight gain
Gastrointestinal	Peptic ulcer disease, diarrhea, nausea, vomiting
Infections	Bacterial, fungal, viral
Hematologic	Leukopenia, thrombocytopenia
Malignancies	Solid tumors, post-transplant lymphoproliferative disorders
Metabolic	Diabetes mellitus
Neurological	Headache, tremor, neuralgia
Ophthalmological	Cataracts, glaucoma
Psychological	Depression, mood changes
Renal	Acute or chronic dysfunction

The cost of transplant medications accounts for approximately 25% of the total cost of care in the first year after transplantation and up to 90% in subsequent years.[8] The absolute dollar amount of immunosuppressants and adjunct therapy is also very high. The average wholesale price of one immunosuppressive agent may range between $6,000 to $12,000 per patient per year. In most situations, long-term immunosuppression consists of double- or triple-combination therapy. Furthermore, in the period immediately following transplantation, many centers use induction therapy that involves expensive agents such as monoclonal or polyclonal antibody preparations.[9,10] With the introduction of more induction therapies and other expensive immunosuppressive agents, the potential for cost savings by increasing participation of clinical pharmacists is undoubtedly considerable and will continue to increase. Some literature has demonstrated this in solid organ transplant patients, but more rigorous studies will be needed before this concept is widely accepted.[11]

CLINICAL PRACTICE

The clinical role of the transplant pharmacist is variable, depending on the practice of the transplant center. Although each clinician may be unique in his or her position, all share the common goals and objectives of improving patient care. Inpatient responsibilities may include daily participation in medical and/or surgical rounds. The transplant pharmacist offers recommendations to optimize drug regimens for patients, based on their own history of illness. The use of immunosuppression therapy is often considered a balancing act between

Table 3 Drugs that interact with calcineurin inhibitors

Decrease concentrations of CNIs
Carbamazepine, cholestyramine, dexamethasone, isoniazid, nafcillin, octreotide, phenobarbital, phenytoin, primidone, rifampin, sulfadimidine, sulfinpyrazone, ticlopidine
Increase concentrations of CNIs
Clarithromycin, danazol, diltiazem, erythromycin, fluconazole, fluvoxamine, grapefruit juice, itraconazole, ketoconazole, methylprednisolone, methyltestosterone, nicardipine, norethisterone, protease inhibitors, verapamil

CNIs, calcineurin inhibitors.

suppression of rejection and immunosuppressive drug toxicities. The fulcrum should always be adjusted to the requirements of the individualized patient. For example, with older transplant recipients in whom the immune response is dampened, it may be more appropriate to select a lower-intensity immunosuppressive regimen to decrease side effects. In contrast, African Americans are considered immunologic high-risk recipients with increased risk for rejection and, therefore, will require more intense immunosuppression to ensure successful therapeutic outcomes.[12,13] Certain patients may be predisposed to abnormalities that are part of their disease or a result of the transplant, and a particular immunosuppressive drug may exacerbate or worsen them. To prevent jeopardizing the allograft or further complications in these patients, it may be necessary to modify the doses of certain immunosuppressants or avoid them entirely.

Once a particular regimen is chosen, pharmacists will frequently perform pharmacokinetic and pharmacodynamic evaluations for immunosppressants, antibiotics, and other agents. Many of the immunosuppressants such as cyclosporine, tacrolimus, and sirolimus have significant intra- and interpatient differences that may lead to suboptimal blood concentrations.[14,15] Therapeutic drug monitoring of immunosuppressive drugs is essential to make accurate predictions for appropriate drug therapy. Furthermore, many of the drugs used in the management of transplant recipients are extensively metabolized by the cytochrome P-450 enzyme system. Drugs, foods, or nutrients that induce, inhibit, or compete for the same isoenzyme could effect blood concentrations of these immunosuppressive agents (Table 3).[16,17] Drug interactions that increase blood concentrations could expose transplant recipients to serious adverse effects, whereas drug interactions that decrease blood concentrations may cause rejection episodes and possible loss of the graft as a result of inadequate immunosuppression. Pharmacists can prospectively review the patient's medication profile including over-the-counter (OTC) medications, herbs, and dietary supplements to predict such interactions and to help reduce adverse outcomes.

PROTOCOLS AND GUIDELINES

It has been suggested that there are as many transplant drug protocols for managing patients as there are transplant centers. This situation has been created by the fact that in the area of transplantation, there is an absence of consensus statements and guidelines in the management of immunosuppressive therapy. This is not to imply that adequate literature addressing transplant issues is lacking, only that it has not reached the standardization and review procedures achieved in other specialties. Guidelines and consensus statements regarding the optimal management of transplant recipients have not been established because there are few circumstances in which the support of one treatment over another is overwhelming. This is probably due to the large sample size required to show statistically significant differences and the variability of patients in regard to demographics, socioeconomics, and other risk factors. Most of the resources currently available to aid in the selection of specific medications are publications from the primary literature. National and international conferences play a significant role in disseminating information concerning advances in therapy and new ideas. Symposia provide another way to learn of contemporary practices, usually in a setting that fosters networking while addressing individual practice issues. They also provide more opportunity to discuss cases with colleagues, draw upon the experience of others, and learn innovative ways that other centers address common problems. This puts a greater onus on the transplant pharmacist to continuously review the current literature, as well as to evaluate it based on its merit and relevance to one's own practice setting and specific population. Again, this provides an opportunity for pharmacist involvement with the transplant team. Evaluation of the literature from transplant and nontransplant sources becomes important. At times, one will need to extrapolate information from nontransplant patients to overcome certain voids of information concerning transplant patients. Of course, experience and clinical training will determine when this extrapolation is appropriate and when it is not. Herein lies part of the attraction of transplant pharmacy; one must possess very specific knowledge on how to manage a unique group of patients, namely organ transplant recipients, while being able to deal with a multitude of medical issues, each of which also requires specialist knowledge.

Table 4 Useful web resources

http://thedrugmonitor.com
http://transweb.org
http://fujisawa.com/medinfo/cont_educ/tran_trnd/
http://transplantation.medscape.com/Home/Topics/transplantation/transplantation.html
http://tpis.upmc.edu/tpis/immuno/compre.htm
http://ntpr.registry@mail.tju.edu
http://stadtlander.com/transplant/
http://mdconsult.com
http://clinicaltrials.gov
http://unos.org

Table 4 outlines various transplant web resources that a pharmacist specializing in transplantation may find useful. Although some of these web sites include information for patients, others are for health care providers working with the transplant recipients.

EDUCATION

Transplant pharmacists are considered unbiased resources for drug information that promotes better patient care. This service may be provided to a variety of individuals and disciplines, such as patients, caregivers, and health care providers, as well as medical residents, new pharmacists, and pharmacy students.

During the first year after transplant surgery, the average drug regimen of a transplant recipient consists of at least 10 different medications with variable time schedules for administration. For many patients, the significant number of medications and their complex schedules can be overwhelming. This creates the potential for errors and drug noncompliance at a time when the patient's condition makes them especially vulnerable to the results of subtherapeutic pharmacologic treatment.

Pharmacists can educate patients on indications for immunosuppressive therapy, appropriate use of drugs, anticipated adverse effects and expected outcomes (Table 5). Drug regimens must be simplified and made relevant to a patient's individual needs. As time passes after transplantation, the risk of graft rejection will decrease. As a consequence, patients have frequent alterations in therapy as their risk for infections and other complications decreases with the reduction of their immunosuppressive therapy. Patients must be kept aware of these changes, and teaching opportunities during each admission and clinic visit should not be missed. Because of the potential for drug interactions with immunosuppressants, pharmacists usually counsel patients not to treat themselves with any of the numerous OTC medications. The pharmacists may also develop a variety of educational tools to enhance patient learning.[18] This could take the form of recording audio instructions for visually impaired diabetic patients, creating daily medication logs, and providing written information in language appropriate for patient understanding.

Table 5 Common educational needs transplant pharmacists address with patients

Signs and symptoms of infection
Medication adverse effects
Management of adverse events
Drug–drug and drug–food interactions
Blood glucose control and insulin requirements
Pain management
Over-the-counter medication use
Alternative medicine use
Nutritional requirements
Drug compliance

Patient noncompliance to immunosuppressive therapy is a significant cause of graft failure.[19–22] Some investigators have reported rates ranging from 2% to a high of 43% in pediatric renal transplant recipients.[23] In addition to the complexity of the drug regimen, other factors may lead to drug noncompliance. These include concerns in physical appearance due to the side effects of immunosuppressants, poor provider–patient communication (e.g., dosage change that is not fully explained), depression or anxiety, dissatisfaction with medical care, cost of drugs, and misconceptions that missing doses will not cause rejection.[24,25] Potential health and economic consequences of noncompliance to immunosuppressive therapy include cost of initial and additional prescriptions, physician visits, clinic or emergency department visits, hospitalization, diagnostic costs and additional care such as dialysis in case of renal transplant recipients.[26]

Pharmacists can provide various strategies for maintaining drug compliance. They can help patients to select a reminder or "cue" such as clock times, meal times, or daily rituals or activities to assist with medication administration. Meeting with patients more frequently to assess compliance also reinforces the drug regimen. Intervention programs using support groups and partnerships between the recipient, family, and transplant team have also been shown to be effective strategies to increase compliance.[27] Increased emphasis on patient counseling and education about the drug regimen can lead to improved compliance.

A major role of all pharmacists in hospitals and outpatient clinics encompasses education for medical and nursing staff, as well as other colleagues. Understanding the various immunologic pathways that can be modified is essential to understanding the role of the various immunosuppressive medications and their subsequent effects. Knowledge regarding identification and treatment of complications, such as infections, hypertension, diabetes, hyperlipidemia, osteoporosis, renal insufficiency, depression, and cancer, just to name a few, is crucial when caring for transplant recipients. As these patients live longer and become healthier, new issues arise as they contemplate such possibilities as conceiving children, concepts that would not have been entertained previously. Although at one time management of transplant recipients may have revolved around surgical care

and immunosuppression, it now includes every discipline from internal medicine to obstetrics and gynecology and all the pharmacologic issues that go along with each specialty. Each of the professionals contributing to the care of the patient needs to have some understanding of the transplant pharmacotherapy treatment used. This will undoubtedly affect their differential diagnosis, how they treat the patient, and what kind of problems need to be brought to the attention of the transplant team, who often continues to care long-term for the patient in some manner.[28]

Education may be provided through informal in-service programs about new drugs, new drug indications, and countless other topics. Tailoring these educational programs to each discipline may pose a challenge to the presenter because of the varied background and needs of the many people involved in the care of a transplant patient. For example, educational needs of a surgeon are often different from those of a medical specialist such as a nephrologist or hepatologist or those of a nurse or pharmacist.

Pharmacists may also perform formal presentations at professional meetings and symposia. Drug information can be regularly disseminated in a form of drug monographs, newsletters, and continuing education articles. In addition, many transplant pharmacy specialists have didactic teaching responsibilities, provide clinical rotations for pharmacy students in transplantation, and serve as preceptors.

RESEARCH

The development of newer immunosuppressive drugs has promoted a need for investigating their safety and efficacy to ensure appropriate use. Research on various approved or investigational immunosuppressants continues to be executed at an accelerated rate. Many transplant pharmacists have established precedents for successful drug research practices.[12,29,30] Most work with clinically relevant trials in areas such as drug pharmacokinetics, pharmacodynamics, and patient outcomes. This provides the transplant pharmacist with additional avenues to demonstrate to the team his or her unique suitability at coordinating and conducting such research. As is recognized by the FDA, the role of a person with a doctorate degree in pharmacy can be to serve as primary investigator in collaboration with physicians. This is due to the recognition that pharmacists have the appropriate training and the clinical perspective to participate or manage clinical drug research. Pharmacists may be involved in all aspects of the research project, including protocol development, approval from the institution's Investigational Review Board, budget analysis, patient recruitment, obtaining informed consent, data gathering, data analysis, drawing conclusions, and finally submission for presentations and publication.

Since the infancy of transplantation, the goal of drug therapy has been to create an agent that can promote true immunologic tolerance, defined as graft acceptance without immunosuppression. As a result, the National Institutes of Health, various pharmaceutical companies, and many independent scientists have all taken this into developments to foster investigation into strategies that might help to discover such a compound. Some pharmacists are currently performing such translational research in the hope of eventually crossing paths with clinical practice.

Emphasizing cost containment while achieving rational pharmacotherapy has become an important feature of many formulary decisions. A transplant pharmacist may also develop pharmacoeconomic studies that examine the financial impact associated with different immunosuppressive regimens. Such analysis extends beyond comparison of the acquisition costs of the individualized immunosuppressive agent. Other charges, such as the costs of organ procurement, room and board, laboratory tests, operating room, nuclear medicine, and physician and surgeon professional fees, must also be included because they may substantially add to the total cost of transplantation. Feasibly, a more expensive immunosuppressant agent or regimen may prove to be more cost effective than cheaper agents if graft survival is increased or the incidence of morbidity is decreased.[31] A panel of investigators drawn from major transplant centers and representatives of the pharmaceutical industry drafted standards for economic and quality-of-life studies. This panel recommended specific guidelines for the design and conduct of trials for economic analysis of transplantation. These recommendations serve as a template for better design of pharmacoeconomic trials to evaluate the cost effectiveness of transplantation in the future.

The field of transplantation, therefore, is fertile ground for numerous pharmacist-driven research projects of significant clinical and experimental relevance. The results of such research can serve to guide protocol decisions to improve patient outcomes and, ultimately, improve patient's quality of life.

INDUSTRY PRACTICE

Although the available number of transplant-related industry practice positions is relatively small, some

pharmaceutical companies offer medical or scientific liaison positions well suited to pharmacists with prior transplant experience. These positions require the individual to interact with physicians, nurse coordinators, and other pharmacists regarding issues of research and education. Coordination of multicenter studies and facilitating communication among centers through symposia, continuing education programs, and advisory boards are especially vital in the transplant discipline. Many transplant practitioners rely heavily on these sources for up-to-date clinical information. Advances in transplantation pharmacotherapy are happening with increasing frequency each year to the point where there is no standard of practice. Much reliance is placed on "experts in the field," often identified by industry professionals who travel between centers.

