# Gene Therapy

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## INTRODUCTION

Extraordinary in its scope and significance, the human genome project (HGP) has revealed the complete 3 billion base pair sequence that includes the estimated 35,000 genes of the human genetic blueprint.[1]

One important outgrowth of the HGP is the development of technologies for the transfer of therapeutic genes to humans. Undoubtedly, improved biomedical technology, coupled to a better understanding of the genetic basis for most human diseases, is resulting in the rapid identification of new disease targets and the development of innovative gene therapy strategies.[2]

The number of clinical trials involving human gene therapy has dramatically increased since the initiation of the first approved trial in the United States to treat adenosine deaminase (ADA) deficiency in 1990.[3] Since this time, more than 3500 patients have been enrolled in trials worldwide, with more than 2400 in the United States.[4] The pharmaceutical industry is actively supporting gene-based therapy by investing billions of dollars, and most major academic medical centers have developed gene therapy programs.[5] The majority of active trials involve gene therapy for malignancy (68%), AIDS (18%), and cystic fibrosis (8%).[4]

Valuable experience has been gained through recipients of gene therapy, documenting the technical feasibility of human gene therapy and demonstrating, in most trials, a relative lack of treatment-related adverse effects. In particular, patients receiving both ex vivo gene therapy, a procedure where cells are removed, transfected, and placed back into the host, and in vivo gene therapy, in which the gene vector is placed directly in the patient's body, have tolerated the administration procedures without acute adverse effects. Despite this, close attention has focused on the relative lack of proven efficacy from preliminary phase I and II trials. In general, clinical trials have demonstrated short-term expression of the gene product, overall low efficiency of gene expression in the tissue(s) of interest, and lack of clinical efficacy. For these reasons, the entire field of gene therapy has been critically evaluated at the National Institutes of Health (NIH). In particular, conclusions from one panel strongly encouraged a redirection back to basic scientific research, with a particular emphasis on improving vector design.[6]

## ASPECTS OF GENE DELIVERY

### Definition

Gene delivery is the introduction of genes or cells containing genes foreign to the human body for the purposes of prevention, treatment, diagnosis, or curing disease.

The introduction of exogenous deoxyribonucleic acid (DNA) into mammalian cells for therapeutic intention can be accomplished by several techniques that include physical, viral, and nonviral methods, each with advantages and disadvantages. The majority of clinical experience is derived from viral and nonviral vectors and is therefore discussed. In all cases, several fundamental attributes are required for a gene therapy vector to be suitable for human use. The vector should be safe to the recipient, capable of efficient gene delivery and expression in the targeted tissue, and capable of mass production for human use. Based on these major criteria, the "ideal" gene delivery system has yet to be identified. Of the more than 425 clinical trials conducted worldwide, the field remains dominated by retroviruses (37.6%), adenoviruses (20.2%), and plasmid-based, nonviral vectors such as cationic liposomes (17.6%).[4] Numerous other vectors and techniques are being used in phase I trials, but alone they do not comprise greater than 5%


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Table 1 Comparison of viral transfer techniques

| | Retrovirus | Adenovirus | Naked DNA | Liposome |
|---|---|---|---|---|
| Genome transfer | RNA | DNA | DNA | Either |
| Virus titer | $10^6$–$10^9$ | $10^{11}$–$10^{12}$ | NA[a] | NA |
| Purification | Difficult | Yes | Yes | Yes |
| Maximum size | 8 kB | 8 kB | 50+ kB | 50+ kB |
| In vivo | No | Yes | Yes | Yes |
| Integration | Yes | No | Low | Low |
| Efficiency | High | Very high | Moderate | Low |
| Safety issues | Mutagenesis | Immune reaction | ? | ? |
| Nondividing | No | Yes | ? | ? |
| Limitation | Cell division required | Transient expression | Low efficiency | Low efficiency |

Key: DNA, deoxyribonucleic acid; RNA, ribonucleic acid.
[a]NA, not applicable.

of the market share and therefore are not reviewed. Each of the three major categories of vectors used in clinical trials has unique attributes and limitations that include, but are not limited to, DNA-carrying capacity, tropism for target cells, in vivo transfer efficiency, duration of gene expression, and potential to induce inflammation (Table 1).

## VECTORS

The fundamental goal of gene therapy is to correct a singular genetic defect in the cells responsible for causing disease in the host. To accomplish this, the gene of interest must be isolated and packaged into a delivery vector and then introduced to the recipient. The therapeutic gene must enter into the cell intact and travel to the nucleus where it interacts with the host cell machinery, ultimately being turned into a therapeutic protein (Fig. 1). A major limitation of most gene therapy is poor transfer efficiency of the gene to the target cell population. To overcome this obstacle, scientists have turned to the most efficient, naturally occurring gene vectors known to human kind—viruses. The primary objective is to produce virus-based vectors that retain the essential "gene delivering" features, while also eliminating characteristics associated with infection and host toxicity. Due to the pathogenic nature of viruses, substantial effort has also been devoted to the development of synthetic vectors that chemically mimic the natural gene delivery features of viruses. The most common viral and nonviral vectors used in clinical trials share certain attributes but are quite distinct in many ways. As is discussed, these features have a substantial impact on therapeutic strategies and, in certain situations, limit the use of vectors in different disease states.

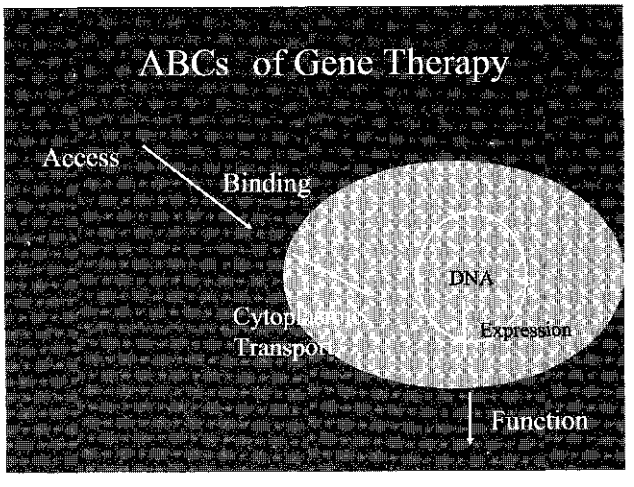


Fig. 1 Overview of gene therapy.

### Retroviral Vectors

Retroviral vectors work by reverse transcribing their viral ribonucleic acid (RNA) genome, which includes the therapeutic gene insert, into a double-stranded DNA that becomes stably incorporated in the host cell genome (Fig. 2).[7] The virus components associated with replication are removed, thereby preventing infectious risk to the host and providing space for the inserted gene. The simplest type of retroviral construct is the single gene vector. In this system, the entire gene cassette of a functional gene is placed in the retroviral construct with gene expression controlled by the retrovirus gene promotor. The most widely used retroviral vectors in cli-

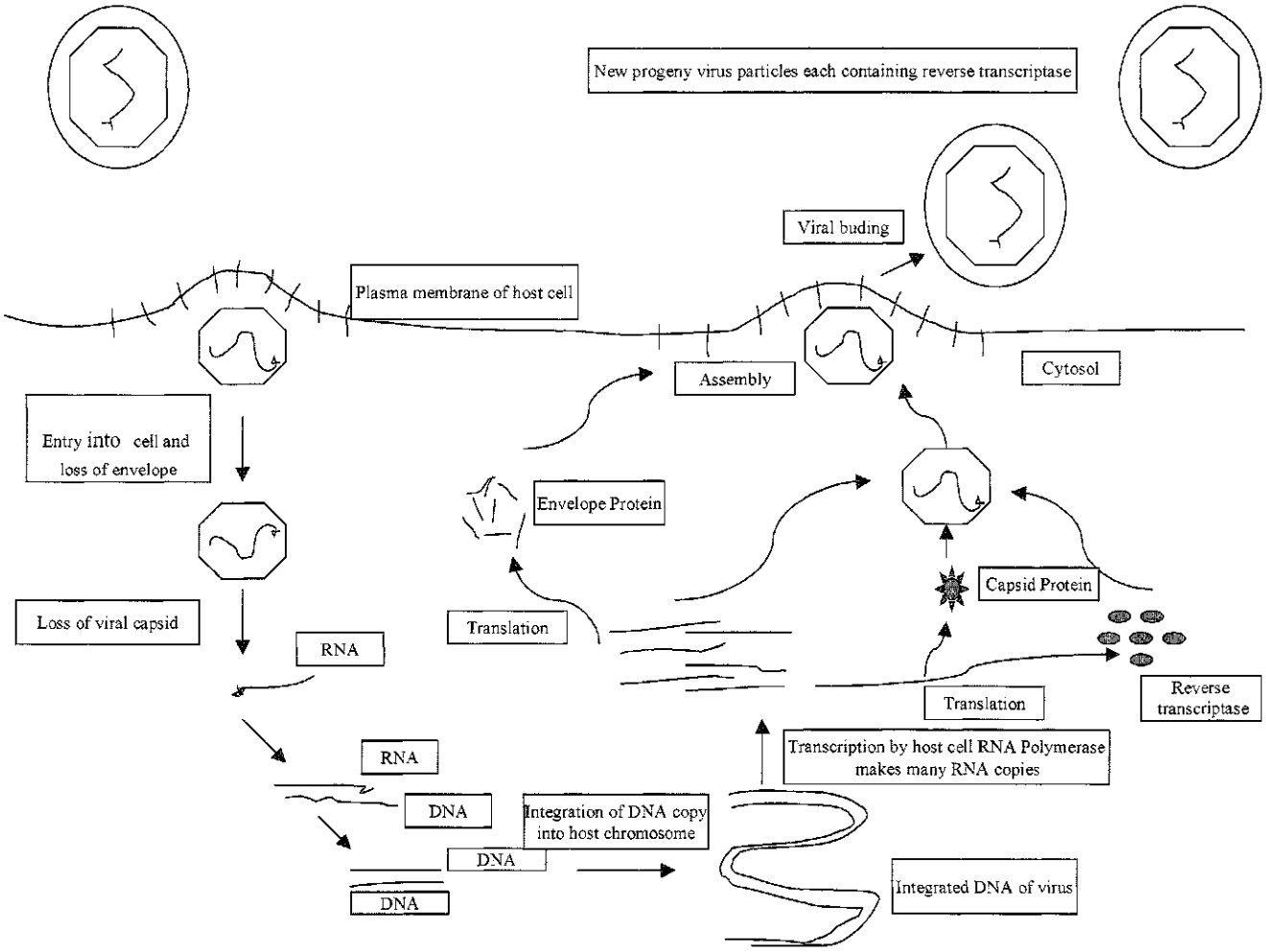


**Fig. 2** Overview of retroviral vector administration.

nical trials are the double gene constructs. They possess the therapeutic gene, as well as a second marker gene, such as the neomycin phosphotransferase gene. A significant advantage of the double gene construct is that cells expressing the gene marker protein can be selected in culture and then readministered to the patient. Retroviruses integrate the gene insert into the host cell so they are particularly suited for chronic diseases that require long-term gene expression to correct the disease phenotype.[8] One of the biggest limitations of retroviruses is that they are relatively unstable following systemic administration.[7] For this reason, most human applications require removal of the target cells for ex vivo gene transduction. Retroviral vectors also require that cells undergo replication during transfection to stably integrate the gene of interest. Therefore, most clinical protocols involve induction of cell replication during ex vivo cell culture to enhance transfection efficiency. However, many cells exist in a differentiated state; that is, they do not replicate and may not readily be removed from the host, thereby preventing the use of retroviruses. An additional theoretical limitation of retroviral vectors involves insertional mutagenesis. Integration of the genetic material is random and may occur anywhere in the host genome. It is therefore theoretically possible that random integration could disrupt expression of other key proteins.

## Adenoviral Vectors

The most extensively used adenoviruses are serotypes 2 (Ad2) and 5 (Ad5) because both are not associated with serious infectious disease in humans.[7] Similar to retroviral vectors, elements of adenovirus DNA genome are removed to prevent replication once inside the

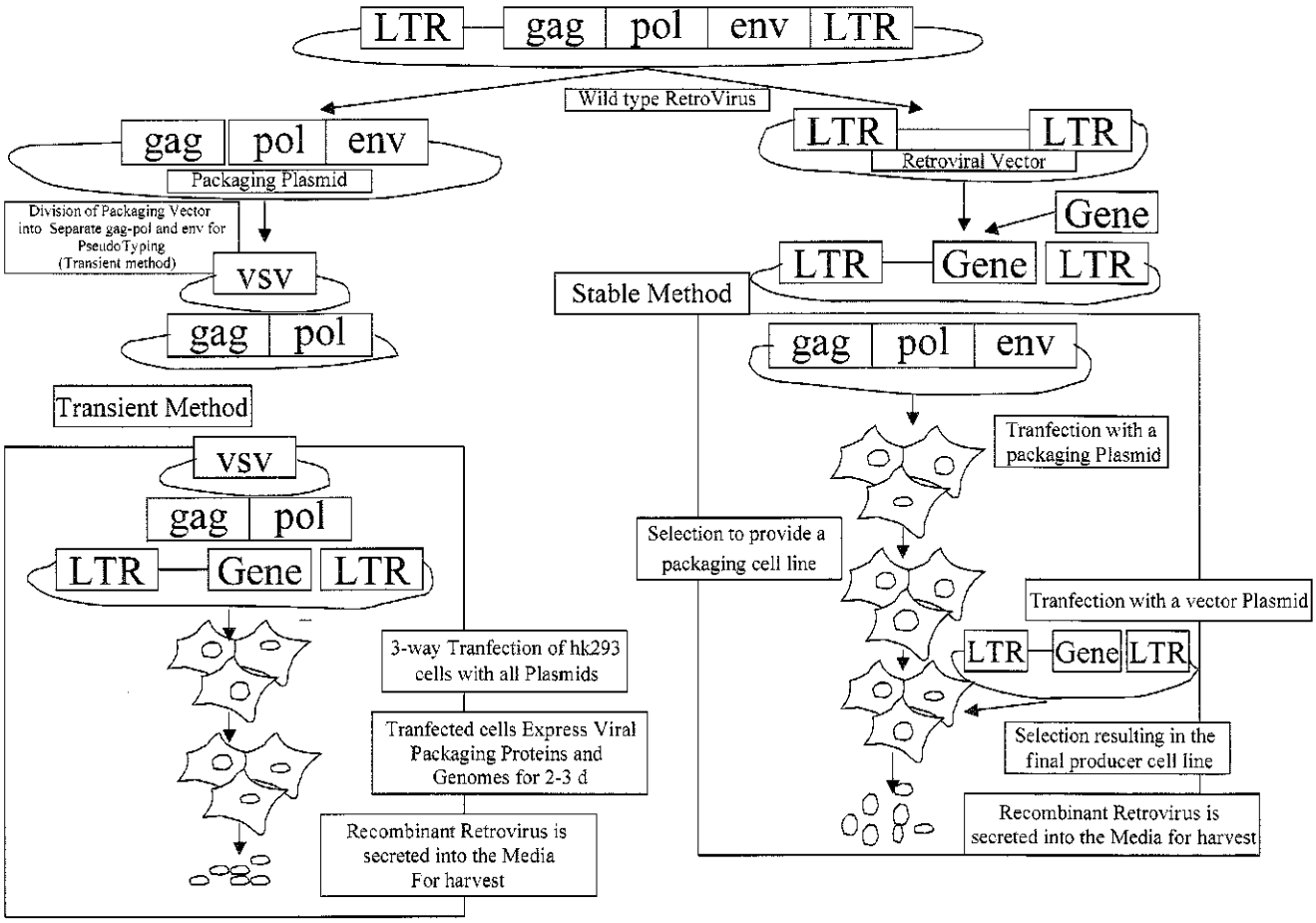


**Fig. 3** Overview of gene therapy preparation.

mammalian cell. Removal of these elements also provides space for insertion of a therapeutic gene (Fig. 3). An additional reason for tailoring the adenoviral vector genome is to eliminate the expression of antigenic viral proteins that precipitate a host inflammatory response. A distinct advantage of adenoviral vectors is that they have broad cell tropism and can transfect nondividing cells. They can also be administered systemically via the intravenous, intramuscular, and intranasal routes. From a formulation standpoint, adenoviral vectors are superior because relatively high titers can be achieved ($10^{10}$ colony-forming units/milliliter) to ensure convenient dosing in a minimal volume. Despite these attributes, the adenoviral vectors possess features that limit their utility. Unlike retroviral vectors, the gene cassette resides in the nucleus independent of the host cell genome. Because stable integration is not achieved, expression of the gene product is transient. This can be an advantage if temporary expression will correct the defect; however, in most strategies, persistent gene expression is required to correct the underlying disorder. Therefore, maintenance dosing of the vector is required to sustain therapeutic benefit to the patient. In this situation, the other major limitation of the adenoviral vectors, host toxicity, becomes a consideration.[9,10] The adaptive host response becomes important because memory is generated against the vector, thereby amplifying the immune response upon repeat administration and reducing the duration of gene expression. For these reasons, substantial effort is underway to eliminate adenoviral vector-induced inflammation by selectively removing key antigenic determinants associated with the host response. The fundamental challenge is to make a safe vector without removing the ability of the modified virus to efficiently deliver its genetic payload.

### Plasmid-Based Vectors

Successful transfection depends on both the efficiency of DNA delivery to the cell (e.g., the fraction of DNA getting into the nucleus) and the efficiency of DNA expression (e.g., the amount of gene that is transcribed). In theory, the nonviral vector systems are attractive candidates due to their potential versatility. Despite their use in clinical trials, the lipid-based systems have several drawbacks. Many targeting strategies have been developed but few have worked in vivo. Once the nonviral plasmid expression cassette enters the nucleus, it exists as an episome, similar to the adenoviral vector; therefore, transient expression is achieved. In general, the lipid-based systems have a superior safety profile and gene therapy recipients tolerate high doses without any notable adverse events. The "Achilles heel" of the nonviral vectors have been inefficient introduction and expression of DNA into target cells when compared with viral vectors. Another major obstacle with these macromolecular aggregates that prevents efficient gene delivery in the host is opsonization.[11] They are recognized as large, hydrophobic macromolecules and are cleared within minutes from the circulation. Therefore, the fundamental challenge of the plasmid-based systems is to improve transfection efficiency in vivo. This will likely be achieved by incorporating more features of the most efficient gene delivery systems, viral vectors, while also maintaining a superior toxicity profile.