CONCLUSION

Pharmacists working with transplant patients are continuing to define their practice model to meet the pharmaceutical and primary care needs of all transplant patients throughout the spectrum of care. The role for transplant pharmacists will continue to expand as the field of organ transplantation becomes a viable option for more patients. In a relatively short period of time, for example, kidney transplantation has gone from being an experimental procedure in the 1950s to being a cost-effective treatment for end-stage renal failure. The type of practice one chooses does not need to be limited to any one of the possibilities listed here. A transplant pharmacist position can involve different combinations of these responsibilities and others, as necessary, tailored to the preferences of the practitioner and the needs of the center. As transplantation of other organs becomes more attractive, the need for qualified pharmacists as part of the transplant team will continue to increase. The field of transplantation provides numerous opportunities for pharmacists, many of which can still be individualized to suit the strengths and preferences of the practitioner. Of all the reasons that demonstrate the need for transplant pharmacists, none is as convincing as the needs of the patient. The patient's needs define what roles are available to pharmacists and how valuable those services are to the transplant community and society in general.

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Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans

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INTRODUCTION

The Tri-Council Policy Statement is a Canadian document that has been adopted, in 1998, as the standard of ethical conduct in Canada when performing research involving human subjects. It reflects the desire to promote research conducted according to the highest ethical standards. The Policy was developed by three groups: the Medical Research Council of Canada, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada in an effort to aid and support research in Canada. The three councils are aware that issues regarding ethical conduct are complex and continually evolving and therefore intend to update this document regularly.

GOALS AND RATIONALE

The Policy attempts to address the responsibilities of researchers, institutions, and Research Ethics Boards (REBs) to their subjects. Ethical principles are shared across disciplines such that subjects should expect equal rights as well as benefits and risks across all fields. The Policy provides a framework of common procedures by which the ethics review process may be standardized. The Policy continues to recognize the diversity of various fields, but promotes the sharing of general ethical principles. Thus, this document can lend itself to many areas. The Policy is not intended to address specific ethical dilemmas but to provide guiding principles and standards as well as promote thought regarding areas of controversy.

The Policy describes ethics as using morally acceptable means to attain morally acceptable ends. Guiding principles are found in Table 1. It is critical that the subjects' interests are primary when conducting research, and that it is understood that benefit and harm are not viewed by the subject in the same manner as the researcher. Trust by the subject or hope for cure places further emphasis on the need for accuracy and full objective disclosure regarding the proposed research. It is important that the researcher maintain the right to pursue knowledge freely but with responsibility. This means ensuring the highest scientific and ethical standards including honesty and accountability. The law regulates research standards with respect to areas such as privacy, equality, property, and competence. With the continuing advances in knowledge, technology, and areas of controversy, ethics will likely play a role in defining the law in the future.

The Policy acknowledges that principles and guidelines require flexibility and exceptions to the rule. There can be many approaches to an ethical problem and debate regarding the answers will likely always occur. This will ensure continued thought and evolution in applying ethical principles to research with humans.

This summary of the Policy is divided into ten sections similar to the original document: ethics review; free and informed consent; privacy and confidentiality; conflict of interest; inclusion/exclusion of populations; aboriginal peoples; clinical trials; human genetics research; research involving human gametes, embryos, or fetuses; and human tissue.

ETHICS REVIEW

Research requiring ethics review is that which includes living human subjects as well as human remains, cadavers, tissues, biological fluids, embryos, or fetuses. The REB is mandated by its institution to approve, reject, modify, or terminate submitted research proposals to be conducted within the institution or by its members. The REB is to have five members: two with knowledge in research, one in ethics, one in law (specifically biomedical research), and one without affiliation to the institution who is from the community.

The exposure of a subject to minimal risk is thought to be equivalent to that encountered in everyday life. Greater

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Table 1 Guiding principles for ethics

- Respect for human dignity
- Respect for free and informed consent
- Respect for vulnerable persons
- Respect for privacy and confidentiality
- Respect for justice and inclusiveness
- Balancing harms and benefits
- Minimizing harm
- Maximizing benefits

risk requires increased scrutiny of the project. Risk must also be considered in terms of interventions the patient would have been exposed to outside of the clinical trial setting. Risks can be categorized as therapeutic or not, the latter requiring recognition and consideration by the REB. The REB must ascertain that any protocol that poses more than minimal risk to the subject is properly designed to answer the research question. Compensation considered greater than that usually available to people is also worth higher scrutiny to ensure undue incentive is not offered.

Ethics Review Procedures

The proportionate approach to review is taken, which is geared toward the principle that the greater the invasiveness or potential risk, the greater the care that should be taken to review the proposal. Three levels of review are recommended: 1) full REB review, 2) expedited review for projects of minimal risk, annual renewals, chart reviews, or projects where REB conditions have been met, and 3) departmental review. The scope of research that requires REB review is found in Table 2.

Regular meetings are essential for full REB reviews with records of minutes documenting all decisions and dissents with explanations. Decisions must be made impartially. If desired, an investigator may participate in the discussion with an opportunity to reply to comments but cannot be present for the decision process. Protocols may be resubmitted if rejected. If a decision cannot be reached initially an appeal board may be utilized; however, appeals following REB decisions are not considered.

When a member of the REB has a personal interest in the project he or she cannot be present during the decision-making process, although disclosure of conflict and opportunity to rebut are allowed. All ongoing research must have a follow-up review proportionate to the level of risk. Such review often consists of evaluating the submission at an annual update. Ethics review must be performed by the appropriate REB of all involved institutions or jurisdictions. Ethics review must be performed by the REB of the institution that employs the researcher(s) as well as by any REB with jurisdiction over the location of the research.

FREE AND INFORMED CONSENT

Requirements

Free and informed consent is essential prior to participation as well as throughout a study and is usually documented in writing. The need for consent may be altered or waived when there is minimal risk or low probability that the action will have negative implications for the subject, when the research is not possible without alteration or waiver, or when such action does not involve therapeutic intervention. After participation, additional information should be provided if possible and appropriate, and consent may be obtained following subject debriefing. For subjects not proficient in the language of the consent form, consent may still be obtained provided an objective competent translator has fully informed the subject as to the contents of the consent form and has assisted the subject in participating in discussion of the study.

Consent must be given fully and with the knowledge that it can be withdrawn at any time without consequence. Power and undue influence are of concern particularly in

Table 2 Scope of research that requires REB review

Funding	Available or not
	Internal or external source
Subjects	Recruitment internal or external to institution
	Compensation awarded or not
	Is subject focus of research?
Location	Within Canada or not
	Inside or outside institution
	In person or from a distance (e.g., by mail)
Researchers	Staff or students
Data collection	Direct from subjects or indirect (e.g., chart review)
Publication	Planned or not
Study design	Observational, experimental, correlational, or descriptive
	Pilot study or full project
Purpose	For basic or applied knowledge
	For teaching or for acquisition of knowledge
Competition	Is a similar project approved elsewhere?

restricted or dependent subjects and under such circumstances must be judged in context.

REB review is generally necessary for studies of naturalistic observation. However, studies observing participants in rallies, demonstrations, or meetings, for example, do not require REB approval, although issues of privacy must be considered.

Informing Potential Subjects

Consent may not be obtained without full disclosure of all information that may affect consent and an opportunity for discussion. Obtaining consent includes:

- Invitation.
- Indication of the research purpose.
- Identity of the investigator(s).
- Nature of the study and time commitment.
- Procedures.
- Foreseeable harms and benefits.
- Alternatives to the research or consequences of nonparticipation.
- Assurance that one is free to not participate or may decide at a later time or date.

The likelihood of publication of the findings and any conflicts of interest by the investigators, institution, or sponsors must be indicated. Other information may be necessary to include for select projects, such as subject responsibilities, confidentiality as to subject identity, and anticipated use of the data.

Competence

Competence refers to a prospective subject's ability to understand the information provided and its consequences, and make a free and informed decision in accordance with personal values. If a subject is not considered competent, a balance must be sought as to the subject's vulnerability versus the injustice of exclusion from potentially beneficial research. There is a moral preference to use competent subjects. Subjects not legally competent should only be asked to participate when the research question can only be addressed using the identified group, and the risk is minimal when there are no direct benefits. The researcher must also demonstrate how the subject's best interests are protected and the method of obtaining free and informed consent from an objective third party. If the subject should become competent during the study, consent must be obtained for continued participation. Of note, some subjects even if not legally competent may be able to express their wishes in a meaningful way, e.g., children, patients with Alzheimer's disease. Their dissent precludes participation.

Research in Emergency Health Situations

Research that is to be performed on an individual without his or her consent is subject to all legislation and regulations as pertinent, and may be allowed by the REB if:

- A serious threat exists requiring immediate intervention and research offers a possibility of benefit when no standard therapy exists.
- Risk is not greater than with standard care or that benefits justify risk.
- Third party authorization cannot be secured despite diligent efforts.
- No prior directive by the subject is known to exist.

This is an uncommon situation that may occur if a subject has lost consciousness or competence. Additional safeguards to protect the subject's rights and interests may include additional scientific/medical/REB consultation, procedures to identify subjects in advance to obtain consent prior to occurrence of an emergent situation, monitoring procedures by safety boards, and careful REB review for assessment of harms and benefits of participation.

PRIVACY AND CONFIDENTIALITY

The need for privacy when participating in research is based upon a subject's dignity and autonomy and thus warrants respect. As a result, all information regarding a research subject must be kept confidential. The researcher has a duty not to share any information without a subject's free and informed consent. Respect for privacy is an internationally recognized ethical standard and is reflected in Canadian law as a constitutional right. However, there are some circumstances where public health and safety require protection and such privacy may be lost, e.g., child abuse, sexually transmitted diseases. The REB can play an important role in assessing the balance between the need for research versus invasion of privacy, thus protecting individuals from harm as a result of unauthorized use of personal information.

Personal Interviews and Data Collection

REB approval is required for interviews and documentation of personal information by research subjects, and free

and informed consent is necessary. REB approval is not necessary for access to public information or materials. REB approval requires consideration of the purpose and type of data, limits on its use, safeguards for confidentiality, modes of observation that may identify the subject, anticipated secondary uses of the data, and anticipated linkage with other data. Subjects must be informed who will have access to any identifying information, e.g., government or agencies, research sponsors, or the REB, and must provide consent for such access to occur.

Secondary Use of Data

When data are used for purposes other than the research for which they were collected, REB approval must be sought if individuals are identifiable. Researchers must demonstrate that knowledge of the subjects' identities is necessary for the current use, that confidentiality will be maintained and that the involved individuals have not objected. If deemed appropriate, the REB may require either informed consent from those who contributed the data, an appropriate strategy for informing subjects, or consultation with representatives of those who contributed the data. REB approval is also required for situations when a researcher wishes to contact individuals to whom data refers. Linkage of databases where research subjects may be identifiable requires REB approval.

CONFLICT OF INTEREST

With increasing concern for conflicts of interest, such issues must be identified by the researcher, institution, and REB for professionalism, to maintain public trust, and for accountability. All conflicts, whether actual, perceived, or potential, must be disclosed to the REB and addressed. They must also be disclosed to the subject during consent. For the REB to identify and best address conflicts, it should be provided with details of the research project, budgets, commercial interests, consultative relationships, and other information as relevant. REB members must withdraw from the discussion and decision-making when their own research is under review. Methods to address and resolve conflicts must be developed. REBs must be given the authority and financial and administrative independence from the institution to fulfill their duties.

INCLUSION/EXCLUSION OF POPULATIONS

Choice of inclusion into research studies should follow the principle of distributive justice, i.e., no member in society should bear an unfair share, nor be unfairly excluded in research participation. Vulnerable subjects have been excluded to avoid the issue of exploitation yet have thus also been denied the potential benefits of participation. Researchers shall not exclude potential research subjects based on culture, religion, race, mental or physical disability, sexual orientation, ethnicity, gender, or age, unless a valid reason applies. Women must not be excluded on the basis of gender or reproductive capacity although harms and benefits must be considered. Incompetent subjects must not be excluded from research that may be beneficial to themselves or the group they represent.

ABORIGINAL PEOPLES

The aboriginal peoples are recognized as having a unique culture and history and perspective in life. Research regarding their customs and community has in some cases been respectful; however, there has also been inaccurate, insensitive research conducted causing stigmatization and thus apprehension with respect to future research proposals. Thought must be given to language differences and different ideas about public and private life. Involvement of academic or community members from this group is essential for appropriate ethics review. The needs and concerns of the people along with respect for their property, culture, traditions, and unique viewpoints must be considered by investigators. The community must also be given the opportunity to respond to findings prior to completion of research reports.

CLINICAL TRIALS

Clinical trials are addressed in the context of biomedical research. Research can include case studies, cohort studies, randomized controlled trials, or multicenter trials. While the methodology of these studies is greatly varied, the guiding ethical principles and procedures remain the same. To begin research there must be clinical equipoise, or a reasonable uncertainty warranting pursuit of an answer. Such an approach should ensure bias is minimized in all therapeutic arms and that participation is not considered disadvantageous. Research is generally categorized into four phases as found in Table 3.

Research with new medical devices must be carefully evaluated to ensure free and informed consent can be obtained. REBs must aid researchers to prevent conflicts of interest. This could be concerning subject selection or

Table 3 Phases of research

Phase	Description	Comments
I	Dose-finding studies of new medications to determine acute toxicity. Healthy subjects or patients.	These studies warrant close REB review with continuous monitoring independent of the trial sponsor. This is especially important as more of these trials include patients refractory to standard therapy, and with the increasing number of new medications. Unexpected adverse events are a major concern.
II	Determination of short-term pharmacologic toxicity, some degree of efficacy. Patients with specific diseases.	Phase I and II studies must be carefully examined for free and informed consent procedures. An independent continuous review may be necessary.
III	Determination of pharmacologic efficacy to increase survival or quality of life, some toxicity. Patients with specific diseases.	Phase II and III often include placebos to assess toxicity of a new agent. Use of placebo must be justified and minimization of harm ensured.
IV	Determination of long-term efficacy and toxicity of marketed drugs. Postmarketing surveillance studies.	These studies are often conducted in private practice for postmarketing with a per-capita fee paid to assess side effects and patient acceptance. Such payments can create bias. REBs must assess the science and ethics of these studies as much as with the other phases.

payment by sponsors to the investigators. Safety standards of new devices must be assured. Continued provision of therapy beyond the trial termination must also be examined.

If research is to be used for regulatory approval of a drug, the International Conference on Harmonization (ICH) guidelines that have been adopted by Canada must be followed. Budgets must be evaluated to ensure no conflicts of interest exist. Placebo-controlled studies are not considered acceptable when effective standard therapies or interventions are available. Investigators must inform subjects as to why placebos are necessary when used, and, if any treatment is to be withdrawn and the associated impact. Although sponsors may obtain preliminary data for analysis, final analysis and interpretation should be by the researchers to ensure the accuracy and integrity of the work.