## VECTOR PRODUCTION AND ADMINISTRATION

Large-scale production and purification of gene therapy vectors is critical in advancing the clinical utility of this new class of medicine. Under ideal circumstances, a highly purified vector stock should be manufactured with a relatively stable shelf-life, in a dosage form that is easy to dispense and ultimately administer to the patient. The ideal system does not currently exist for any of the vectors used in clinical trials.[12]

In general, vector production is analogous to generating a recombinant protein. The product is a macromolecule that must be derived from cultures of living prokaryotic or eukaryotic cells and purified on a large scale. The viral components required during vector production can be defined as cis and trans elements. Cis elements, for example, transcription initation promotors, must be carried by the virus itself. Trans elements are removed from the original viral genome to eliminate infectious risk but are required during production to formulate a functional viral vector. The trans elements are provided by a packaging mammalian cell line, thereby providing the necessary elements to build a functional vector during viral production but without producing an infectious viral particle. Distinct production, formulation, and patient administration skills are required for each unique product. From a manufacturing perspective, no standardized test currently exists that can be used to predict virulence or pathogenicity of each unique vector. Currently, each lot of vector must be individually evaluated by the manufacturer. All vectors are tested on three basic principles in preclinical development and large-scale production before use in clinical trials. Each vector must demonstrate evidence of safe vector system design, appropriate production of vector stocks under good manufacturing process guidelines, and documentation of purity under good laboratory practice guidelines. One review discussed this topic extensively.[13]

The final product must be free of adventitious agents that primarily include bacterial or viral pathogens and other biologic contaminates contributed during cell culture, such as DNA from prokaryotic or eukaryotic host cells and endotoxin. Purity testing for these factors must be performed throughout the production procedure and meet defined criteria before administration into humans.

The formulation and packaging of gene delivery vectors is labor intensive and places a potential burden on this rapidly advancing field. Vectors currently used in clinical trials are limited by short shelf-lives. The vector is then provided to the investigator(s) as a frozen, ready-to-use product typically in a glycerol–salt solution. The vector must be handled as a biohazard, with strict safety precautions enforced by all personnel prior to, during, and shortly after administering the vector to the patient. Significant effort is under way to develop convenient dosage forms for synthetic gene delivery vectors that will sustain potency on the shelf and allow convenient production, formulation, and patient administration. Therefore, this class of vector has a distinct advantage over modified viruses. Administration to the patient can be done either in vivo or ex vivo as already described. The major advantage of ex vivo gene therapy is that it ensures delivery of the gene to the intended cells. The major disadvantages include the amount of time, expertise, and specialized facilities required to accommodate this strategy. In contrast, in vivo gene therapy involves direct administration of the vector into the patient, which is much more convenient. However, this creates unique challenges because the product must be received fresh, handled as a

biological hazard, and provided to the patient usually within hours of receiving the product. Currently, no guidelines have been published to address the safe preparation and handling of gene therapy products. Handling usually requires that therapies are prepared in biological cabinets under sterile conditions. Appropriate barriers, including gloves, gowns, and masks should be worn by those preparing and administering the dose. Gloves and other supplies used in preparation should be autoclaved or decontaminated by ultraviolet light prior to disposal in biohazardous waste containers. Patient secretions including blood, urine, feces, and respiratory secretions may be decontaminated with bleach prior to disposal.

## PATIENT MONITORING

The pharmacokinetic and pharmacodynamic parameters of gene delivery vectors are largely uncharacterized in humans. However, essential concepts have been described regarding the many unique aspects inherent to in vivo distribution of macroparticulate DNA carrier systems. The distribution of most vectors is predictable and, in most cases, is limited by physical characteristics of a macromolecule. In general, all gene delivery systems are rapidly cleared from the systemic circulation, within minutes, after placement into the bloodstream. This often limits the capability of the vector to transfect cells in the targeted tissue. Fortunately, many of the vectors used in clinical trials can withstand physical manipulation, allowing site-specific administration in an attempt to enhance expression in defined tissues. Perhaps a greater challenge is to determine how long a particular gene will be expressed in a specific tissue once the vector has delivered the therapeutic gene to the targeted cells. Preliminary investigations have addressed this concern, but are limited to theoretic calculations from in vitro data.[14] Ultimately, this information is essential to develop a gene dosing regimen for a given patient, vector, and disease. Many trials involve treatment of chronic disorders, including AIDS, malignancy, and cystic fibrosis in which the gene is being delivered to differentiated cells with a limited life span. Therefore, it is presumed that many patients will require maintenance dosing of a vector to sustain expression of the therapeutic gene product over time.

Monitoring clinical efficacy of gene therapy has received little attention. For example, in published trials involving patients with ADA deficiency, the investigators routinely measured serum ADA protein concentrations to document sustained expression of the therapeutic gene.[15] In additional, the patients were extensively monitored for evidence of improved immune function and decreased number of infections. In the case of cystic fibrosis, the cystic fibrosis transmembrance conductance regulator (CFTR) protein is not released by transfected cells and remains associated with the cell membrane in patients. Knowles et al. had to physically remove nasal epithelial cells and then use advanced molecular techniques to document protein expression and function.[16] Gene therapy strategies undoubtedly create unique challenges for the clinician trying to determine when the next dose of a gene therapy vector should be administered. Measurement of sustained gene expression, or a lack thereof, will likely become common laboratory

**Table 2** Monogenic diseases: phase I and II ongoing gene therapy clinical trials as of February 1, 2001

| Indication | Gene | Number of open trials | Countries |
|---|---|---|---|
| Chronic granulomatous disease | P47 phox | 2 | U.S.A. |
| Cystic fibrosis | CTFR | 10 | France, U.K., U.S.A. |
| Fanconi's anemia | FACC | 1 | U.S.A. |
| Gaucher's disease | Glucocerebrosidase | 1 | U.S.A. |
| Hemophilia B | Factor IX | 1 | China |
| Hurler's syndrome | IDUA | 1 | U.K. |
| SCIDS | ADA | 5 | France, Italy, Japan, Netherlands, U.K. |
| SCIDS | MDR | 1 | Netherlands |
| Purine nucleoside phosphorylase deficiency | PNP | 1 | U.S.A. |

Key: CTFR, cystic fibrosis transmembrane conductance regulator; FACC, factor C; IDUA, α-L-iduronidase; SCIDS, severe combined immunodeficiency; ADA, adenosine deaminase; MDR, multidrug resistance; PNP, purine nucleoside phosphorylase.

procedure for gene therapy recipients and require specialized molecular assay techniques.

## GENE THERAPY CLINICAL TRIALS

### Monogenic Disorders

Monogenic, or single gene disorders, are rare hereditary disorders usually identified in childhood. They represent the purest approach to gene therapy, where potentially, the correction of a single gene defect by gene therapy may lead to correction of the disease state. The major limitation of gene therapy for monogenic disorders is that the rarity of these conditions limits the number of patients able to participate in clinical trials. The majority of gene therapy trials for monogenic disorders has focused on severe combined immunodeficiency syndrome (SCIDS)[17,18] and cystic fibrosis (CF).[19,20] In addition, small trials are ongoing in Fanconi's anemia, hemophilia, and other diseases (Table 2).

### SCIDS

Patients with SCIDS, a rare genetic disorder in which ADA is absent, have a greatly impaired immune system. The initial success in gene therapy came in 1989, with the report of the successful transfection of the normal ADA gene into T lymphocytes. In the two patients studied, both had normal immune function restored without adverse effects. Subsequent studies have demonstrated that both stem cells and CD34+ umbilical cord cells can be engineered to produce ADA and restore immune function. Although this disease is extremely rare, it represents the first successful clinical use of gene therapy.[17,18]

### Cystic Fibrosis

CF should be the ideal candidate for gene therapy because it is a single gene defect and thus presents a clear target. The main clinical problem is in the lungs, and the likely target is the surface epithelium. Methods of topical delivery to the airway surface are already well developed. All the required components for gene therapy were in place, and CF gene therapy progressed rapidly from preclinical to clinical studies. The gene, although large, could easily be inserted into a virus or produced as a plasmid; cellular studies showed that CFTR gene transfer could produce functional chloride channels and subsequently showed that cystic fibrosis cell lines could be corrected. The next steps were the demonstration of relatively efficient gene transfer to the airway epithelium using reporter genes in rodents, followed by partial correction of the disordered airway electrophysiology in CF mice. Clinical trials soon followed and more than 150 volunteers with cystic fibrosis participated. The results have been both encouraging, as gene therapy appears to be possible, and frustrating, as it just do not work that well. There is good evidence of low levels of gene transfer and small changes in ion transport, but progress has been hampered by inefficient gene transfer, immunity to viral vectors, and a systemic inflammatory reaction provoked by plasmid DNA, resulting in no clinical benefit to date.[19,20]

### Cancer

In contrast to monogenic disorders, cancer is generally caused by multiple genetic defects, providing no clear single target for gene therapy. However, because cancer is the second leading cause of death in the United States, gene therapy is under intensive investigation. Rather than correcting the multiple genetic defects found in tumors, cancer investigators have generally investigated approaches to conferring drug sensitivity, either by transvecting tumor cells with a gene encoding an enzyme such as herpesvirus thymidine kinase (HSV-TK)[21] that can metabolize a nontoxic drug to its toxic form (suicide genes) or with p53 (Table 3).[22]

The majority of gene therapy clinical trials are for cancer, with trials ongoing for almost all types of cancers. In addition, gene therapy for cancer is closest to the clinic, with both p53 and HSV-TK gene therapy in phase III clinical trials (Tables 4 and 5).

### HSV-TK

The HSV-TK gene converts nontoxic nucleoside analogs such as ganciclovir into phosphorylated compounds that kill dividing cells. Therefore, cells genetically modified to express the HSV-TK gene can be killed by the administration of ganciclovir.[21]

This cytotoxic effect of transduced cells on nontransduced cells is termed the bystander effect.[23] Because only a small number of cells will be transduced with the cytotoxic gene, when these cells die, they release toxic products that in turn kill the surrounding (or bystander) cells. The TK-ganciclovir approach is currently used in several clinical trials for a variety of malignancies, including gliomas.[24]

Adenoviral (Ad)-mediated intrapleural HSV-TK-ganciclovir gene therapy has been tested primarily in phase I and II clinical trials in patients with mesothelioma,

**Table 3** Oncology: phase I and II ongoing gene therapy clinical trials as of February 1, 2001

| Indication | Gene | Number of trials | Country |
|---|---|---|---|
| Breast | c-erb-b2 | 1 | U.K. |
| Cervical | HPV | 1 | U.K. |
| CML | HSV-TK | 2 | U.S.A. |
| Colon cancer | CC49 zeta TcR chimera | 2 | U.S.A. |
| Head and neck | INF | 1 | U.S.A. |
| Head and neck | IL-12 | 1 | U.S.A. |
| Glioblastoma | HSV-TK | 6 | Finland, France, Spain, Switzerland, U.S.A. |
| Lymphoma | MDR1 | 1 | U.K. |
| Lymphomas and leukemias | Specific idiotype | 3 | U.S.A., U.K. |
| Melanoma | IL-2 | 6 | Germany, France, Italy, Netherlands, U.K., U.S.A. |
| Melanoma | IL-7, IL-12, Gm-CSF | 3 | Germany |
| Melanoma | IL-4 | 2 | Italy |
| Melanoma | GM-CSF | 1 | Netherlands |
| Melanoma | IL-6 | 1 | Poland |
| Melanoma | HLA-B7/beta 2 micro | 2 | U.S.A. |
| Melanoma | MART1 + gp100 | 2 | U.S.A. |
| Mesothelioma | IL-2 | 1 | Australia |
| Metastatic cancer | IL2 | 2 | France, Switzerland |
| NSCLC | P53 | 1 | U.S.A. |
| NSCLC | IL-2 | 1 | U.S.A. |
| NSCLC | GM-CSF | 1 | U.S.A. |
| Ovarian | HLA-A2 | 1 | Singapore |
| Ovarian | P53 | 2 | U.S.A., U.K. |
| Ovarian, prostate, and breast | BRCA1 | 2 | U.S.A. |
| Ovarian | Mov-gamma | 1 | U.S.A. |
| Pancreas | Cytochrome p450 | 1 | Germany |
| Prostate | IL-2 | 1 | U.S.A. |
| Prostate | PSA | 3 | U.S.A. |
| Prostate | P53 | 1 | U.S.A. |
| Prostate | GM-CSF | 2 | U.S.A. |
| Prostate | HSV-TK | 1 | U.S.A. |
| Renal cell | IL-2 + HLA B7 | 1 | Germany |
| Renal cell | HLA B7/Beta 2 micro | 2 | U.S.A. |
| Superficial solid tumors | IL-2 | 1 | Switzerland |

glioblastomas, or ovarian cancer. The gene was administered intrapleurally in patients with mesothelioma or ovarian cancer and by direct injection during surgery in those with glioblastomas. In most phase I trials, the dose-limiting toxicity was not reached. Side effects have been minimal and included fever, anemia, transient liver enzyme elevations, and bullous skin eruptions, as well as a temporary systemic inflammatory response. Using RNA polymerase chain reaction (PCR), in situ hybridization, immunohistochemistry, and immunoblotting, HSV-TK gene transfer has been documented in approximately 50% of patients. Clinical activity has been minimal, although this may be related to the patient population studied, which is generally those with advanced refractory disease. Ongoing approaches are evaluating gene therapy in combination with chemotherapy.[24]

## P53

P53 is the most frequently mutated gene in human cancer, with an up to 50% mutation frequency in solid tumors. Most commonly, these genetic changes are missense mutations in one allele, although deletions or chain termination mutations can occur.

**Table 4** Oncology: phase III ongoing gene therapy clinical trials as of February 1, 2001

| Indication | Gene | Number of trials | Country |
|---|---|---|---|
| Glioblastoma | HSV-TK | 1 | Multicountry |
| Head and neck | P53 | 1 | U.S.A. |
| Melanoma | HLA-B7/Beta 2 microglobin | 1 | U.S.A. |
| Ovarian cancer | P53 | 2 | U.K., U.S.A. |

Key: HSV-TK, herpesvirus thymidine kinase.

Because normal or wild-type p53 is important in cell cycle regulation and apoptosis, restoration or modulation of p53 function is under intensive investigation for cancer therapy, with the hypothesis that restoration of p53 function may make cancer cells more susceptible to the effects of DNA damage inflicted by conventional chemotherapy or radiotherapy and able to undergo apoptosis.[22] Three main approaches are under evaluation. First, there is virus-mediated gene transfer in which a viral genome is engineered to contain foreign genes that are expressed in the host cell genome after infection. Second, there is the use of a cytolytic virus that can replicate only in cells that lack p53 function, and by targeting such cells could destroy tumors with mutant p53. Third, there is the discovery or design of small molecules that can interfere with the negative regulation of p53, pharmacologically activating the p53 response.

A single clinical trial using wild-type p53 gene transfer in nine patients with non-small cell lung cancer in whom conventional treatment had failed has been reported.[25] In this study, the LNSX retroviral vector was injected directly into the tumor either percutaneously with radiological guidance or via a bronchoscope. In situ hybridization and DNA PCR showed vector-p53 sequences in posttreatment biopsies, and apoptosis was more frequent in posttreatment than in pretreatment biopsies. No treatment-related toxicity was noted, and tumor regression occurred in three patients. Further extensive trials of adenovirus encoding wild-type p53 are currently underway.

The DNA tumor virus adenovirus produces a 55-kDa protein from the E1B region of its genome, which binds and inactivates p53. It was hypothesized that an adenovirus lacking E1B would not be able to replicate in normal cells but would in cancer cells lacking p53 function. For this reason, ONYX-015, an E1B gene-attenuated adenovirus was compared with normal adenovirus in human and colonic cancer cell lines with and without p53 function. As expected, the ONYX-015 virus replicated as efficiently as the normal virus in the cell line lacking wild-type p53, but not in the line with normal p53 function.[26] This vector is in early clinical trials.

**Table 5** Infectious disease: phase I and II ongoing gene therapy clinical trials as of February 1, 2001

| Indication | Gene | Number of studies | Country |
|---|---|---|---|
| EBV and CMV | CMV pp65 | 1 | U.S.A. |
| HIV | HIV env/rev | 3 | U.S.A., Switzerland |
| HIV | CD-zeta TcR chimera | 2 | U.S.A. |
| HIV | Antisense to pol 1 | 2 | U.S.A. |
| HIV | Rev+pol 1 | 2 | U.S.A. |

Key: EBV, Epstein-Barr virus; CMV, cytomegalovirus; HIV, human immunodeficiency virus.

**Table 6** Cardiology: phase I and II ongoing gene therapy clinical trials as of February 1, 2001

| Indication | Gene | Number of trials | Country |
|---|---|---|---|
| Coronary artery disease | VEGF | 1 | Finland |
| Coronary artery disease | FGF | 1 | U.S.A. |
| Peripheral artery disease | VEGF | 7 | Finland, U.S.A. |

Key: VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor.

## Cardiovascular Disease

Angiogenesis, or growth of new blood vessels, appears essential in revascularization after myocardial infarction as well as in treating coronary artery disease and peripheral artery disease. Therefore, cardiovascular gene therapy has concentrated on vascular endothelial growth factor (VEGF) in these diseases[27] (Table 6).

## Low-Density Lipoprotein (LDL) Receptor

Familial homozygous hypercholesterolemia is a rare hereditary monogenic disorder caused by mutations of the LDL receptor gene. Individuals have severe hypercholesterolemia associated with premature atherosclerosis. In a single study, patients were treated with gene therapy

**Table 7** Other ongoing gene therapy clinical trials as of February 1, 2001

| Indication | Gene | Studies | Countries |
|---|---|---|---|
| Amyotrophic lateral sclerosis | CNTF | 1 | Switzerland |
| Alzheimer's disease | Nerve growth factor | 1 | U.S.A. |
| Anemia of end-stage renal disease | EPO | 1 | U.S.A. |
| Cubital tunnel syndrome | HIGF-1 | 1 | U.S.A. |
| Hip fracture | Parathyroid hormone | 1 | U.S.A. |
| Rheumatoid arthritis | HSV-TK | 1 | U.S.A. |
| Rheumatoid arthritis | IRAP | 1 | U.S.A. |
| Severe inflammatory disease of rectum | IL-4 and IL-10 | 1 | Austria |

Key: CNTF, ciliary neurotrophic factor; EPO, erythropoetin; HIGF, human insulin-like growth factor; HSV-TK, herpesvirus thylimidine kinase; IRAP, insulin responsive aminopeptidase.

with the LDL receptor. Expression of the receptor was documented, but LDL cholesterol levels remained substantially elevated 3 to 6 months after gene transfer, $611 \pm 27$ vs. $550 \pm 51$ mg/dL, before and after gene therapy, respectively.[28]

## VEGF

Formation of new blood vessels by the angiodan VEGF is an experimental strategy for treating myocardial ischemia. The VEGF proteins function by interacting with specific receptors on endothelial cells, which initiates a cascade of events culminating in endothelial cell migration, proliferation, aggregation into tubelike structures, and networking of the arterial and venous systems.[27]

Gene transfer represents one approach to delivering an angiogen to the heart in which the carrier DNA (cDNA) coding for VEGF is delivered to the myocardium, with the myocardial cells used to secrete the VEGF. Studies in experimental animals have shown that replication-deficient, recombinant adenovirus (Ad) gene transfer vectors are advantageous for delivery of angiogens such as VEGF, in that Ad vectors provide a high transfection efficiency, remain highly localized, and express VEGF for a period of 1 to 2 weeks, which is sufficient to induce collateral vessels to relieve the ischemia but not long enough to evoke abnormal angiogenesis.[27]

In a phase I evaluation, VEGF121.10 was administered to 21 individuals by direct myocardial injection into an area of reversible ischemia either as an adjunct to conventional coronary artery bypass grafting or as sole therapy via a minithoracotomy. There were no adverse effects attributed to the gene transfer, and patients had decreased angina.[29]

Other trials of VEGF have been reported. A case report demonstrated improvement in blood supply to an ischemic limb after intra-arterial gene transfer of a plasmid encoding for VEGF.[30] The use of a plasmid-based gene delivery system, although inefficient, was reasonable in this situation because VEGF is a potent secreted product. A phase 1 trial of intramuscular delivery of a plasmid-encoding VEGF in the setting of severe peripheral vascular disease was reported.[31] Gene transfer was performed in 10 limbs in nine patients with nonhealing ischemic foot ulcers. Increased circulating VEGF levels were demonstrated after intramuscular gene delivery. Various measures, including ankle-brachial index and magnetic resonance angiography, showed qualitative evidence of improved distal flow in 8 limbs.