HUMAN GENETICS RESEARCH

The study of genes that determine human traits is very topical and not without controversy. Identification of genes that comprise the human genome, their function, and their ability to predict disease or a predisposition to disease is central to this research. However, because genetic material in one individual is shared by biological relatives, privacy and confidentiality affect not just the individual who may wish to consent to research participation. The effects of such research and how information will be used and interpreted are unknown, requiring prudence in pursuing research in genetics. An individual may feel his/her identity and self-worth are threatened, not to mention any associated stigma that may occur toward the group to which the individual belongs.

Important considerations are as follows:

- Consent is critical in genetics research, and concern that the individual's family may be coercive and that information may affect other members in the family should be considered.
- Results of genetic tests must be protected from any third party access unless free and informed consent is given. DNA banking allows family and clinical information as well as genetic material to be a resource for other researchers; however, removal of the subject's and family's identity is important. Any potential harm must be disclosed to the REB as well as how it will be dealt with. For example, information about an individual's susceptibility to disease may provoke anxiety, particularly if effective therapy or prevention is not available.
- Genetic counseling must be available for subjects as needed. The issue of cultural differences in the perception of this research must be accounted for.
- Gene alteration, including gene therapy, using human germline cells or embryos, is not considered ethically acceptable. Gene alteration done for therapeutic reasons and using human somatic cells may be considered.

Irreversibility and lack of long-term follow-up suggest the use of this technology should be with care.
- Genetic research should be performed for the pursuit of knowledge or therapeutic benefits in disease, not to enhance or improve a population by cosmetic manipulation.
- Banking or storing of genetic material may yield benefit or harm. A defined term of storage and provisions for confidentiality and anonymity including for the future must be addressed.
- The likelihood of commercial use of genetic material and information must be discussed and consent obtained.

RESEARCH INVOLVING HUMAN GAMETES, EMBRYOS, OR FETUSES

There are complex concerns as to the possible harm to the embryo or fetus as well as the respect they deserve, and a cautious and controlled approach to such research is essential.

The human reproductive cells (ova and sperm) may be used for research provided free and informed consent is given. Use of gametes derived from cadavers is prohibited and use of gametes from fetuses or individuals unable to consent for themselves is deemed unacceptable. The use of gametes acquired by commercial transaction is considered unethical. Creation of hybrid individuals (e.g., a mix of human and animal gametes or transfer of somatic or germ cell nuclei between cells of humans and other species) is unethical and does not show consideration for human life and dignity.

It is not ethical to create human embryos specifically for research. If an embryo was created for reproduction but is no longer needed, it may be used for research if 1) consent is given, 2) no commercial transaction took place, 3) no genetic alteration of the gametes or embryo occurred, 4) manipulations not directed to normal development are not used for continued pregnancy, 5) that the research occurs within 14 days of the creation of the embryo by joining the gametes. It is not ethical to participate in research cloning human beings (ectogenesis).

With maternal consent, research may be undertaken in utero for fetuses with genetic or congenital disorders. Use of fetal tissue cannot affect a woman's decision regarding continuation of her pregnancy, nor can fetal tissue be directed for use in specific individuals as the fetus deserves respect as a potential person not just a source of tissue.

HUMAN TISSUE

Human tissue should be respected to maintain the dignity of the donor. Canadian law allows competent persons to donate, although not sell, human tissue for research. Concerns for confidentiality of tissue identity has led to the following categorization:

1. Identifiable tissue: donor known.
2. Traceable tissue: by database.
3. Anonymous or anonymized tissue: donor identity stripped.

The REB must consider the likelihood of the traceability of tissue in a research project with respect to privacy and confidentiality.

Collection of human tissue for use in research requires the researcher to demonstrate to the REB that free and informed consent will be obtained from competent donors, or from an authorized third party for incompetent donors or deceased donors without advance directive regarding the topic. Minimally, researchers must provide the research purpose; the type, location, and amount of tissue to be taken; the manner of acquiring the tissue with respect to safety and invasiveness of the procedure; the uses of the tissue; and how its use could affect privacy. Consent is also necessary for use of previously collected tissues when identification is possible.

CONCLUSION

The Tri-Council Policy strongly promotes research and attempts to provide guidance regarding ethical principles that ensure an individual's rights and interests are protected. Rapidly advancing knowledge and technology present us with new research issues and controversies that will require continual review of ethical guidelines and much opportunity for thought and debate regarding future research.

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UK Clinical Pharmacy Association

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INTRODUCTION

The UK Clinical Pharmacy Association (UKCPA) was launched in 1981 and since then membership has risen to over 2000 members. The success of UKCPA reflects the fact that the organization has been a fundamental part of the recognition of clinical pharmacy as part of the mainstream of pharmacy practice. As envisaged by the founders of UKCPA, clinical pharmacy is not a specialty within pharmacy but a discipline that is practiced by all pharmacists working with patients. Pharmaceutical care developments in all areas, including Primary Care, are now showing the relevance of the examples of practice that UKCPA has promoted. UKCPA members' activities have also had an influence on the Schools of Pharmacy to embrace clinical pharmacy within the core curriculum and to teach the skills by problem-based learning. The UKCPA workshops have been a major part of the well-known high quality conferences of which the Association is proud. The UKCPA has developed an organizational structure and a team approach in its work. Access to UKCPA has been further enhanced following the launch of our Website last year. (www.ukcpa.org).

Following is a description of the organization.

BUSINESS MANAGEMENT GROUP

The Business Group (BMG) focuses on ensuring the Association runs smoothly and efficiently. UKCPA is regularly invited to comment on new professional development proposals and it is the role of the BMG to respond on behalf of UKCPA, taking into account comments received from consultation.

The success of recruiting new members is assigned to the Membership and Marketing Committee.

This committee has set three main goals for the forthcoming year:

- To maintain and increase the current membership by highlighting the opportunities that UKCPA can offer.
- To identify and co-operate with other pharmacy groups in order for mutually beneficial collaborations to take place.
- To strengthen and increase the corporate membership.

UKCPA can only benefit if enthusiastic pharmacists are attracted to the organization. In return it can offer an exciting arena for such people to learn, participate and meet other pharmacists contributing to the profession. Clinical pharmacy now envelops all strands of the profession and it is the role of the Marketing and Membership Committee to publicize this information.

UKCPA publishes a newsletter 'In Practice' a range of practice guides and workshop support material. The two annual symposia attract over one hundred submissions of research and practice development work and the conferences provide a highly interactive format and polished performances. Conference presentations (oral communications and posters) are published as short papers or abstracts in the UKCPA official journal *Pharmacy World and Science*. All this is the remit of the Publications Committee.

Handling UKCPA conference communications and the adjudication process requires a scrupulous process to make it work for members. UKCPA has developed a housestyle and is a transparent process of adjudication and feedback to assure the final quality of work presented and published. This applies equally to the adjudication process for the four industry sponsored awards, AstraZeneca Travelling Fellowship Award, the four GlaxoSmithKline Poster Awards, the Pharmacia Pharmacoeconomics Award and the Wyeth Education and Training Award. New awards for 2002 are Unichem Community/Primary Care Pharmacy Award, Napp Palliative Care Award and the Merck Pharmaceuticals for Medicines Management Award.

The UKCPA Office plays an important role in helping the association organize many of the UKCPA events.

It is the Education Programming Committee who have the responsibility of identifying and implementing the educational content.

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The committee, which is made up of the Chairs of six Practice Interest Groups and four General Committee members, oversees the main educational events described in the programme. It has a challenging job in co-ordinating the main symposia while seeking to be visionary, to ensure the content of future symposia will attract participants some 12 months in advance of the planned event. There is much to do with the planning, implementation and review of each programme, which attracts up to 350 participants.

Practice Interest Groups reflect the broad range of interest and experience among members and provide a network of support among members by maintaining a data base of members and their area of expertise. Each group regularly contributes to 'In Practice,' reviewing current research/developments in their field and training opportunities. The groups comprise:

Care of the Elderly
Critical Care
Education and Training
Medicines Management in Primary Care
Quality Assurance
Surgery and Theatres
Infection Management
Each group sends a message.

Care of the Elderly

The aim of the group is to enhance the pharmaceutical care of elderly people, within both primary and secondary care. It does this by facilitating the continuing education and networking of its members.

The Group organizes study days, mini-symposia and workshops. Topics have included the pharmaceutical care of patients with stroke, dementia and osteoporosis plus a day on ophthalmological problems.

Critical Care Group

The Group provides support for all pharmacists who have an interest in the field of critical care, which includes intensive care, high dependency and coronary care. The groups core objectives are:

- To continue to provide regular, objective and high quality educational meetings.
- To provide supportive documentation, especially for those new to the field.
- To promote the role of the critical care pharmacist within a multi-disciplinary setting through a closer liaison with the Intensive Care Society.
- To push forward the debate on specialist pharmacists.
- To promote and support research within the field of critical care.

Education and Training Group

Training is a component of most jobs: many people are expected to teach others, but many have had little guidance on how to perform this key activity successfully. The Education and Training Group of UKCPA aims to share and promote good practice in the field, and to support these individuals in their role.

Training sessions are organized, either as part of the full UKCPA symposia, or as 'stand alone' days. For example, a recent study day on the topical issue of competency-based training was held. The group has also written a guide for good practice in education and training, as a short practical aide memoir for consideration when planning an educational event. Commissioned resource guides in key areas such as teaching communication skills and assessment have also been published.

Medicines Management in Primary Care Group

The Medicines Management in Primary Care Group was formed four years ago to provide support for the increasing number of pharmacists developing a clinical role in Primary Health Care Teams. The objectives are to:

- Provide education and training for pharmacists to develop clinical pharmacy in primary care.
- Facilitate liaison between primary and secondary care pharmacists.
- Encourage communication between all pharmacists working in this area by providing a forum for exchange of ideas.
- Promote innovation and encourage practically applicable research.

Recent workshops have included patient perspectives, therapeutic topics including cardiovascular and gastrointestinal systems, medicine resource management, medication review and pharmacist-led clinics.

Quality Assurance Group

The QA group was formed in the early days of UKCPA when intervention monitoring was the flavor. Since then, the Group's focus has broadened to address a whole range

of issues which are general to all clinical pharmacists, managers including those in Primary Care.

Recent examples of workshop topics at our two annual UKCPA symposia included sessions on compliance/concordance, PILs, off-label use of medicines, medication errors and ADR reporting. For the future, clinical governance and all its implications are high on the agenda and, to paraphrase the definition, we intend to help. . . .create an environment in which pharmaceutical care will flourish.

Surgery and Theatres Pharmacy Group

The Surgery and Theatres Pharmacists Group aims to enable pharmacists world-wide to network and share best practice thereby furthering the role of pharmacy in these fields of medical practice. A system has been developed to allow pharmacists to share guidelines and protocols through a Resource Centre. Access to the Group's services are via the internet. The Group has its own website at www.users.globalnet.co.uk/~phoward/satg.htm.

Other services provided are an interactive Newsgroup that allows members to canvas views of other members, a bibliography of key references, an on-line newsletter, links to over 180 related sites, and a network of subgroups. The Newsletter reviews initiatives that pharmacists have introduced successfully. It also reviews the surgical and anaesthetic literature.

The Group also has a directory of members that allows pharmacists to contact specialists in a particular area for advice or information.

The Group would like to see a member from all 700+ hospitals within the UK ensuring all hospitals have access to best practice.

Infection Management Group

The Infection Management Group is a new group formed this year.

UKCPA has links with the European Society of Clinical Pharmacy. This has afforded opportunities for our members to network beyond the UK with opportunities for some industry sponsored award winners to present posters at an ESCP meeting on an annual basis. This link has enriched our symposia by ESCP member attendance or ESCP contributed workshops.

In early 2000 the General Committee met to prepare a UKCPA business plan for the next few years. Use this opportunity to influence future activities of the Association through sending your comments/suggestions to: UKCPA, Alpha House, Countesthorpe Road, Wigston, Leicestershire, LE18 4PJ. E-mail: pkennedy@ukcpa.u-net.com. Web site: www.ukcpa.org.

PROFESSIONAL RESOURCES

United States Pharmacopeia

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INTRODUCTION

Standards established by the *United States Pharmacopeia* (USP) are accepted worldwide as the highest assurance of the quality of medicines and other products used to improve the health of the public. We discuss the development of the publication and the organization, and its current and future initiatives toward promotion of worldwide health.

A BRIEF HISTORY

The first *Pharmacopoeia of the United States*, published in 1820 by USP, was an important milestone in American medicine and pharmacy. It was a compendium of about 217 of the best understood drugs and drug preparations and a lexicon of standard drug names. Three medical visionaries—Lyman Spalding and Samuel Mitchill from New York and Jacob Bigelow from Boston—were largely responsible for this work. They intended the *Pharmacopeia* to accomplish a degree of drug standardization and to facilitate communication between physicians and pharmacists. Today, USP publishes more than 3400 official standards monographs for drugs and other healthcare products.

MISSION AND FOCUS

According to Roger L. Williams, M.D., USP's Executive Vice-President and Chief Executive Officer, USP pursues its mission to promote public health through multifaceted activities:

- Establishing and disseminating officially recognized standards of quality for therapeutic products.
- Collecting information from practitioners to help reduce and prevent medication errors.
- Educating healthcare professionals and patients on the appropriate use of therapeutics and improving the health of special populations worldwide.

DISTINCTIVE STRENGTHS

As a pharmacopeial organization, USP has certain unique characteristics:

1. *Non-governmental with statutory recognition*: USP is the world's leading nongovernmental pharmacopeia. According to the Federal Food, Drug, and Cosmetic Act, USP standards are enforceable by the Food and Drug Administration (FDA) for all drugs manufactured and sold in or imported into the United States. The standards are also officially recognized in many other countries.
2. *Volunteers lead the way*: USP achieves its goals through the contributions of volunteer experts representing pharmacy, medicine, and other healthcare professions, as well as science, academia, the U.S. government, the pharmaceutical industry, and consumer organizations. Volunteers constitute USP's membership, Board of Trustees, and scientific decision-making committees. They are supported by a staff of over 350.
3. *Standards set by a participatory process*: USP standards are developed by an exceptional process of public involvement. The process gives those who manufacture, administer, regulate, and use therapeutic products the opportunity to comment on the development and revision of standards used to measure the quality of these products.
4. *Role that expands beyond standards*: Unlike most of the world's major pharmacopeias, USP's role is not limited to the establishment of written and chemical pharmacopeial standards. USP also helps to monitor and prevent medication error problems through reporting programs for healthcare professionals. The valuable information and feedback obtained through these programs enables USP to enhance the accuracy and utility of its standards.

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ORGANIZATIONAL STRUCTURE

USP's direction and priorities are determined by more than 400 credentialed members through resolutions that they vote to adopt at quinquennial meetings of the USP Convention. Members also elect the USP Convention officers, Board of Trustees, and Council of Experts—the scientific decision-making body.