## Multidrug Resistance (MDR)

In a therapeutic approach, stem cells may be isolated from patients and genetically modified to express the MDR gene.[32] These cells are then retuned to the patient prior to administration of chemotherapy, making the stem cells resistant to chemotherapy.

## Other Diseases

Gene therapy is under evaluation for many diseases, ranging from rare inherited single gene defects to common disease such as HIV, deafness, autoimmune diseases, bone regeneration, and many others[4,33,34] (Tables 5 and 7).

# ETHICAL ISSUES

The first death attributable to gene therapy occurred in September 1999, when an 18-year-old patient with ornithine transcarbamylase deficiency died, apparently as a direct result of the experimental gene therapy studies.[35,36] This prompted two senate hearings and resulted in recommendation for implementation of new policies by the Recombinant Advisory Council (RAC), Food and Drug Administration (FDA) and NIH, which require earlier review of researcher's plans for monitoring safety and

quarterly meetings.[37–39] A few of the safeguards implemented include thorough public evaluation of protocols before investigational new drug assignment for FDA and institutional review board (IRB) approval; the development of a single, uniform mechanism for reporting adverse events to the RAC, FDA, and other relevant agencies; establishment of a public database of all adverse events; and nonparticipation of investigators with financial interests in study outcomes in patient selection, the informed consent process, and direct management of clinical studies.

Further evaluation of this tragic event has identified that vector-associated toxicity was not the sole cause for this patient's death. The FDA determined that human subjects in this investigation were not adequately protected and that there was substantial financial conflict of interest. Subsequently, the NIH has discovered hundreds of unreported adverse events among volunteers enrolled in gene transfer experiments. These findings have catalyzed broad examination of the entire clinical research process, with the Secretary of Health and Human Services calling for broad reforms in informed consent, clinical monitoring, and conflict of interest.

## CONCLUSION

Gene therapy is in its infancy. Early and ongoing success in SCID, combined with promising studies in cardiovascular and oncology therapies, supports optimism for these novel strategeis. However, several important issues remain, including the best vector for transfer and appropriate protection for both patients and health care providers. The Orkin–Motulsky report clearly stated that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host."[6] As such, the report clearly identified key recommendations to ensure continued progress in this field. The recommendations were to 1) continue research at the basic level to improve vector design and studies that will further identify pathogenic mechanisms of disease, 2) improve trial design with quantitative and qualitative assessment of gene transfer and expression, 3) maintain adequate financial support for gene therapy studies and promote interdisciplinary collaborations at the basic and clinical levels, and 4) disseminate information to the public that clearly identifies limitations of the field as well as exciting new discoveries.

Many new gene delivery vectors and protocols are currently in developmental stages that aim to improve on the earlier prototypes. The relatively small number of vectors used in clinical trials underscores the complexity of DNA delivery and our lack of knowledge about how these macroparticulates are handled and expressed in the human body. It is hoped that the recent reprioritization of gene therapy studies will improve the design of vectors, enhance our understanding of the biological interactions between gene-carrying vectors and the body, eliminate adverse events, and improve information gained from future clinical trials. Assuming these events occur, experts still predict that gene therapy is still more than 5 to 10 years from routine use in patients.

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# Generic Drugs and Generic Equivalency

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## INTRODUCTION

All drugs that are approved for sale generally carry at least two names. The drugs are given a proprietary or trade name given by the company that first develops them. These companies often are referred to as the innovator company. The drug is assigned a nonproprietary or generic name, which is agreed to by the WHO International Nonproprietary Nomenclature (INN) Committee and the U.S. Adopted Names Council (USAN). A new drug is usually first marketed with some patent protection and at a price that, at a minimum, recoups the cost of development over the remaining life of the patent or other exclusivity arrangement. Eventually, protection from competition is lost to other pharmaceutical companies, often companies or divisions of companies that specialize in marketing off-patent drugs. These companies or divisions are called generic companies. They can apply to the appropriate regulatory body such as the Food and Drug Administration (FDA) for permission to market the same active ingredient under its nonproprietary or generic name. The generic manufacturer is not required to do a complete clinical trial to prove effectiveness and safety because that has already been well established for the drug. However, it is required to show that the new drug product is equivalent to the original drug product. For the purposes of this article, we define the drug as the chemical that has the pharmacological effect and the drug product as a dosage form that contains the drug and other ingredients or excipients that allow the formulation of the dosage form. There is a large economic incentive for the development of generic drug products, especially for highly successful drug products. The pharmaceutical company that first brought the product to market maintains the price at the original level or higher to continue the cash flow into the company. This allows the other companies to develop a formulation of the drug and to win approval to market with the knowledge that, even at a fraction of the selling price of the innovator's product, the company can make a good profit. Some innovators defend their market share by arguing quality and reliability. The FDA must act as an impartial arbitrator of this debate. The debate is clearly about money, but is argued in a scientific forum. The key question is, "Are we sure that the two products, if used in the same way in the same patient, will yield the same result." If a drug product is subject to this debate, the innovator always says "no" and the second and subsequent manufacturers always say "yes." In the United States, the FDA sets the standards against which the question is resolved, and scientists take sides usually on the issue of "are the current FDA standards good enough." If the FDA gives an "A" rating to a drug product, it is in effect telling the prescriber that the drug product will yield the same therapeutic and side-effects profile as the innovator drug product. The Orange Book specifies the equivalence rating from the FDA. Almost all generic drug products currently marketed are rated A; the FDA has not approved a generic without an A rating in decades. Finally, the consumer pays the price, either in the unnecessarily high cost of drugs if unnecessary studies are performed and generic competition delayed or in risky drug substitution if the FDA is too relaxed in its standards. The tests required by the FDA have changed over the years. They have become more proscriptive and are based on sound statistical grounds. The FDA has also increased the level of oversight of the pharmaceutical companies that manufacture generic equivalents of innovator products. Thus, the regulatory process has become more stringent, and the level of assurance that the public has that a generic product is both safe and effective has gone up. The FDA has often stated that there are no known therapeutic failures from switching among products that have been ruled as equivalent by the FDA.

## LEGISLATIVE AND REGULATORY HISTORY

In the early 1970s, most states had antisubstitution laws that required the dispensing of the innovator product when the prescriber wrote for a drug by trade name. Most physicians had learned only the trade name of the drug product, and these laws ensured that generic substitution would be at a minimum (1). The American Pharmaceutical Association (APhA) along with other groups pushed for the repeal of these laws and opened the way for the growth

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of the generic industry. The lack of bioequivalence data available at that time led to the formation of the Generic Drug Bureau within the Food and Drug Administration. As a result of the efforts of that group, the FDA produced a book, *Approved Drug Products With Therapeutic Equivalence Evaluations*, in the late 1960s. This became known as the Orange Book because of the cover color. The book has been published annually with monthly updates. The contents are now available on the FDA Website (2).

In 1984, the Drug Price Competition and Patent Term Restoration Act was passed. This act, also known as the Waxman–Hatch Bill of 1984, encouraged the development of new innovative drugs by established procedures, extended patent rights, and facilitated the FDA approval process for generic drugs (3). To address the first goal, the law created a mechanism to extend the period of patent protection for manufacturers of innovative new drugs generally ensuring at least 5 years of market exclusivity after approval. To address the second goal, the law established an Abbreviated New Drug Application (ANDA) for applications after 1962. Drugs chemically equivalent to those previously approved by a full application process need only be proven bioequivalent, not clinically equivalent. Depending on the drug, proof of bioequivalence can involve in vitro dissolution studies, in vivo single-dose bioavailability studies, in vivo multidose bioavailability studies, or a combination of these. However, in vitro dissolution studies alone are not adequate proof of bioequivalence for purposes of an ANDA.

## SCIENTIFIC BASIS FOR GENERIC DRUG PRODUCT EQUIVALENCY: BIOAVAILABLITY–BIOEQUIVALENCY

The goal of the testing of generic products is not to establish the clinical usefulness of the drug but only to ensure that the generic product or new formulation has the same relative bioavailability as or is bioequivalent to the innovator product.

Bioavailablity has been defined as a measure of the rate and extent of absorption of a drug into the systemic circulation after administration of a dosage form. An intravenous i.v. dose is considered by definition to be 100% bioavailable. All other routes of administration will produce a total bioavailability less than or equal to that of the i.v. dose. Thus, only a drug that is completely absorbed into the systemic circulation can have the extent of bioavailability equal to the dose stated on the label. In addition to the extent of absorption, the rate of absorption plays a key role when evaluating the potential therapeutic impact of a particular dosage form. Knowledge of the time to onset of drug action, which is directly related to rate of absorption, is a significant concern, especially in acute clinical situations such as asthma attack, hyperglycemic shock, and pain.

The bioavailability of drugs from specific dosage forms is affected by the nature of the inactive ingredients or pharmaceutical excipients and the process used in its formulation. (For additional information, see Bioavailability of Drugs and Bioequivalency in this Encyclopedia.) When comparing similar dosage forms from different manufacturers or different lots from the same manufacturer, it is most useful to determine the relative bioavailability of the two products or lots. Some scientists have attempted to establish an in vitro test that could successfully predict in vivo bioavailability. However, to date, none has been developed.

Pharmacokinetics means the application of kinetics to drugs. It can be defined as the study of the time course and fate of drugs in the body. Teorell is often given credit for the origin of pharmacokinetics with his publications, *Kinetics of Distribution of Substances Administered to the Body* (4, 5). This science is the theoretical support for the use of bioequvalency testing to establish therapeutic equivalence among dosage forms of the same drug. The first approach to a pharmacokinetic understanding of drugs in the body, called compartment analysis, considered the body as a group of compartments through which the drug must pass. The compartment itself does not exist but represents the average of many processes that give rise to the observed phenomenon. The size of the imaginary compartment can be calculated and is useful in understanding the process of absorption, distribution, and elimination or metabolism of the drug. Regardless of the model used, a plot of the plasma concentration of the drug versus time yields a curve that can be described by a polyexponential equation. The area under that concentration–time curve (AUC) is directly related to the amount of drug absorbed. The time to reach peak concentration and the peak concentration itself are related to both the dose and the rate of absorption.

An important limitation of compartment analysis is that it cannot be applied universally to any drug. A simpler approach that is useful in the case of bioequavalency testing is the model independent method. It is based on statistical-moment theory. This approach uses the mean residence time (MRT) as a measure of a statistical half-life of the drug in the body. The MRT can be calculated by dividing the area under the first-moment curve (AUMC) by the area under the plasma curve (AUC) (6).

(See other articles in this Encyclopedia for more detailed discussion of these subjects.)

## MEASUREMENT OF RELATIVE BIOAVAILABILITY OR BIOEQUIVALENCY

Drug products often undergo bioavailability testing in the early stages of development. Changes in formulation necessitated by results of clinical trials or stability testing or changes in the availability of excipients or changes in suppliers of excipients often require that the manufacturer perform a relative bioavalability or bioequivalency test to ensure that subsequent lots of a product will yield the same amount of active ingredient at the same rate as was possible in earlier formulations.

Bioequivalency studies are usually performed on young, healthy, male adult volunteers under controlled dietary conditions and fixed activity levels. This is because the goal of the study is not to establish the clinical usefulness of the drug but only to ensure that the two formulations have the same relative bioavailability or are bioequivalent.

### Key Parameters

When assessing bioequivalence, the following three parameters that characterize the plasma or blood concentration–time profile of the administered drug are usually measured:

1. Peak height, $C_{max}$, represents the highest concentration of the drug in the systemic circulation;
2. Time to peak, $t_{max}$, represents the time for peak height to occur after the drug was administered;
3. Area under the curve, AUC, represents the total integrated area under the concentration–time curve.

The first two parameters are indicators of absorption rate, whereas the third is directly proportional to the extent of drug absorbed into the systemic circulation from the dosage form. Figure 1 is an example of a concentration–time curve for a single dose of drug to a subject.

Although it is theoretically possible to determine the rate and extent of absorption of a drug by measurement of the rate and extent of the appearance of the drug in the urine, this is not considered as reliable a method for evaluation of a drug product's bioequivalency as are blood level data. Thus, the studies commonly performed to demonstrate bioequvalence fall into two catagouries: single-dose and multidose or steady-state studies. There are advantages and disadvantages to each. Single-dose studies are less expensive and expose healthy volunteers

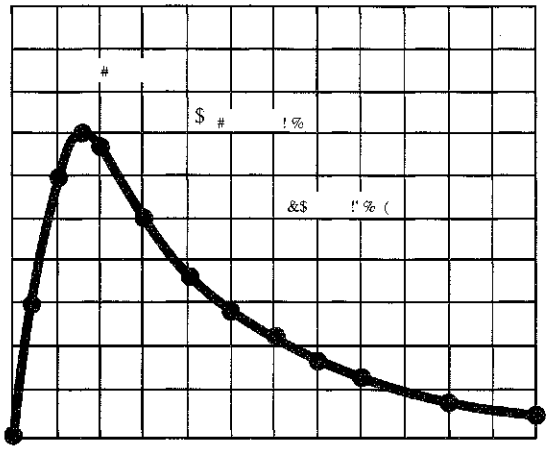

**Fig. 1** Blood concentration curve.

to less drug during the course of the study. However, these studies require more sensitive analytical methods and have higher subject-to-subject variability. In both cases, a cross-over study design is used to control for sequence effects. The study is designed to control for or take into account as many variables as possible. The subjects are randomly assigned to groups. Blood samples are obtained from each subject before dosing and at fixed time intervals after dosing. Currently, the data are then analyzed using appropriate statistical ANOVA. The results must meet FDA guidelines for mean and 90% confidence interval for each of the three key parameters. For oral solid dosage forms, the FDA requires that for a product to be considered bioequivalent, the ratio of the parameter for the two products, together with their 90% confidence interval, must fall between 0.8 and 1.25, using log-transformed data. This, in effect, means that drug products that differ by more than 10% in their rate and extent of absorption will not be approved as generic equivalents.

## CURRENT SCIENTIFIC ISSUES

Two issues have been raised recently with regard to the approval of generic drugs. The first has to do with the issue of "Narrow Therapeutic Index Drugs," and the second has to do with the use of individual bioequivalence in place of average bioequivalence. The former concern has been addressed in detail by Drs. Benet and Goyan (7). They concluded that narrow-therapeutic-range drugs were the least likely to have therapeutic failures among generic

drugs, with proof of bioequivalency. The use of average bioequivalence data is under attack. This is because of the concern that there might be a significant subject–by-product interaction. Regulatory agencies now assume that this is not the case (8). The advantage of using individual bioequivalence studies is the reassurance that if subject/product interactions do occur, the study design would control for them, and a more statistically valid measure of the rate and extent of absorption of the drug from the two product would be determined. Some of the disadvantages associated with shifting from average to individual bioequivalence testing are cost, numbers of subjects needed, and diversity of the study population required. [See other articles that address the impact of the new metrics on the reliability and cost of the performance of bioequivalence testing (9–12).]

## THE CHANGING POLITICAL ECONOMY OF GENERIC DRUGS

The modern generic drug industry in the United States really only dates from the passage of the Waxman–Hatch Act in 1984. Within 5 years of passage, generic drugs captured 40% of the market for prescriptions written inthe United States. Since that time, the generic drug market share has stablized between 40 and 50% of the prescriptions written. However, the dollars paid for generic drugs are only 10% of the total sales of drugs in the United States. That statistic alone tells us that the consumer receives enormous benefit from the substitution of therapeutically equivalent generic drugs when available.

A horrendous scandal hit the industry in the late 1980s, wherein firms representing 75% of the production of the generic industry pled guilty to one or more criminal charges involving filing false applications with the FDA, paying illegal gratuities to FDA personnel, and/or related crimes to gain an unfair competitive advantage in the emerging marketplace. Surprisingly, this scandal produced only a small delay in the market share march of generic drugs and only a temporary loss of consumer confidence in generic products.

The scandal was tied to a phenomenon that still dominates the business strategies of generic drug firms to this day: the need to obtain approval to manufacture and distribute before other firms enter the market. Because of the "commodity" nature of the business and the relative ease of entry into the industry, firms devote most of their resources and managerial talent to obtaining first or second approvals from the FDA for their products. Once a generic drug has four or more competitors, it is no longer profitable for additional generic companies to enter the market.

Generic drug manufacturers typically will continue to manufacture drugs that produce little or no profit because large purchasers that are their prime customers (chain drugs stores, buying groups for smaller community pharmacies, etc.) prefer to buy from companies that can supply most of the common generic drugs. For example, if a generic drug firm no longer produces amoxicillin because it can make more money by shifting its antibiotic production facilities to, for example, a cephalosporin drug for which it has less competition, a large chain may chose to buy its entire generic antibiotic line from another company that supplies both.

The profitable generic drug companies are profitable because they have found a strategy to maintain some control over the price of their products. In the early years (1984–1988), the best way to get "first approval" from the FDA apparently was to be first to file, to get assays or bioquivalence studies done on difficult to duplicate drugs, or to find some way to get an expedited approval from inside the agency. Unfortunately, this sometime involved payoffs to FDA review chemists (those FDA experts assigned the task of evaluating biostudy results, the crucial piece of a generic drug application, remained remarkably free of the scandal). More often, it involved submitting false information to the FDA (including, in a few cases, false biostudies). Many generic drug firms did not survive the scandal, and others survived only after the previous management and ownership were purged from the firms.

For a short period, it was believed that the profitable segment of the business involved not production but distribution. After all, if commodity prices approach marginal cost and the marginal cost of manufacturing drugs is minimal, but the price to the consumer remains significantly more than marginal, there must be middlemen somewhere making the money. Clearly, those middlemen were not in the retail pharmacy where profits continued to be squeezed. Distributors were thought to be the new profit centers. But a funny thing happened on the way to that particular bank... .