USP membership is on a 5-year cycle. Within each membership category, eligible organizations (Fig. 1) are invited to appoint their representatives. Membership composition is determined to ensure suitable representation of those sections of the healthcare system that are impacted by, and in turn impact, USP's activities. D. Craig Brater, M.D., Dean of the Indiana University School of Medicine, is the USP Convention President for 2000–2005.

USP's Board of Trustees is elected for a 5-year term and has fiduciary responsibility for the organization. Larry L. Braden, R.Ph., is the Chairperson of the 2002–2003 USP Board. A complete list of Board members is available at www.usp.org.

Sixty-two scientific experts serve on the Council of Experts and chair expert committees, which are responsible for making scientific decisions. Visit www.usp.org for a list of USP's 2000–2005 expert committees and chairpersons. The Council of Experts is chaired by Roger L. Williams, M.D., USP's Executive Vice-President and CEO.

USP PRODUCTS

USP-NF

Official pharmaceutical standards are published in a single volume combination of the *United States Pharmacopeia* (*USP*) and the *National Formulary* (*NF*), commonly referred to as *USP-NF*. This authoritative reference provides pharmaceutical standards of identity, strength, quality, purity, packaging, storage, and labeling. Monographs and general chapters relating to drugs for human as well as veterinary use are found in *USP*, and those relating to excipients are found in the *NF*. Monographs for bota-

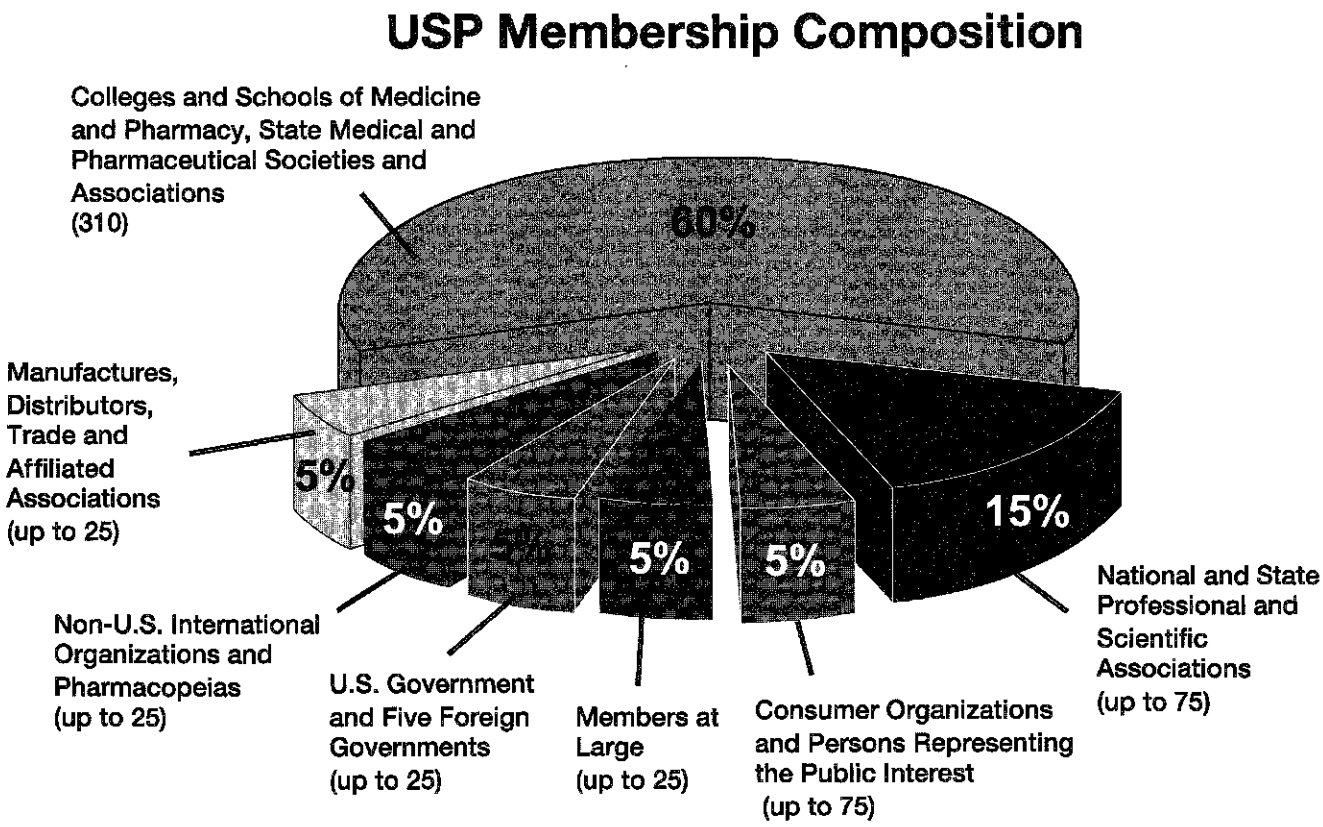

Fig. 1 USP convention membership.

nicals used as dietary supplements and having a FDA-approved or USP-accepted use are found in the *USP*. Monographs for botanicals recommended for official adoption by the USP Council of Experts and for other botanicals with no accepted or approved use, but with no safety concerns, are found in the *NF*. Monographs for nutritional supplements—vitamins and minerals—appear in a separate section.

USP-NF monographs include assays and various analytical methods—identification, dissolution, content uniformity, etc. *USP-NF* also provides guidance and standards on biotechnology, radiopharmaceuticals, pharmacy compounding, and pharmaceutical waters. General chapters outline requirements for microbiological, biological, chemical, and physical tests and assays.

USP-NF is available in four formats—a thumb-indexed hardcover, online, a CD for Windows®, and an Intra net version.

Statutory recognition

In the United States, the Federal Food, Drug, and Cosmetic (FD&C) Act affords recognition to *USP* and *NF* as official compendia and to the articles contained therein. According to sections 201(g) and (h) of this Act, the terms "drug" and "device" include articles recognized in the official *USP* or *NF* or any supplement to any of them. Section 501(b) provides that a drug is adulterated if it does not conform to *USP* standards for strength, quality, and purity. Section 502(g) requires a drug to conform to packaging and labeling requirements in the official compendium.

The Dietary Supplement Health and Education Act of 1994 (DSHEA) and the Food and Drug Administration Modernization Act of 1997 (FDAMA) extended the utilization of the *USP* and *NF* by amending the FD&C Act. Section 403(s)(2)(D) of the FD&C Act provides

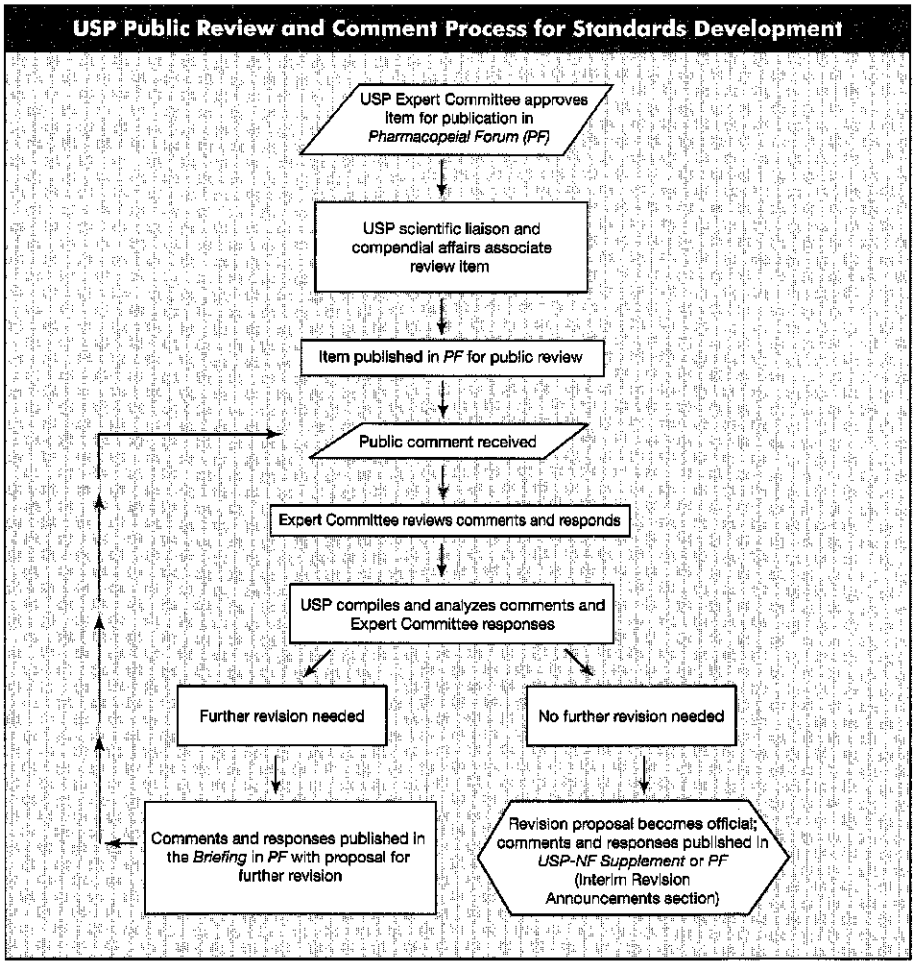

Fig. 2 USP standards development.

that a dietary supplement represented as conforming to the specifications of an official compendium shall be deemed misbranded if it fails to do so.

Pharmacopeial Forum

Pharmacopeial Forum (*PF*) is the journal through which USP institutes the public review and comment process for standards development and revision (see Fig. 2 for a process overview). Proposed changes to official *USP-NF* standards are published in *PF* so that all interested parties may review them, offer their opinions, and prepare for their impact. *PF* also provides notice of binding revisions to the official standards. It includes authoritative scientific articles and comments on current pharmaceutical industry issues.

Reference Standards

USP establishes and validates chemical Reference Standards that help to ensure pharmaceutical quality. USP Reference Standards are used to conduct the official tests for product identity, strength, quality, and purity specified in *USP-NF*. Potential Reference Standards are rigorously and collaboratively tested in USP, FDA, and industry laboratories (see Fig. 3). USP currently has more than 1250 pharmaceutical Reference Standards—one of the world's largest collections—and about 500 new items under development.

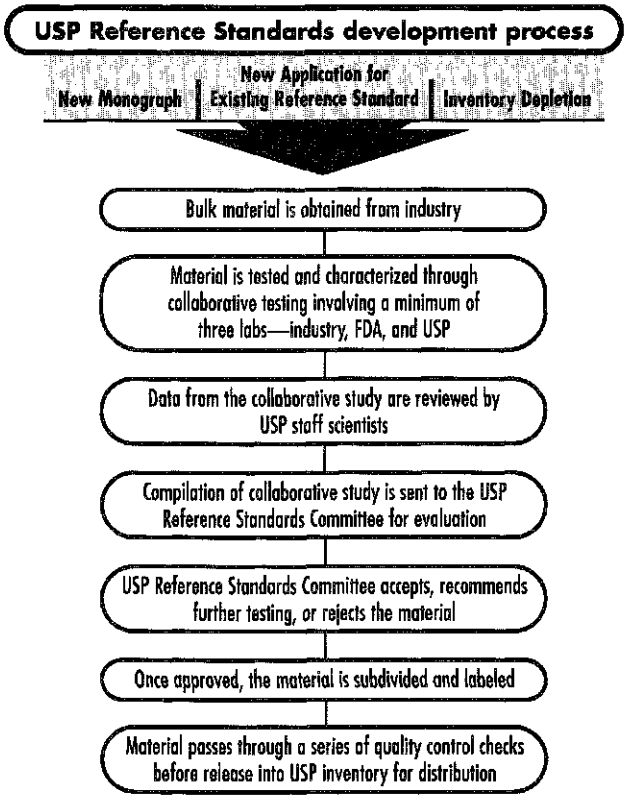

Fig. 3 Reference standards process. © The United States Pharmacopeial Convention, Inc. All rights reserved. Used with permission.

MedMARx℠

MedMARx℠ is an effective, proactive solution to the serious and costly problem of medication errors in the United States. It is an Internet-accessible, anonymous, national database through which hospitals can report, track, and analyze medication errors to help prevent their recurrence. Errors are reported to MedMARx in a standardized format and categorized according to a nationally recognized index. This allows facilities to share information anonymously and learn from others' errors and preventive strategies. Participating facilities also receive national medication error alerts and reports on key error trends. MedMARx is backed by more than 30 years of USP experience in operating voluntary medication error and drug product problem reporting programs for healthcare professionals.

CURRENT INITIATIVES

Dietary Supplement Verification Program

In 2001, USP created the Dietary Supplement Verification Program (DSVP) to help inform and safeguard the growing number of consumers who use dietary supplements. The program responds to the need to assure the public that dietary supplement products contain the ingredients stated on the product label. If a product submitted to DSVP meets USP's rigorous standards, it will be awarded the DSVP verification mark. The mark helps assure consumers, healthcare professionals and supplement retailers that a product:

- Contains the declared ingredients on the product label.
- Contains the amount or strength of ingredients declared on the product label.
- Meets requirements for limits on potential contaminants.
- Has been manufactured properly by complying with USP and proposed FDA standards for "good manufacturing practices" (GMPs).

New Monograph Development

Currently, there are no public standards for about 35% of drugs in the U.S. market. USP seeks to develop public

quality standards for all therapeutic products in the market, especially for the top 200 prescribed drug products and active pharmaceutical ingredients. Increased cooperation is being obtained from the pharmaceutical industry for a program to prepare and publish proposed standards monographs for newly approved drugs and drug products six years before patent expires.

International

USP, through its participation in the Pharmacopeial Discussion Group (PDG), is working closely with the European and Japanese Pharmacopoeias to explore the harmonization of pharmacopeial standards for excipients, microbiological testing, general methods of analysis, and methods of analysis for biotechnology-derived products. Several general test methods have already been harmonized. USP serves on Quality Expert Working Groups at the International Conference on Harmonization (ICH). It also works through the Pan American Health Organization and with individual countries around the world to ensure drug quality.

New Priorities

The USP Convention membership, at its April 2000 Quinquennial Meeting, adopted resolutions directing USP to explore in the next 5 years:

- The impact of applied genomics on drug discovery and development and therapeutic applications.
- Approaches to assure equivalence of complex active ingredients, including botanicals and dietary supplements.
- The application of modern biopharmaceutic principles to assure the equivalent performance of immediate- and modified-release drug products.
- Compounded drug formulations for special populations.
- Packaging, labeling, nomenclature, and dosage form characteristics for medicines to reduce medication errors.
- Standardized imprint coding for all solid oral dosage forms.
- Methods research on botanical ingredients.
- Compounding guidelines for veterinary extra-label use of medications.
- Education and training programs for health professionals to support the appropriate use of the *USP-NF* and expand its use.

MEETINGS

The USP Convention membership meets once every 5 years to discuss the areas of healthcare in which USP should be involved. These quinquennial meetings help to define USP's strategic focus and priorities for a 5-year period.

USP conducts open meetings as needed to invite the views of interested parties on issues of current significance in the pharmaceutical industry and the nature of USP's involvement with these issues. Notices of open meetings are posted on USP's web site at www.usp.org.

Universal Precautions and Post-exposure Prophylaxis for HIV

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INTRODUCTION

As early as 1982, the Centers for Disease Control and Prevention (CDC) began issuing precautions for the handling and care of laboratory specimens from patients infected with the human immunodeficiency virus (HIV-1). The goal was to minimize the risk of exposure to infectious blood and blood-containing body fluids. Although it was previously recognized that blood and hypodermic needles posed a significant risk to the healthcare worker, this issue moved to the forefront of clinical practice with the recognition of the HIV/AIDS epidemic, when it became clear that healthcare workers would be at increased risk for exposure to HIV-1 and other blood-borne pathogens. In 1987, the CDC issued guidelines that were designed to minimize the risk of HIV-1 transmission in the healthcare setting. These guidelines have since become known as the "universal precautions."[1] Universal precautions became mandatory in 1991 with the passage of the Occupational Safety and Health Administration (OSHA) Blood-Borne Pathogens Standard, which required healthcare employers to establish, at minimum, an exposure control plan and offer training to employees.[2–4] Since their introduction, there have been numerous modifications of these guidelines by the CDC, Public Health Service (PHS), and OSHA. These modifications incorporate new scientific knowledge and address additional concerns that have arisen in the area of occupational exposures.[5–10] Recently, the Public Health Service interagency working group, comprised of members of the CDC, Food and Drug Administration (FDA), and NIH, issued updated guidelines that consolidate recommendations regarding the management of healthcare workers who have experienced occupational exposure to blood and other body fluids that may contain HIV.[10]

WORKING DEFINITIONS

Universal precautions are intended to supplement standard infection control procedures and rely on the use of protective barriers such as gloves, goggles, facemasks, as well as proper safety conduct, such as hand washing, avoiding recapping of needles, and proper disposal of medical waste. The concept of universal precautions is based on the underlying assumption that blood and certain body fluids from all patients is potentially infectious for HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), methicillin-resistant *Staphylococcus aureus* (MRSA), or any other blood-borne pathogen. In this context, potentially infectious body fluids include: cerebrospinal fluid, vaginal secretions, semen, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid.[1,10] Universal precautions do not apply to body substances such as feces, sweat, tears, urine, human breast milk, vomitus, nasal secretions, sputum, or saliva unless visibly bloody; but this in no way lessens the need for practicing standard infection control procedures.[1,10] The term "healthcare worker" is very broad and refers to any person whose activities involve contact with patients or with blood or other body fluids from patients in a healthcare setting.[3,4,8,10] An "exposure" that places a healthcare worker at risk for HIV or other blood-borne pathogens and requires consideration for post-exposure prophylaxis is defined as any percutaneous injury, contact with mucous membrane or nonintact skin (i.e., chapped, abraded, or skin with dermatitis), or contact with intact skin when the duration of contact is prolonged (i.e., several minutes or greater) or extensive with blood, tissue, or body fluids.[10]

RATIONALE FOR UNIVERSAL PRECAUTIONS

Given the HIV/AIDS epidemic, in addition to the increase in other viral infections such as HBV and HCV, the need

to adopt some form of protective measures, and thus the rationale for universal precautions, is clear. It has been suggested that there are three main reasons for applying universal precautions.[11] The first stems from the inability to test and identify every patient to discern if they are infectious. Therefore, it is most prudent to assume that all patients are infectious and thus act accordingly. The second reason is psychological in nature and takes into account human behavior and performance regarding identification and labeling practices. Lastly, there are administrative and legal reasons that embrace OSHA's mandate for employers to provide a safe working environment for employees.

Table 1 Factors associated with an increased or decreased risk of occupational HIV transmission following an exposure

Increased risk of transmission	Decreased risk of transmission
Exposure to large quantity of blood	Use of gloves
Exposure occured during placement of needle into artery or vein	Mucous membrane exposure
Exposure occurred during invasive procedure	Prompt initiation of post-exposure prophylaxis
Deep injury	Intact skin exposure
Visible blood on needle/object	
Source with increased viral load	

TRANSMISSION RISK AND EPIDEMIOLOGY

The true risk of transmission following occupational exposure is difficult to determine due to the high rate of underreporting of exposures and the underlying risk of healthcare workers being infected with HIV-1 outside of the workplace. However, one prospective study determined that a percutaneous exposure to HIV-infected blood is associated with a 0.3% risk of transmission.[12] The risk is lower after a mucous membrane exposure at 0.09%.[12] The risk associated with HIV transmission after skin exposure has not been precisely defined, because presently, no HCW enrolled in any prospective study has seroconverted following an isolated skin exposure; nonetheless, the risk is thought to be less than for mucous membrane exposure.[10,13] The risk of HIV transmission following exposure to bodily fluids other than blood, such as cerebrospinal fluid, vaginal secretions, semen, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid is not presently known. Factors that increase or decrease the risk of HIV transmission following an occupational exposure are listed in Table 1. The increased risk resulting from exposure to blood from terminally ill AIDS patients likely reflects an increased viral load.[14] In these instances, it has been suggested that the risk of HIV transmission exceeds 0.3%, but the practical utility of using HIV titers from source patients as a marker for transmission is unknown, and a low HIV titer does not rule out the possibility of HIV transmission.[14]

As of June 1997, documented HIV seroconversion temporally associated with occupational HIV exposure was reported in 52 healthcare workers.[10] Forty-seven cases involved exposure to HIV-infected blood, 45 exposures were percutaneous in nature, and most involved a hollow-bore needle (91%).[10] The remaining five cases involved exposure to HIV-infected bloody body fluid, concentrated virus in laboratory, and one case was unspecified. This data may not represent the true number of occupational HIV infections, because not all workers are evaluated for HIV infection following occupational exposure, not all workers with occupational exposure/infection are reported, and an estimated 40% or more of needlestick injuries may go unreported.[15–17] Needlestick injuries, whether a consequence of recapping or improper disposal techniques, continue to be a frequent and important mode of HIV exposure.[15] A large prospective surveillance study, the CDC Cooperative Needlestick Study, found more than 80% of all exposures were related to needlestick injuries.[18] Surveillance data indicates laboratory technicians, followed by nurses and physicians, represent the most common occupations associated with occupational HIV transmission.[19] Some have argued that universal precautions may not significantly decrease exposure, as a glove cannot prevent a needlestick injury. However, there is evidence that despite the ability of needles to pass through latex gloves, there may be a substantially lower blood innocula associated with the use of latex gloves, perhaps suggestive of a reduced likelihood of occupational infection.[20,21]

POST-EXPOSURE PROPHYLAXIS FOR HIV

Post-exposure prophylaxis, or the administration of pharmacological agents with the intent of preventing occupational HIV transmission after exposure, may be useful in certain circumstances. The decision to use post-exposure prophylaxis is complex and depends on a number of important factors, which should be evaluated on an individual, case-by-case basis. This decision should take

into account the nature of the exposure, including volume of blood or body fluid involved, source of exposure and risk of transmission, time between exposure and start of post-exposure prophylaxis, and documented efficacy of post-exposure prophylaxis. The potential benefits of post-exposure prophylaxis must be weighed against the potential hazards in deciding treatment duration, potential adverse effects of antiretroviral agents, viral resistance, and pregnancy. Fig. 1 outlines general considerations and procedures that should be followed after an occupational exposure. Note that the algorithm is a suggested approach and does not represent all possible scenarios; each ex-

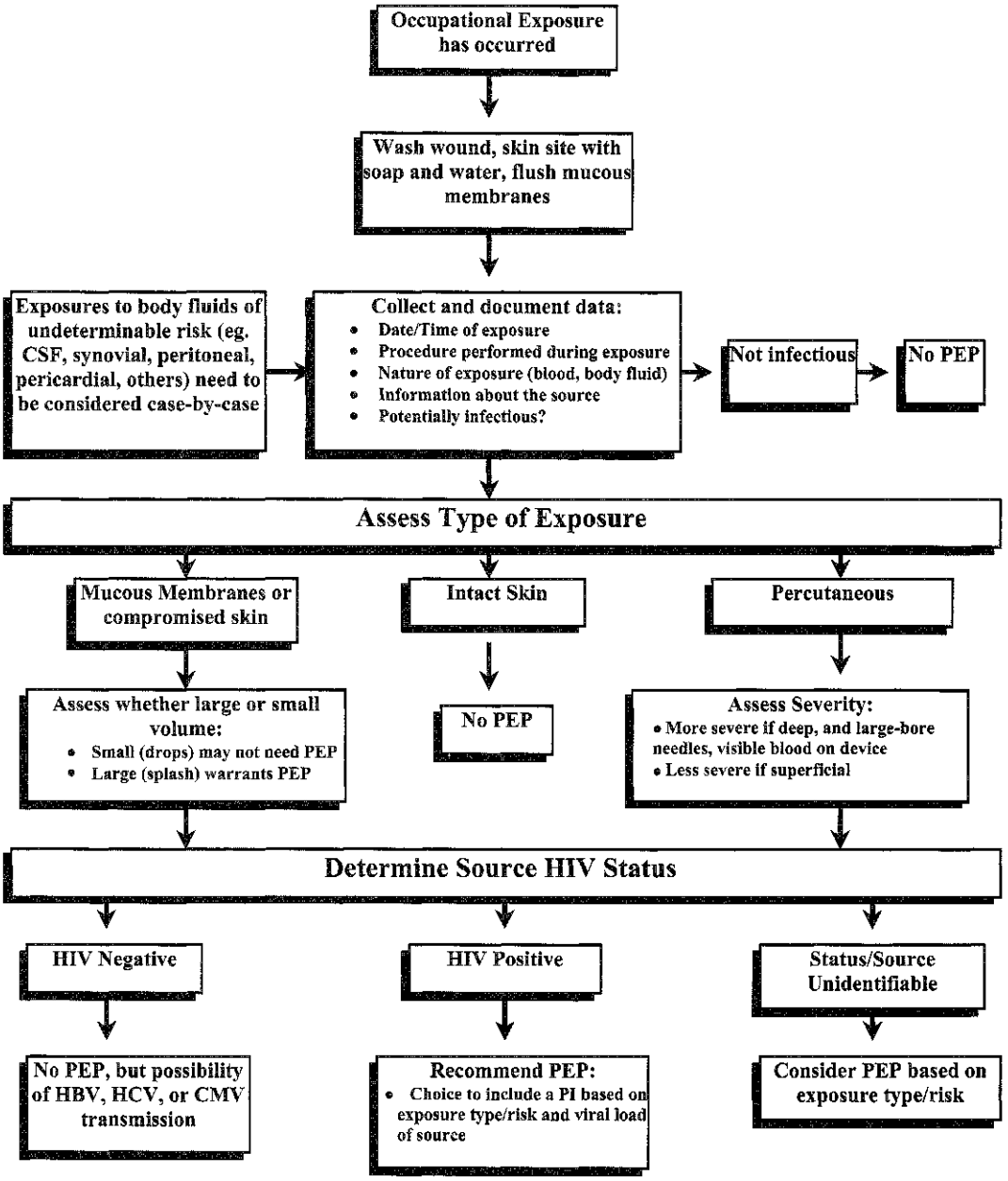

Fig. 1 General schematic of the considerations and procedures following an occupational exposure. This algorithm serves only as a suggested approach; although it reflects the PHS guidelines, it is not meant to replace published guidelines. In addition, this algorithm does not apply to other types of infectious exposures, such as sexual exposures. For specifics, please refer to the text and to the Public Health Service guidelines.[10]

posure needs to be individualized on a case-by-case basis. Additionally, this algorithm only pertains to occupational exposures and not to exposures differing in nature, such as sexual exposures.

Because evidence suggests that systemic infection does not occur immediately following primary HIV exposure, there appears to be a period of time in which initiation of post-exposure prophylaxis promptly after occupational exposure may prevent or inhibit systemic infection by limiting viral replication and proliferation. The consensus is that post-exposure prophylaxis should, therefore, be initiated as soon as possible following exposure, ideally within a few hours of exposure, because some animal data show a reduction in post-exposure prophylaxis efficacy with delayed initiation.[22,23] Post-exposure prophylaxis may be beneficial even up to 36 hour after exposure, but the efficacy of post-exposure prophylaxis given this late is largely undetermined. The optimal duration of post-exposure prophylaxis is unknown, but presently, the Public Health Service guidelines recommend a 4-week regimen of zidovudine and lamivudine with or without a protease inhibitor.[10]

Following an occupational exposure, it is vital that healthcare workers are cognizant of institutional policies and procedures to allow for the timely and organized collection of data and initiation of post-exposure prophylaxis if indicated. Institutions must have policies and procedures in place to react quickly to occupational exposure to avoid unnecessary delays in therapy. The date and time, details pertaining to the type of activity being performed, nature of the exposure (type, amount, severity, percutaneous, mucous membrane, time of contact, condition of skin), and details about the source (HIV infected, viral load, history of antiretroviral therapy) should be recorded in the healthcare worker's medical record. It is recommended that skin sites or wounds that are contaminated should be washed with soap and water.[10] The use of antiseptics may be considered, but application of caustic substances such as bleach is not recommended, as this would compromise the integrity of the skin barrier. Mucous membranes should be flushed extensively with water.[10]

Following each occupational exposure, proper assessment of the risk for HIV transmission should be performed by qualified personnel. If at all possible, the source patient should be evaluated for HIV, HBV, and HCV status to help rule out viral infection.[10] Information pertaining to intravenous drug use and other source risk factors relevant for consideration of post-exposure prophylaxis should be sought. If this information is unavailable, the source person should be notified of the incident and consent sought to facilitate testing for serologic evidence for viral infection. If the source is seronegative for virus at the time of exposure, with no clinical manifestations of HIV infection, then no further testing of the source is needed.[10] Inevitably, there will be occasions where the source is unknown. In these instances, the Public Health Service recommends assessing the risk for HIV transmission and the need for post-exposure prophylaxis based on integration of the nature of exposure and epidemiological information.[10]