Consumers became outraged at the rapid increase in the price of pharmaceuticals as the innovator companies (and some generic firms) rushed to raise prices and as generic drug company after generic drug company was pushed out of the industry in the wake of investigations by a Congressional committee and a federal grand jury. Second, the Administration, in response to public concern about the cost of pharmaceuticals, pressured the pharmaceutical industry and forced lower prices and significant rebates to the federal and state government

programs that paid for drugs. Wholesale distributors of all drugs subject to the federal rebates suffered.

Finally, the firms that thought they could profit most from the scandal entered the market. These were innovator firms, many of which had already played a significant role in the distribution of generics. Ultimately, the profit margins from generic drug sales were not sufficient to carry the overhead of the branded companies, and most left the market or returned to their distributor role. Even in the case of the firms manufacturing and marketing generic versions of their own branded products, giving them significant advantage over the remaining pure generic firms in developing and filing of the ANDAs with the FDA and the added advantage of relatively less scrutiny from the scandal-rocked agency, most had exited the marketed by the end of the decade.

Some innovator firms entered the generic drug market so that they could have a product line consistent with their new business strategy: disease state management. This strategy, a function of the rise of HMOs and the return of the concept of scarcity to prescription drug dispensing, was intended to involve the development of a continuum of drug therapies for the treatment of a specific illness (diabetes, depression, etc.), wherein the patient would be tried on the older, less-expensive drug first and, if it did not work, the next most cost-effective drug would be administered and so on until the least cost-effective drug would be the treatment of last resort. Unfortunately, the branded companies that selected this strategy found themselves competing with doctors, hospitals, and insurance companies for control of the treatment regime of individual patients, a losing proposition for the entity with the least amount of information about and access to the individual patient.

Another factor in reducing prices of all drugs that had some form of competition was the rise of the HMO and its pharmaceutical watchdog, the pharmacy benefit manager (PBM). These PBMs create a formulary of approved drugs (drugs for which they would reimburse partially or fully) based on bids from competing companies.

Much of the public's confusion regarding generic drugs arose from a practice of the PBMs to pressure doctors to substitute different chemical entities in the same therapeutic class for the prescribed medicine. Such a switch is called a theraputic substitution as opposed to the switching among manufacturers of therapeutically equivalent drugs (generics and the innovator drug or other FDA "AB"-rated substitutes). Therapeutic substitution involves a switch to a different drug, whereas generic substitution involves a switch to the same drug from a different manufacturer. If a patient is switched between FDA "AB"-rated drugs, the FDA offers the assurance that they can expect the same therapeutic and side-effect profile as the brand drug or another "AB"-rated generic drug. The FDA offers no such assurance if the switch occurs among different drugs, even if they are in the same therapeutic class. For example, aspirin and Tylenol may be equally effective in the treatment of headache, but the FDA makes no such certification, whereas it makes exactly that certification for Bayer aspirin and Safeway aspirin.

The dominance of the HMO (and related organizations) and their PBMs (and related organization types) served to accelerate the substitution of generic drugs at the turn of the 21st century. However, even that pressure could not slow the re-emergence of a high rate of price increase, greater than consumer or comparable wholesale prices as a whole, in prescription drugs. Innovator companies learned that establishing very high prices for "breakthorough" drugs could more than compensate for the loss of patent protection on a highly profitable drug.

Furthermore, the United States is the only developed country in the world that has chosen not to explicitly control the price of any drug product and has used its market power as a huge buyer relatively sparingly. Consequently, U.S. prices for drug products still under patent are usually substantially above those charged anywhere else in the world. Generic prices approach cost except for those few generics that have managed to eliminate or limit for a specific period competition from other generics.

Those generic drug firms that prospered in this restrictive price environment all had one or more niche drugs that were immune from corrosive price competition. Some companies mastered a manufacturing process that produced bioequivalent medicine that the innovator itself found difficult to master lot to lot. Others took advantage of certain exclusivity provisions in the law for those that challenged a product patent in court, ostensibly to cover the cost of litigation. In other cases, the settlement of those cases provided some form of licensing or distribution rights that permitted the sale of a generic product while the patent was still valid. Finally, a fortunate firm might find itself in possession of the exclusive right to purchase the raw material from the only source available to generic drug manufacturers.

All generic drug firms capable of generating the necessary cash to develop and market new drugs are moving toward that lucrative market. For the time being, the United States has chosen to use the market mechanism as its only important control on drug prices. Generics are the competition, and competition is our only real form of price control.

According to the Congresslonal Budget Office (CBO), consumers saved $8–10 billion in 1994 because of the use of generic drugs. In that same 1998 report, CBO cited the Waxman–Hatch Act, generic substitution laws passed by the states, and government health programs as seminal events leading to the acceptance of generic drugs and the resulting savings.

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PROFESSIONAL DEVELOPMENT

# Government, Clinical Pharmacy Careers in

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## INTRODUCTION

Approximately 7000 pharmacists serve the federal government in a variety of roles and organizations, including the Department of Veterans Affairs (VA), the Department of Defense (DOD), and the U.S. Public Health Service (PHS). Pharmacists in the uniformed services, Army, Navy, Air Force, and PHS, may be either commissioned officers or hired via the civil service system. Opportunities for clinical practice and research in the federal government represent a large, but relatively unknown option.

## DEPARTMENT OF VETERANS AFFAIRS

The VA health care system now includes 4000 pharmacists, 173 medical centers, nearly 670 outpatient and community clinics, and 131 nursing home units. The VA is affiliated with more than 1000 schools across the United States, including pharmacy, medical, and dental schools. Each year, approximately 100,000 health professionals receive training at VA medical centers. The VA system has been a leader in opening new career pathways for pharmacists that reward the achievement of exceptional skills. For example, pharmacists can receive increases in pay by completion of advanced degrees or by passing the board certified pharmacotherapy specialist (BCPS) examination. There are a number of programs to provide additional training for VA pharmacists and transition them from distributive roles to clinical functions.

Veterans Affairs pharmacists serve in a number of clinical roles including, but not limited to, pharmacist-run ambulatory clinics, members of interdisciplinary care teams, patient education, pharmacokinetic evaluations, therapeutic consultation, and research.[1] These services are provided in various inpatient, long-term, and ambulatory patient care settings. Most clinical pharmacists will have advanced professional degrees (M.S. or Pharm.D.), postgraduate training, and/or sufficient professional experience. Clinical pharmacy specialists are advanced practitioners who provide clinical services for specialized services. These services include anticoagulation, psychiatry, geriatrics, diabetes, infectious diseases, and medication refill. They also may have prescribing authority within a defined scope of practice. There are 185 pharmacy residency programs at VA medical centers, many with a strong emphasis on ambulatory and primary care.

## U.S. ARMED SERVICES

The mission of the medical departments in the Army, Navy, and Air Force is to provide effective health care to U.S. forces in times of conflict and to provide high-quality health care in peacetime.[2,3] There are currently approximately 1500 pharmacists working in these units, both as commissioned officers and civil service. Some pharmacists within the armed services are deployed with troops to provide pharmacy services during training missions or wars. Therefore, they must participate in training exercises and workshops designed to simulate these types of experiences. Other pharmacists work at military hospitals and outpatient clinics, providing more traditional clinical pharmacy services. Pharmacists participate in a variety of clinical roles, including patient rounds, drug information, and patient counseling. Some pharmacists undergo a credentialing process that gives them prescriptive authority and enables them to assume responsibility for the management of the patient within defined roles and limits. Armed services ambulatory care pharmacists play active roles in direct patient care within such therapeutic areas as diabetes, asthma, hyperlipidemia, and hypertension.

Pharmacists within the Army are also members of a bioterrorism readiness force that is prepared to respond to medical emergencies arising from the terrorist use of weapons of mass destruction. Many pharmacists within the armed services do not possess Pharm.D. or other advanced degrees, although there is a strong com-

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mitment to support those individuals who pursue additional education. There are a number of residency and fellowship programs available to these pharmacists, and opportunities exist to attain a nontraditional PharmD degree.

## U.S. PUBLIC HEALTH SERVICE

The PHS is organizationally part of the Department of Health and Human Services.[4] Pharmacists are probably most familiar with such agencies as the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Indian Health Service (IHS), and National Institutes of Health (NIH). In addition, the PHS has memorandums of agreement with the Federal Bureau of Prisons (BOP), Immigration and Naturalization Service, and U.S. Coast Guard (USCG), to provide primary health services. The Office of Emergency Preparedness and the National Disaster Medical System are also located within the Department of Health and Human Services.

### Centers for Disease Control and Prevention

There are currently nine pharmacists who serve at the CDC coordinating the CDC Drug Service, which distributes 13 special immunobiological materials and drugs to physicians in the United States. Special biological and antiparasitic drugs that the CDC distributes include botulism and diptheria antitoxin, bithionol, ivermectin, pentostam, and other medications with restricted usage in the United States. These pharmacists also ensure procurement of drugs, maintenance of treatment investigational new drug applications (INDs), and timely reporting to the FDA. Other pharmacists who also possess a Master's degree in Public Health perform epidemiology and field work in foreign countries. The CDC has been charged to maintain a stockpile of pharmaceuticals that can be immediately deployed in response to chemical or biological terrorism events within the United States.