EFFICACY OF POST-EXPOSURE PROPHYLAXIS

Although there are some data in animals, there is limited information available that can be used to assess the efficacy of post-exposure prophylaxis in humans. This is a manifestation of the infrequent rate of seroconversion of healthcare workers following exposure to HIV-infected blood and makes it doubtful that a prospective study with adequate statistical power could be performed. The notion of using zidovudine as post-exposure prophylaxis was addressed by the CDC in 1990 and has been shown to be beneficial by a retrospective case-controlled study, which documented the risk for HIV infection among healthcare workers who used zidovudine as post-exposure prophylaxis reduced by 81%.[6,14] However, there are at least 14 instances of zidovudine post-exposure prophylaxis failure, and there is growing concern regarding transmission of zidovudine-resistant virus, especially if the source patient's HIV treatment regimen included zidovudine.[10,24] Despite the fact that zidovudine has been shown to be effective in reducing perinatal transmission, it cannot be concluded that it is effective in reducing occupational exposure HIV transmission, because the occupational exposure route is not similar to the mother-to-infant route of transmission.[25]

OPTIONS FOR THERAPY

Because the treatment of HIV infection is rapidly evolving and takes into consideration multiple issues such as viral resistance and optimal drug combination regimens, there is growing concern over which drug or drugs should be used as the standard for post-exposure prophylaxis. Presently, there are no data available to assess whether the addition of other antiretrovirals to zidovudine enhances the efficacy of post-exposure prophylaxis regimens, or whether the increased prevalence of zidovudine resistance is an important factor for post-exposure prophylaxis regimen selection and efficacy. The CDC states that zidovudine should be considered for all post-exposure prophylaxis regimens, because it is the only agent that data supports efficacy for

post-exposure prophylaxis. Lamivudine should usually be added for increased antiretroviral activity and activity versus zidovudine-resistant viral strains.[8] The current Public Health Service guidelines maintain that it is reasonable to continue zidovudine as the drug of choice in post-exposure prophylaxis regimens, and there has been no additional information to suggest altering lamivudine as the second agent for post-exposure prophylaxis.[10] Table 2 lists the commonly used antiretroviral agents in post-exposure prophylaxis regimens, along with the usual dose and expected adverse effects. Other nucleoside reverse transcriptase inhibitors (NRTIs) that may be used with zidovudine for post-exposure prophylaxis are didanosine and zalcitabine, resulting largely from documented efficacy and use in combination with zidovudine for treatment of HIV.[26] The addition of protease inhibitor drugs such as indinavir, nelfinavir, and efavirenz are generally reserved for an expanded post-exposure prophylaxis regimen following high-risk exposures in lieu of their additional toxicity and drug interactions. Nonnucleoside reverse transcriptase inhibitors such as delavirdine and nevirapine are generally not included in post-exposure prophylaxis regimens.

The use of any drug, even as a prophylactic measure, may be associated with adverse effects. Adverse effects of antiretroviral medications are well-described in the HIV population; however, there is sparse data about adverse effects in the non-HIV-infected individuals. Between October of 1996 and December of 1998, an HIV post-exposure prophylaxis registry prospectively followed

Table 2 Post-exposure prophylaxis regimens

Drug(s)[a]	Indication	Drug regimen	Adverse effects	Specifics
Zidovudine	In combination with lamivudine for occupational exposures that have recognized risk for HIV transmission	*Basic regimen*: Zidovudine 300 mg BID, given with lamivudine for 28 days	Nausea, vomiting, headache, fatigue, anemia, neutropenia	Renal excretion of metabolite Food may affect peak plasma concentrations but not overall exposure
Lamivudine	In combination with zidovudine for occupational exposures that have recognized risk for HIV transmission	*Basic regimen*: Lamivudine 150 mg BID given with zidovudine for 28 days	Occasional nausea, headache, diarrhea, rash	Renal excretion, requires dose reduction based on creatinine clearance Food does not affect bioavailability
Indinavir	For use with zidovudine and lamivudine in cases where there is an increased risk for HIV transmission (i.e., source has high viral titer or large volume exposure)	*Expanded regimen*: Zidovudine 300 mg BID, lamivudine 150 mg BID, and indinavir 800 mg TID for 28 days	Dose-related hyperbilirubinemia, nephrolithiasis, metallic taste, rash, dry mouth/ mucous membranes	Hepatic elimination Give with water at least 1 hr prior, or 2 hr after a meal; food will substantially reduce bioavailability Minimum of 48 oz fluids daily to reduce nephrolithiasis Numerous drug interactions
Nelfinavir	For use with zidovudine and lamivudine in cases where there is an increased risk for HIV transmission (i.e., source has high viral titer or large volume exposure)	*Expanded regimen*: Zidovudine 300 mg BID, lamivudine 150 mg BID, and nelfinavir 750 mg TID for 28 days	Diarrhea, rash, asthenia, anemia	Hepatic elimination Food will increase bioavailability; take with light snack

[a]Consider potential drug interactions with other concurrent medications.
(From Refs. [10] and [27].)

healthcare workers receiving post-exposure prophylaxis following occupational exposure and monitored them for adverse effects.[27] Of the 250 healthcare workers who completed a post-exposure prophylaxis regimen, and for whom follow-up data was available, 76% reported some symptoms or adverse events.[27] The most frequently reported symptoms were nausea (57%), fatigue/malaise (38%), headache (18%), vomiting (16%), and diarrhea (14%). Minor laboratory abnormalities were reported in 8% of healthcare workers.[27] Of those healthcare workers who discontinued all post-exposure prophylaxis drugs, 50% cited symptoms or adverse effects as the reason for discontinuation.[27]

Little is known regarding the potential effects of antiretroviral drugs on the developing fetus. Although carcinogencity or mutagenicty is evident in screening tests for zidovudine and all other FDA-licensed NRTIs, limited data on zidovudine use in the second or third trimesters of pregnancy was not associated with serious adverse effects.[10,25] Whether lamivudine is teratogenic is unknown.[8] This complicates the decision to provide post-exposure prophylaxis to pregnant women; however, pregnancy should not preclude the use of optimal post-exposure prophylaxis, and post-exposure prophylaxis should not be denied to a healthcare worker solely on the basis of pregnancy.[10] In these situations, the patient shall reserve the right to decline post-exposure prophylaxis after they have been informed about the risk of HIV transmission given the nature of the exposure, limited data regarding teratogenicity in various trimesters of pregnancy, and the risks versus benefits of post-exposure prophylaxis therapy.

The impact that an occupational exposure can inflict on a healthcare worker and their family is enormous. Healthcare workers should receive post-exposure counseling and education, along with a detailed synopsis of what events the healthcare worker may expect, including the need for follow-up HIV antibody testing. Additionally, facts about the risk for transmission and other issues such as the choice, efficacy, adverse effects, and adherence of post-exposure prophylaxis medications should be discussed. Additionally, the possible need for sexual abstinence or use of a condom to prevent secondary transmission to their partners should be addressed in a manner allowing for questioning and feedback. Organ dysfunction, concurrent disease states, and other medications the healthcare worker was previously taking on a regular basis, and the potential for drug interactions with post-exposure prophylaxis medications must be considered. Exposed healthcare workers should be reminded to refrain from donation of blood, plasma, organs, tissue, and semen donation, and to temporarily discontinue breastfeeding.[10]

Table 3 Available resources and registries for HIV post-exposure prophylaxis

Resource or registry	Contact information[a]
Centers for Disease Control	Telephone: (404) 639-6425 (For reporting HIV seroconversion in HCWs that received postexposure prophylaxis) or www.cdc.gov/hiv (for general information)
National Clinicians' Postexposure Hotline	Telephone: (888) 448-4911; (888) 737-4448; (888) PEP4HIV
Food and Drug Administration	Telephone: (800) 322-1088 (For reporting unusual or severe toxicity from PEP regimens)
Antiretroviral Pregnancy Registry	Telephone: (800) 258-4263
UCSF On-line information	http://arvdb.ucsf.edu (For information about antiretroviral drugs)
National HIV/AIDS Clinician's Consultation Center	http://www.ucsf.edu/hivcntr
HIV/AIDS Treatment Information Service (ATIS)	http://www.hivatis.org Telephone: (800) 448-0440

[a]Contact information is subject to change.

There are numerous factors to consider before and after initiation of a post-exposure prophylaxis regimen, which may lead to providers and educators feeling overwhelmed and unsure about some choices that need to be made. To facilitate this process, Table 3 lists some available resources and registries that one may contact to aid in the decision process.

CONCLUSION

The practice of universal precautions is Federal Law in the United States, and it is the responsibility of every employer or institution that healthcare workers have the resources and training necessary to adhere to these safety precautions.[2] Additionally, support for continued practice of universal precautions needs to come from all levels of administration. Observations by Gershon et al. indicate that one of the strongest correlates with compliance is the institutional "safety climate."[15] This implies that if healthcare workers perceive their work environment to be conducive to practicing universal precautions, then they will be more likely to do so.

Each occupational exposure needs to be considered on a case-by-case basis. The risk of occupational HIV transmission appears to be greatest if the exposure is percutaneous in nature. In order to optimize post-exposure prophylaxis, the duration between exposure and initiation of therapy must be kept at a minimum; preferably within a few hours. Despite the concern of viral resistance, post-exposure prophylaxis regimens should include 4 weeks of zidovudine plus lamivudine, and under certain circumstances, a protease inhibitor.

Although the focus of this discussion emphasizes HIV infection, healthcare workers must be aware that other blood-borne pathogens such as HBV and HCV may also be of significant concern. The healthcare worker is encouraged to refer to alternative references for more detailed discussions pertaining to these infections.[28,29]

Unfortunately, healthcare worker exposure to infectious blood and body fluids will continue to be a reality. Hopefully, with the practice of basic infection control in conjunction with universal precautions, this can be kept at a minimum. Universal precautions will likely be an evolving process considering the increased prevalence of viral resistance, and the continued emergence of new, and more difficult to treat infectious entities.

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DISTINGUISHED PERSONALITIES

Walton, Charles

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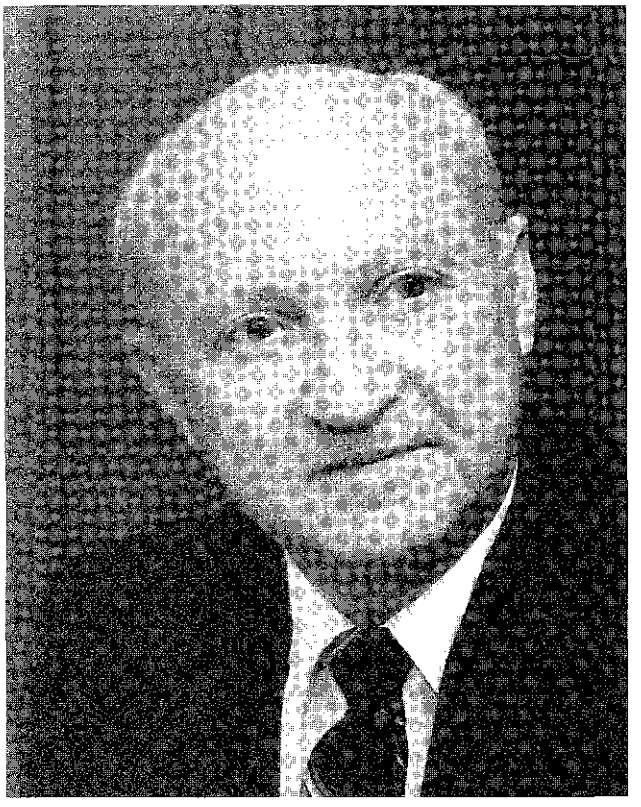

INTRODUCTION

Charles Walton has contributed substantially to the development and maturation of clinical pharmacy. Among his most important contributions were the development of drug information, the introduction of rational therapeutics into the pharmacy curriculum, and his strong advocacy for a sustained clinical practicum as an essential component in the training of competent clinical pharmacists. He is regarded by many in the discipline as the father of drug information training and one of the founding fathers of the American College of Clinical Pharmacy.

BIOGRAPHY AND ACCOMPLISHMENTS

Charles Anthony Walton was born on April 3, 1926, in Auburn, Alabama, but was raised in Tallassee, which is 35 miles northeast of Montgomery. He recalls how people passing through his hometown accused the city fathers of leaving out the "ha" in spelling the name of their town. Tallasseeans, according to Walton, are a noble people and would tell such critics that they needed to travel further south into the panhandle of Florida if it was laughter they wanted.

Walton's interest in pharmacy began when he was a young lad and an avid listener of radio. Television had

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not yet been invented. Walton was particularly interested in radio commercials and some of their dramatic claims. He remembers one mellifluous radio announcer saying "Take Sal Hapitica for the smile of health and brush with Ipana for the smile of beauty." But what really piqued his interest in drugs was the radio commercial that advertised Carter's Little Liver Pills. He found it incredible that such a small, round pill could produce such extraordinary and wonderful outcomes. In fact, he was so intrigued with commercials that he decided that when he grew up he would pursue either a career in radio announcing or in the study of drugs. His Southern drawl, however, pretty much excluded a career in radio.

After graduating from Tallassee High School, Walton enlisted in the United States Navy and served two years during the Second World War. After completing his tour of duty in the Navy, he enrolled as a freshman at Auburn University, where he would later study pharmacy. He was a good student of pharmacy and his interest and curiosity in pharmacology continued to grow. However, the faculty did not readily encourage his enthusiasm and desire to do postgraduate work in pharmacology and suggested instead that he enter pharmacy practice where he could earn a decent living. But there was one faculty member who learned of Walton's desire to continue his education and pursue a graduate degree in pharmacology. She had a master's degree in hospital pharmacy from Purdue University, and she alone urged Walton to follow his dreams and enter graduate school. He did just that. After one year at Purdue, Walton was awarded a master of science degree in pharmacology, and in 1950 he accepted a faculty position at the University of Kentucky School of Pharmacy in Louisville.

Later on Walton took advantage of a part-time sabbatical to begin work on a Ph.D. degree in pharmacology at Purdue. He completed the program in 1956. Shortly after that, the University of Kentucky School of Pharmacy moved to Lexington, and, in 1960, opened a medical school on this new Lexington campus. The presence of a medical school on the same campus as the pharmacy school led Walton to dream about training pharmacy and medical students in the same educational environment. He presented his idea to the two deans. The dean of the medical school supported the idea, but the dean of the pharmacy school had some reservations, and so Walton's dream was temporarily suspended.

Walton may have been dismayed but he was not distracted. He soon became acquainted with the Director of Hospital Pharmacy at the University of Kentucky Medical Center—a very bright and energetic young man who had some novel ideas of his own. Charles Walton and Paul Parker rapidly developed a strong collegial relationship. They were so enthusiastic and passionate about their ideas that often they would work well into the early morning hours generating new concepts and crafting plans to expand the mission of pharmacy. These late-night meetings were charged with so much creative energy that, the next days, neither man felt tired, but instead longed to get back together to continue their stimulating discussions. Walton recalls one occasion when Parker invited him to his Lexington home to explore the idea of training pharmacists to provide rational drug information to hospital formulary committees and to physicians taking care of patients in the hospital. They worked tirelessly during the night, drafting a concept paper that outlined the establishment of a hospital pharmacy service that would be dedicated to the advancement of rational therapeutics. They called the new service initiative drug information. They knew that their idea would be popular with the medical school's chairman of medicine, Ed Pellegrino, because Pellegrino was a pioneer and national leader in the teaching and practice of rational drug therapy. A key development in the concept came about with the hiring of David Burkholder as the first director of the drug information center. Working together, Burkholder and Pellegrino developed the first hospital formulary that was based entirely on the principles of rational therapeutics. (Today, we refer to rational therapeutics as evidenced-based medicine.) The major underlying principle is that no drug should be used in the hospital setting that has not been proven in proper studies to be safe and more effective than alternative therapies.

The idea of melding drug information with pharmacists monitoring drug therapy at the patient's bedside came from a drug information conference held in the early 1960s at the Carnahan House, located on a horse farm near Lexington. The conference was sponsored by the American Society of Hospital Pharmacists (ASHP). At that conference, William Smith presented the so-called "9th floor project" being conducted at the University of California at San Francisco. The marriage of drug information to hospital pharmacists working at the bedside gave birth to a new concept in pharmacy that the conference delegates referred to as clinical pharmacy. Those representing ASHP at the conference expressed some concern that a new competing organization might emerge. The conference attendees toyed with the idea of establishing an association of clinical therapologists. A delegate from Canada quickly moved that the organization be named the International Association of Clinical Therapologists (IACT). It was all in jest.

Walton became the director of the hospital pharmacy's Drug Information Center in 1967. He also started working more closely with the hospital pharmacy residency pro-

gram directed by Paul Parker. He continued his teaching of pharmacology in the pharmacy school but with a different slant, incorporating in his lectures the principles of rational therapeutics. At that time, James Doluisio, who had recently joined the pharmacy school faculty at the University of Kentucky, was serving as chairman of the curriculum committee. Doluisio had been a key player in the development of the Pharm.D. Program at the Philadelphia College of Pharmacy and Science. Walton was asked to chair a committee to develop a doctor of pharmacy program at Kentucky. Working closely with Doluisio and Parker, Walton's committee successfully established a strong post-baccalaureate Pharm.D. program deeply rooted in rational therapeutics and including a sustained clinical practicum through the hospital pharmacy residency program. Walton's dream of pharmacy students being educated and trained alongside medical students had finally become a reality.

In 1973, Doluisio became Dean at the University of Texas College of Pharmacy in Austin. One of his first administrative decisions was to hire Walton to develop a Pharm.D. program in Texas. Because there was no medical school in Austin, Doluisio negotiated an agreement with the University of Texas Health Science Center in San Antonio to establish a jointly administered post-baccalaureate Pharm.D. degree program. And, because there was no existing hospital pharmacy residency program at the health science center in San Antonio, a one-year sustained clinical practicum was incorporated as part of the academic program. Walton was appointed associate dean for clinical programs and recruited a young, dedicated faculty to help build the Pharm.D. program at Texas. The new program contained a strong didactic background in the biomedical sciences and provided experiential training in medicine, pediatrics, psychiatry, ambulatory care, and drug information.

Walton strongly insisted that pharmacists engaged in therapeutic decision making and pharmacotherapy consultations had to be well-trained clinicians who were directly involved in the management of patients. The founders of the American College of Clinical Pharmacy (ACCP) were strongly influenced by Walton's philosophy on what constitutes a credible clinical pharmacy practitioner as they developed the mission, goals, and purpose of the organization. In fact, Walton played a prominent role in the early development of the College not only as a source of encouragement, wisdom, and guidance but also by serving ACCP as an advocate before the pharmacy academy, particularly the American Association of Colleges of Pharmacy. The major impetus of ACCP was to strive for excellence. The new organization was criticized by some as being composed of elitists. When questioned about this, Walton said, "If striving for excellence makes me an elitist, then I am an elitist." Because of his important contributions to the development of the ACCP, Walton was inducted as the first honorary fellow of the College.

Charles Walton will forever be admired for his intellect, his humor, his wisdom, and his passion for excellence. To the pioneers in clinical pharmacy and to many of those who followed in their footsteps, Charles Anthony Walton is a hero and beloved friend.

DISTINGUISHED PERSONALITIES

Weaver, Lawrence

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INTRODUCTION

Lawrence C. Weaver is one of the true patriarchs of clinical pharmacy. He was Dean of The College of Pharmacy at the University of Minnesota from 1966–1984 and 1994–1995. He initiated the post-B.S. Pharm.D. program in 1971. His international efforts have resulted in the establishment of clinical pharmacy educational programs in Europe, Africa, the Middle East, and the Pan-Pacific Rim. He led efforts to facilitate the worldwide access and distribution of orphan drugs required to treat patients with rare diseases while working for the Pharmaceutical Manufacturers Association from 1984–1989. In 1997, the University of Minnesota recognized his life-long contributions and leadership by naming the Pharmacy and Nursing building, Weaver–Densford Hall, in his honor.

PERSONAL BACKGROUND

Born January 23, 1924 in Bloomfield, Iowa to Wilbur and Faye Weaver, Lawrence C. Weaver was the eldest of three sons. He spent his childhood living and learning on the family farm and one-room school in southeastern Iowa. He joined the U.S. Air Force in 1942, served as a pilot, and rose to the rank of Captain. He flew in the China–Burma–India theatre and earned the Distinguished Flying Cross and an Air Medal. He returned to the States and earned a Bachelor's degree in Pharmacy from Drake University in 1949.

Larry married Delores (Dee) Hillman on September 9, 1949 in Oakland, California. Dee and Larry adopted and raised four children. Their extended family includes the thousands of pharmacy students throughout the world who have benefited from their personal support and guidance.

PROFESSIONAL ACHIEVEMENTS

After earning his Ph.D. in pharmacology from the University of Utah in 1953, Weaver joined the Pitman–Moore Company. He was the Head of Biomedical Research that included both human and veterinary research in pharmacology, microbiology, and parisitology. In 1964 while with Pitman–Moore (now a division of the Dow Chemical Company), Weaver organized and directed the Biohazards Department where he pioneered efforts in the emerging field of biological hazard (environmental) control.

Weaver's research interests in Pharmacy Education, Healthcare Delivery Systems, and Drug Combinations in Therapy, among others, led him to become the fourth Dean of the College of Pharmacy at the University of Minnesota in 1966. As the Dean of Pharmacy and Professor of Pharmacology in the School of Medicine, Weaver was farsighted enough to bring the pharmacy program at the University of Minnesota into the newly organized Health Sciences Center in order to foster interdisciplinary education and the clinical role of pharmacists. He introduced the two-year post-Baccalaureate program that became the basis for the Pharm.D. program. His vision of clinical pharmacy faculty and Pharm.D. students practicing and learning side-by-side with physician faculty and medical students became the platform for the future expansion and growth of the Pharm.D. program. His 10-year effort to join the Medical, Dental, Nursing, and Public Health programs on the campus of the University Hospital culminated with approval of funding for the Health Sciences Unit F building, which was built in 1981. He lead the effort to secure the over $20,000,000 required to build the nine-story building that houses the College of Pharmacy and the School of Nursing. The building was dedicated in 1996 when it was renamed Weaver–Densford Hall to honor Lawrence C. Weaver and Katherine Densford, the first Dean of the School of Nursing at the University of Minnesota.

Dean Weaver initiated the two-year post-Baccalaureate Pharm.D. program at the University of Minnesota in 1971. As the Dean of one of the first clinical pharmacy programs in the United States, Weaver collaborated with the Medical School to have his Pharm.D. students take pathophysiology classes with the medical students in order to both bring essential disease-related content to the

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pharmacy curriculum and to introduce medical students and faculty to clinical pharmacists. Dean Weaver was relentless in his belief that clinically prepared pharmacists could substantially improve the quality of health care. Under his leadership, in 1981 the Pharm.D. curriculum expanded from a two-year post B.S. program to a six-year Pharm.D. degree. Weaver felt that the curriculum should be designed to increase the clinical skills of all entry-level pharmacists. The new curriculum featured courses in pharmacokinetics and biopharmaceutics, as well as a pathophysiology and therapeutics course sequence taught for the first time entirely by clinical pharmacy faculty. Larry, as he is known by the thousands of students he taught and mentored, brought a vision of improved patient care through clinical pharmacy service that inspired students and clinical faculty for over three decades.

After 18 years as the Pharmacy Dean, Weaver left academia to become the Vice President of Professional Relations for the Pharmaceutical Manufacturers Association (PMA). In his role as the Executive Director of the PMA Commission for Rare Diseases, he championed the goal of making orphan drugs available to patients throughout the world who suffer from rare diseases. His efforts have resulted in over 800 drugs, serums, and vaccines being designated as "orphans" by the Food and Drug Administration. His continued efforts to help those in need of orphan drugs required interaction with federal agencies, pharmaceutical firms, researchers, practitioners, and patients and their families. He has been described as a peacemaker and a matchmaker who can bring industry, academia, and families together.

WORLD RECOGNITION

Larry Weaver is recognized around the world for his leadership and advocacy for clinical pharmacy. He assisted international pharmacy leaders from several countries in the design and implementation of clinical pharmacy programs. Throughout the late 1970's and 1980's, Weaver served as an educational consultant and advisor to numerous countries including Dalhousie University, Royal Danish College of Pharmacy, Welsh School of Pharmacy, Universities in Cairo, Tanta, Nairobi, Zimbabwe, Republic of South Africa, Amman Jordan, and the University of Sains Malaysia. In his role as Education Advisor to the University of Riyadh, Saudi Arabia, Weaver assisted in the conversion of the curriculum from the European System to the credit system and to the use of English as the language for teaching in pharmacy. He worked with Saudi faculty to establish clinical pharmacy courses and initiated the first continuing education program in pharmacy.

Larry Weaver is one of pharmacy's most well respected leaders due to his endless efforts to establish clinical pharmacy as the standard for American pharmacy education. He served in leadership roles including President and Vice President of both the Academy of Pharmaceutical Sciences of the APhA and the American Association of Colleges of Pharmacy. He also served as a member of first Board of Trustees of the Research Institute for the American College of Clinical Pharmacy.

RECENT SERVICE

In 1994, Weaver was summoned back to the Deanship of the College of Pharmacy at the University of Minnesota. He served in this capacity for two years and directed the implementation of the new entry level Pharm.D. curriculum. Since 1996, Dean Emeritus Lawrence C. Weaver has been a member of the Peters Institute of Pharmaceutical Care, developing educational and research programs in pharmaceutical care practice. Larry Weaver has had a distinguished career in pharmacy.

PROFESSIONAL ORGANIZATIONS

World Health Organization

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INTRODUCTION

The World Health Organization (WHO) is a United Nations specialized agency, which has 193 member countries. Its objective is the attainment by all people of the highest possible level of health. WHO has four main constitutional functions: to act as the directing and cooperating authority on international health issues; to provide assistance including maintaining epidemiological and statistic services; to promote research; and to develop and promote international norms or standards. The work of WHO is carried out by the World Health Assembly, the Executive Board, the Secretariat, and six regional offices.

HISTORY

The origin of WHO dates from the need for international preventive and control measures against epidemics such as cholera and plague, particularly in the European region, during the nineteenth century. Later, different cooperation arrangements were adopted and the International Agency for Public Hygiene was established in Paris (1907) to control epidemics and communicable diseases. Later the Health Organization of the League of Nations was set up in Geneva (1919). During the San Francisco Conference, which laid the foundations for the United Nations Organization (1945), it was decided to establish a permanent and autonomous international organization for health issues. In June 1946, an international health conference convened in New York by the UN Secretariat approved the creation of WHO. Its specific Constitution, following a ratification by 61 states, was set into place on April 7, 1948 (now marked as World Health Day). WHO, once the main player, is now one of many UN and other organizations or institutions concerned with health. The World Bank plays an increased financial and technical role, bilateral agencies and the private sector as well, such as the non governmental organizations, make significant contributions to international health.[1]

MISSIONS

With 193 member states currently, WHO has a constitutional mandate to direct and coordinate international efforts in relation to health, to promote technical cooperation among nations, to develop and transfer appropriate health technology, and to set global standards for health. Finally its overall mission is the "attainment by all people of the highest possible level of health," with special emphasis on closing the gaps within and among countries. According to WHO, health is defined as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." This ambitious and idealistic objective was summarized by the slogan "Health for All by the Year 2000."[5] In spite of major achievements (e.g., smallpox eradication declared in 1980; polio and guinea-worm disease on the threshold of eradication; leprosy, lymphatic filariasis and neonatal tetanus targeted for elimination), this "health for all" objective is currently challenged by the spread of the HIV/AIDS pandemic; by the persistence of malaria and many other parasitic diseases; by tuberculosis, which is still a major health priority since 1948; and increasing gap between least developing and developed countries (e.g., average life expectancy is 38.5 in Zambia and 79.5 in Sweden; 2 million children die each year from diseases for which vaccines exist; etc.), and the growing impact of globalization on health issues.[2]

To carry out its missions, WHO is endowed with a decentralized system including a central office (the Geneva headquarters) and six regional offices. At the central level, the World Health Assembly (WHA), a deliberating body which represents the 193 member states, sets the policy, approves the budget, and passes agreements or conventions (to be adapted by the member states). In addition, it can issue international health regulations for technical matters (WHO normative functions) directly and compulsorily applicable to member states. The WHA elects the Executive Board composed of 32 members and appoints a Director-General (DG) to give effect to the decisions and policies of the Health Assembly and to

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advise it. At the decentralized level, six regional offices have been created by the WHA to take local specificities into account.

The funding for WHO comes from member countries and dues are based on their national economies and as well on extra-budgetary funds allocated by countries or institutions earmarked for specific purposes or projects. The total budget for WHO was about $1.3 billion in 2000, and this amount has not increased in recent years despite increased demands on the organization. One problem has been the persistent failure of some major funders to fully pay their assessed dues and the fluctuation in member states' voluntary contributions.

FUNCTIONS AND ACTIVITIES

Normative and Harmonization Functions

According to articles 2 and 21 of its Constitution, WHO has a regulatory power for developing, establishing, and promoting standards and nomenclature (International Health Regulations). These regulations are limited to technical matters: health and international quarantine regulations; health codification for international travels; international nomenclature of diseases; nomenclature and standards with respect to the safety, quality, and efficacy for pharmaceutical, biological, and similar substances, including their advertising and labeling; international standards for biological; international cooperation for health statistics; food standards (through the joint WHO/FAO "Codex Alimentarius" Commission); and dependence and misuse of drugs regulations.

Numerous matters related to public health and biomedical sciences can be the subject of Recommendations but without compulsory nature contrary to international regulations. WHO Recommendations may be endorsed by the WHA under article 23 or by the Executive Board and issued as resolutions (e.g., WHA 52.19 Resolution on the revised drug strategy, 1999).

They may be issued by an individual WHO Expert Committee and included in their reports (e.g., WHO Expert Committee on specifications for pharmaceutical preparations, technical report number 863, 1996), or issued as special WHO publications under the authority of the DG (e.g., Globalization and access to drugs, health economics and drugs, 1998). Most of the WHO Recommendations are directed at developing countries (e.g., the "International Pharmacopoeia").

In practice, WHO standards, guidelines, and recommendations serve as advice to member states. They can however, be adopted as legally binding national regulations if a national authority so desires, or they may form the basis of national standards and technical regulations.

Operational Activities

In support of its objectives, WHO develops a wide range of operational activities to provide appropriate technical assistance, to stimulate and advance work on prevention and control of epidemic, endemic, and other diseases, and to cooperate with governments for strengthening health services. WHO works closely with other UN organizations or programs [e.g., Food and Agricultural Organization (FAO), United Nations Children's Fund (UNICEF), United Nations Development Program (UNDP), and the World Bank], and maintains working relationships with bilateral agencies and intergovernmental and nongovernmental organizations (NGOs). In addition, nearly 1200 health-related institutions are officially designated as WHO collaborating centers. More than 50 affect the pharmaceutical sector, such as the Uppsala Monitoring Center for pharmacovigilance issues.

Communicable diseases

Approximately, 56 million people died in 1999, of which 14 million died from infectious and parasitic diseases with more than 90% occurring in developing countries. (In rank order: acute lower respiratory infections, HIV/AIDS, diarrhea, tuberculosis, malaria, measles.) To prevent and control them, WHO developed and launched activities and programs in the field such as the Expanded Programme on Immunization (EPI) in collaboration with UNICEF (EPI targets are poliomyelitis, measles, diphtheria, whooping cough, tetanus and tuberculosis); the Onchocerciasis Control Programme; the global programs on AIDS; the "Roll Back Malaria" program; the Africa 2000 Initiative on water supply and sanitation issues; and others.

Noncommunicable diseases

Chronic diseases such as cardiovascular diseases, cancers, and respiratory diseases, affect both developed and developing countries. WHO's priorities are an integrated and coordinated approach to prevent, treat, and cure through disease-specific interventions, global campaigns to encourage healthy lifestyles (e.g., worldwide no-tobacco day), and healthy public policies promotion.

Emergency and humanitarian action

The emergency and humanitarian division of WHO/HQ plays an active role in assisting the member states in

tackling health emergencies. It relies on its emergency preparedness and response programs, providing countries timely support to tackle acute emergency and supporting them during the reconstruction phase. WHO can assure coordination with donors (through consolidated appeals), UN agencies (e.g., UNHCR, UNICEF, WFP) and other entities involved (e.g., ICRC, NGOs). To face large movements or sudden influxes of refugees which create

Table 1 WHO Core functions in pharmaceuticals

Core functions	Objectives	Components	Tools
National drug policy	• Help countries formulate and implement a national drug policy (NDP) and integrate the work into their national health system in ensuring commitment of all stakeholders.	• Implementation and monitoring of NDP. • Health system development supported by essential drugs policies and programs.	Guidelines for developing a NDP. Indicators for monitoring NDP, 1999. Essential Drug List (EDL), 11th list, Nov 1999.
Access to essential drugs	• Ensure equitable availability and affordability of essential drugs.	• Access strategy and monitoring for essential drugs (in particular for priority health policies and newly developed drugs). • Financing mechanisms and affordable essential drugs. • National and local public sector drug supply systems and supply capacity.	Standard indicators to measure equitable access. Drug price information. Operational principles for good pharmaceutical procurement, 1999. Good drug donation practices, 1999. The new emergency health kit, 1998.
Quality and safety of drugs	• Ensure the quality and safety and efficacy of all medicines. • Put into practice regulatory and quality assurance (QA) standards.	• Norms, standards, and guidelines for pharmaceuticals. • Drug regulation and QA systems. • Information support for pharmaceutical regulation. • Guidance for control and use of psychotropics and narcotics.	Norms, standards and guidelines developed and updated. Quality control specifications. Drug nomenclature and classification. WHO certification scheme on the quality of pharmaceuticals. Good manufacturing practices (GMP). Good laboratory practices (GLP). Good clinical practices (GCP), 1995. The International Pharmacopoeia, 1994.
Rational use of drugs	• Ensure therapeutically sound and cost-effective use of drugs by health professionals (prescribers, nurses, and dispensers) and consumers.	• Rational drug use strategy and monitoring through national strategies. • National standard treatment guidelines, EDLs, educational programs. • Independent and unbiased drug information system.	Guide to good prescribing, 1994. Medical products and the internet: a guide to finding reliable information, 1999. The use of essential drugs. 8th report of the WHO expert committee.

(From Ref. [5].)

immediate needs for basic health services (e.g., Rwanda in 1994 and Kosovo in 1999), WHO has collaborated with most international agencies and NGOs to developed a standard kit of essential medicines, medical supplies, and basic equipment called the "New Emergency Health Kit." The same interagency group has developed guidelines for obtaining the maximum benefit from drug donations through the "Guidelines for Drug Donations" development.[3]

Health Research

Research activities range from epidemiological surveillance for new and re-emerging diseases, the tropical disease research program (WHO/TDR in Geneva, Switzerland) tackling epidemiological research, medicines research and development (on malaria, trypanosomiasis, leishmaniasis, Chagas disease, etc.), cancer research (e.g., International Centre for Cancer Research in Lyon, France), and monitoring of the progress of genetic engineering laboratories.

WHO-Specific Activities in the Pharmaceutical Sector

While medicines alone are not sufficient to provide adequate healthcare, their health impact is remarkable. The economic incidence of medicines is substantial, representing less than 20% of total public health expenditure in developed countries ($138 per capita), but 25–66% in developing countries ($8–12 per capita). It is clear that priorities need to be set in order to maximize the health benefits from limited public spending.[4] The rational use of medicines, their accessibility and quality and the development of national drug policies are therefore critical and constitute the four main areas of work for WHO.[5] This is the mission of the "Department of Essential Drugs and Medicines Policy" created within the Health Technology and Pharmaceuticals cluster (EDM/HTP, Geneva Headquarters), in close collaboration with the six regional offices and other stakeholders (Table 1).

Despite the obvious medical and economic importance of pharmaceuticals, there are still widespread and persistent problems:

1. *Lack of access*: Over one-third of the world population still has no regular access to essential medicines.
2. *Poor quality of medicines*: Between 10 and 20% of sampled medicines fail quality control tests in developing countries.
3. *Irrational prescribing and use*: Up to 75% of antibiotics are prescribed inappropriately.
4. *Lack of pharmaceutical research and development* for tropical diseases.[6,7]

Reasons are complex and go beyond simple financial constraints. (In most developed countries, virtually 100% of the population has health insurance; median coverage is 35% in Latin America and less than 10% in Africa and Asia.) Changes in the patterns of disease (e.g., rise of HIV/AIDS, increasing drug resistance for malaria and tuberculosis, increase in chronic diseases and diseases of the elderly) and drug demand also represent major challenges and contribute to increased spending on drugs and growing pressure on health resources. The potential impact of international trade agreements, such as the World Trade Organization Agreement on trade-related aspects of intellectual property rights (WTO/TRIPS), is also a matter of growing concern with relation to access to new essential medicines (e.g., antiretroviral drugs, antibiotics, second-generation vaccines).[8] It highlights the need for strengthened international cooperation and a stronger public health response.

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World Health Organization Essential Drug List

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INTRODUCTION

Health is a fundamental human right. Access to healthcare, which includes access to essential medicines, is a prerequisite for realizing that right. First introduced in 1975, the concept of essential drugs (called "essential medicines" since 2001) is now widely accepted as a pragmatic approach to providing the best of evidence-based and cost-effective healthcare. This is a global concept that can be applied in any country, in private and public sectors, and at different levels of the healthcare system. The first model list of essential drugs (EDL) was prepared by an Expert Committee and published by WHO in 1977 and now includes 306 active ingredients (11th edition of November 1999).[1] The list does not exclude all other medicines but rather focuses on therapeutic decisions, professional training, public information, and financial resources. The essential medicines represent the best balance of quality, safety, efficacy, and cost.

THE ESSENTIAL MEDICINES CONCEPT

Virtually no system in the world offers unlimited access to all medicines and vaccines, even in the wealthiest countries. Careful selection of priority medicines is indispensable and should be based on considerations of quality, safety, efficacy, cost-effectiveness, and local appropriateness. The concept of essential medicines (a term that describes all pharmaceutical preparations used in clinical healthcare practice) is that a limited number of carefully selected medicines based on agreed standard treatment guidelines leads obviously to a better supply of medicines, to more rational prescribing and dispensing, and to the most cost-effective use of health resources. In developing countries, the essential medicines concept has also provided a means by which governments and donor agencies can plan and monitor drug procurement. It is within this framework that in 1978 a conference on primary healthcare (PHC) was jointly convened by WHO and UNICEF at Alma-Ata, Kazakhstan to confirm that the provision of essential medicines was one of the eight components of PHC. Essential medicines are defined as those that "satisfy the healthcare needs of the majority of the population and they should therefore be available at all times in adequate amounts and in appropriate dosage forms and at a price that individuals and the community can afford." Their safety and relative cost-effectiveness are also major considerations in the choice.[2]

Since the first WHO EDL was published 25 years ago, more than 146 countries have adopted national EDLs, the WHO list serving as a model and not as a global standard. The list is biennially updated by a WHO Expert Committee, and the current eleventh revision (November 1999) includes 306 active ingredients (medicines, vaccines, contraceptives, insect repellents, and diagnostic agents) specified by international nonproprietary names (INN) or generic names—50% more drugs than in 1977 and of which 250 are included in WHO clinical guidelines. The list is divided into a main list, a complementary list, and there is a separate category of "reserve antimicrobials." However, selection and dissemination of the list are not by themselves sufficient for ensuring rational drug use. Guidelines (e.g., clinical therapeutic guidelines, guide to good prescribing, WHO ethical criteria for medicinal drug promotion, drugs and therapeutic committee), professional training (e.g., training courses organized by the International Network for rational use of drugs, INRUD, Washington, D.C.), formulary manuals and independent drug information centers (e.g., drug bulletin publications with the aid of the International Society of Drug Bulletins, ISDB) are needed for health professionals to put lists into clinical practice.

Over the past 25 years, the model list has led to a global acceptance of the concept of essential medicines as a powerful means to promote health equity. By the end of 1999, 156 WHO member states had official essential medicines lists, of which 127 had been updated in the previous five years.

SELECTION OF ESSENTIAL MEDICINES

The selection of essential medicines is one of the seven key components of a national drug policy (the other com-

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ponents being legislation, regulation and guidelines, access to essential medicines, quality assurance, rational use of medicines, research, and human resources development). Usually, market approval of a pharmaceutical product is granted by drug regulatory authorities on the basis of efficacy, safety, and quality, and rarely on the basis of comparison with other products already on the market or cost. Different criteria are used for the selection of essential medicines; e.g., medicines with adequate evidence of efficacy and safety; relative cost-effectiveness with comparisons between medicines (comparative efficacy and safety, meta-analysis) and considerations of the total cost of the treatment; pharmacological criteria (e.g., pharmacokinetic properties, bioavailability, galenic stability); and formulations as single compounds, with fixed-ratio combination products being acceptable only when the combination has a proven advantage (e.g., therapeutic effect, adherence to treatment improvement).

There may still be oppositions to the use of the essential medicines list. Physicians may see it as questioning their prescription freedom, pharmacists may be worried about the financial implications, while manufacturers may fear a market erosion, and consumers may think that they are being offered second-rate cheap medicines. These concerns must be considered and addressed, and this is why the selection process should be consultative, and why education plays an important part. In fact, an essential medicines policy is nothing but an extension of the selective exercise carried out by the state, on behalf of the rights a community has to useful and safe products, to identify medicines that deserve marketing approval. The principle of convenience is under consideration in an increasing number of countries, especially as the pharmaceutical industry becomes more prolific, more complex, and uses products that are increasingly powerful and, consequently, more hazardous.

ACCESS TO ESSENTIAL MEDICINES

Despite important achievements, the lack of regular access to essential medicines still remains a major health problem, recently highlighted by the magnitude of the HIV/AIDS pandemic [e.g., in the 11th EDL, while 15 drugs of importance to HIV-related opportunistic infections are present, only two antiretroviral drugs (ARVs) are listed for the prevention of mother-to-child infection, and no ARVs are listed for the HIV treatment itself because of their high costs and prerequisites for treatment implementation and compliance]. These problems are greatest in low-income countries, but middle- and high-income countries are also increasingly facing difficult therapeutic and economic decisions.

To ensure access to essential medicines, WHO has defined a strategy by focusing on four key objectives: rational selection and use (through a strengthening of links between WHO EDL and standard therapeutic guidelines for priority diseases); affordable prices (through good procurement practices and indicative cost information policies, and TRIPS safeguards as parallel import and compulsory licensing for new essential medicines); sustainable financing, national spending on pharmaceuticals varying from $2 to $400 per capita and per year (through public funding and a health insurance scheme to maximize risk-pooling and equity shifts); and reliable health systems ensuring a proper diagnosis and treatment and a responsible supply system.

Despite the obvious medical and economic importance of essential medicines, there are still problems with lack of access, poor quality, and irrational use. In many health facilities in developing and in developed countries, essential medicines are not used to their full potential.[3] While the EDL is regarded as a key aspect of global health and economics, the WHO EDL is, for the past few years, at the center of debates with respect to access issues (such as new essential medicines for HIV/AIDS, tuberculosis, and bacterial infections) and availability issues (such as the lack of pharmaceutical research and development for tropical diseases, most of the current tropical pharmacopoeia having been driven by colonization requirements during the first part of the 20th century).[4] In 2001, still one-third of the world's population (over 50% in the poorest part of Africa and Asia) does not have regular access to the most vital essential medicines.

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