### Food and Drug Administration

The FDA employs more than 250 pharmacists in all phases of the agency's regulation of drugs, biologics, medical devices, medical foods, and veterinary products. Pharmacists serve as reviewers for INDs, new drug applications (NDAs), and generic drug approvals, evaluating the safety, efficacy, packaging, and advertising of prescription and nonprescription drugs. They are also involved in adverse experience reporting and postmarketing surveillance, and function in many other positions ranging from field inspector to project managers, which are the liaison between the pharmaceutical industry and the FDA. Other pharmacists contribute to the FDA with respect to compendial standards, scientific investigations, manufacturing facility inspections, and the FDA's research laboratories. In addition, they also work with expert advisory committees and review panels. Most FDA pharmacists serve at the headquarters in Rockville, MD, but others are assigned to the many regional, district, and local offices throughout the United States that carry out inspection and enforcement activities. A PharmD degree is preferred but not generally required for many FDA positions.

### Indian Health Service

The IHS employs more than 500 pharmacists who are part of a health care team that provides comprehensive care to 1.4 million Native Americans and Alaska Natives in hospitals and ambulatory clinics in 34 states. The IHS pioneered many of the clinical pharmacy services that are now considered standard practice. Pharmacists have direct access to the patient's medical record to ensure appropriateness of drug therapy, monitor for adverse effects, and conduct activities in health promotion and disease prevention. Indian Health Services pharmacists have long been involved in expanded roles such as primary care, and many have prescriptive authority under medical staff protocols. They are actively involved in drug selection, dosing, treatment, and evaluation of therapy. Patient consultation has been an integral part of the IHS pharmacy program for more than 30 years, and private consultation rooms are used to promote effective patient communication. The IHS offers three residency programs: American Society of Health-System Pharmacists (ASHP)-accredited programs in pharmacy practice and ambulatory care, and an American Pharmaceutical Association (APhA)-accredited residency in community pharmacy practice. The IHS also provides their pharmacists with the opportunity to pursue a PharmD degree through a relationship with Idaho State University.

### National Institutes of Health

Opportunities for pharmacists exist in both the intramural and extramural programs. The extramural program accounts for nearly 90% of NIH funding and is

comprised of sites around the world, whereas the intramural program is located on the NIH campus in Bethesda, Maryland. The NIH Clinical Center is a 350-bed hospital devoted exclusively to patients of the intramural clinical research program. Its pharmacy is supported by 50 pharmacists in various roles, including nine clinical pharmacy specialists in the areas of oncology, infectious diseases, critical care, bone marrow and solid organ transplant, mental health, drug information, and ambulatory care. These pharmacists also serve as principal and associate investigators in various NIH studies. Clinical pharmacy specialists generally have a PharmD degree and postgraduate training in residency and/or fellowship programs. The staff also includes pharmacists with expertise in drug formulation, study design, analytical/quality control, and pharmacokinetics. The NIH also offers four ASHP-accredited residencies. There are also opportunities for radiopharmacists within the NIH Clinical Center's Nuclear Medicine and Positive Electron Tomography (PET) Departments.

The research program at NIH also uses pharmacists in many of its 14 institutes. Pharmacists in the National Cancer Institute's (NCI's) Pharmaceutical Management Branch are involved in anticancer drug development, protocol development, collection of clinical data, distribution of NCI investigational drugs and the Treatment Referral Center. In addition, the intramural program of the NCI has a pharmacokinetics laboratory where pharmacists perform basic and clinical research. The National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS pharmacists participate in protocol development and implementation, and act as consultants to more than 300 pharmacists involved in NIAID-sponsored AIDS clinical trials.

### Federal Bureau of Prisons

The BOP employs more than 120 pharmacists who work in both hospital and ambulatory settings in 99 prisons in 38 states. Pharmacists fill medication orders directly from the inmate's medical record, thereby having access to full information on the patient. Pharmacists at the BOP are significantly involved in monitoring compliance, managing drug therapy, ordering and interpreting laboratory studies, and medication counseling for inmates in tuberculosis prophylaxis, mental health, HIV/AIDS, and other more traditional chronic disease clinics. Many pharmacists stationed in hospital settings have a presence on mental health and medical/surgery floors, round with physicians, and provide drug information services to the medical staff. Pharmacists at the BOP are also performing research in the area of patient counseling and compliance.

### U.S. Coast Guard

Officers commissioned by the PHS deliver primary care services to USCG members and their families at 26 shore-based sites. Sixteen active-duty, PHS- commissioned corps pharmacists are detailed to the USCG. In the early 1990s, the USCG adopted the chart prescribing and prescription dispensing model developed by the IHS. The USCG pharmacy program is linked throughout the United States to the DOD Composite Health Care System for computerized dispensing functions.

## COMMISSIONED OFFICER STUDENT TRAINING AND EXTERN PROGRAM (COSTEP)

The PHS offers students in medicine, nursing, pharmacy, and other allied health professions the chance to gain career experience at sites throughout the United States through a program called COSTEP. These salaried positions, available during vacation or elective time, provide students with valuable experience and insight into career opportunities within the PHS.

## CONCLUSION

These programs represent the most common career paths for pharmacists in the U.S. government. However, there are additional federal agencies, such as the Centers for Medicare and Medicaid Services, where pharmacists serve in nontraditional roles. Although generally not considered by pharmacy practitioners and students, the federal government provides a number of innovative and unique practice areas for clinical pharmacists.

## IMPORTANT GOVERNMENT WEBSITES

- Pharmacy programs within the PHS and related links http://www.hhs.gov/pharmacy/
- Links to numerous DHHS agencies http://www. hhs.gov/agencies

- VA
  http://www.va.gov
- U.S. Public Health Service Commissioned corps
  http://www.usphs.gov
- U.S. Army Pharmacy
  http://armypharmacy.org
- U.S. Air Force Pharmacy
  http://www.af-pharmacists. org/
- U.S. Navy Pharmacy
  http://navymedicine.med.navy. mil/navypharmacy
- DOD Pharmacoeconomic Center
  http://www.pec.ha. osd.mil/
- NIH Pharmacy Department
  http://www.cc.nih.gov/phar

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# Health Care Systems: Outside the United States

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## INTRODUCTION

It is quite fascinating how the organization, structure, and financing of health care services can be so very diverse in different countries around the world. One might think that leaders and policymakers would be aware of each other's national health systems and, by emulating the best features, that they would tend to move toward harmonization and greater similarity.

Actually, this assumptions is false. National health care systems vary widely and are more related to variables in each country (1). In fact, the health system in a given country is a mirror of how that society functions at large. Health care delivery systems must be compatible with the: 1) *economic system*: socialist, capitalist, or mixed; 2) *political system*: major or minor role of degree of government centralization; 3) *wealth of the country*: use of primary care facilities, access to specialists and tertiary care facilities; 4) *traditions and conventions as seen in their history*—fundamental, visible things are difficult to change; 5) *geography*: whether the majority of the population is located in a few metropolitan areas, with the remainder scattered in rural areas, or whether the population is spread over hundreds of islands; 6) *infrastructure*: roads, communication systems, and air service; and 7) *extent of and belief in high technology* (2).

There are other factors as well: the system from a previous colonial power, extent of literacy and education, and relationships with outside countries, to name a few.

## BACKGROUND

The remainder of this article examines the health care delivery systems in six very different countries. Even though Canada and the United States are similar countries with a shared border and language and with open communication, their health care delivery systems could not be any more different. Each side of the border is aware of what happens on the other side, however, a series of complex and powerful forces keep them moving in their own directions.

We look at six countries very briefly in this article to highlight the incredibly diverse approaches to health service organization and financing. In essence, most health systems fit into one of the following models:

1. State ownership and control—The best examples are the British National Health Service and the Swedish system in which clinics, hospitals, and most service providers are owned and operated by the government (3).
2. State health insurance program—Here, the government is the sole or major payer. However, some of the facilities and resources are in nongovernment hands. This is the case in much of Europe (4).
3. Mixed systems—This is seen in much of Asia and Central America and usually where there is a small wealthy class and a massive lower class. The lower class receives care from public facilities, and the small upper class uses private-sector, fee-for-service, and self-paid care.

Other scenarios fit into this category as well. The United States has several independent health care systems including the military, veterans, Medicaid (a federal program for the medically indigent), Medicare (a federal insurance program for those 65 years of age and older), private-sector for-profit, and not-for-profit clinics, hospital chains, managed-care organizations, religious, prison health, and university teaching facilities (5).

4. Exclusively private sector—This category is shrinking as nations realize that health maintenance and disease prevention/wellness are important to their national goals of strength and productivity. Switzerland would still fit into this category, where most health care resources are in private hands (6).

## SPECIMEN NATIONAL SYSTEMS

### Canada

#### Organization

Canada uses a national health service, which provides medical services and hospital care to its entire population. The individual provincial governments operate health plans that conform to national legislation but can differ in various aspects. This "Medicare" program guarantees comprehensiveness, universal access, portability, and public administration (7).

Health Canada is the national, federal health agency; however, the operation of health service provision is delegated to the provincial governments, which control virtually 100% of Canada's hospitals. There is a gatekeeper primary health care system, with GPs (general practitioners) or primary care family doctors serving as the entry point. Access to specialists, diagnostic testing, hospitals, and others is through the GP. Individual citizens have the freedom to choose their own doctors, 95% of whom are self-employed in private practice. The provincial government pays these doctors on a fee-for-service basis.

The individual provincial governments offer different supplemental benefits not covered by the national Medicare program, such as drugs, dental care, and vision care to the poor, elderly, and other specific groups. Supplemental benefits for the typical, employed, and nonelderly person come from the purchase of supplemental health insurance from private sources (8).

#### Pharmaceuticals

Canada created the Patented Medicine Prices Review Board (PMPRB) in 1987 to guarantee that pharmaceutical products would not have excessive prices in Canada. The board reviews prescribed and over-the-counter (OTC) prices and publishes annual guidelines for manufacturers. Compliance with PMPRB guidelines is voluntary; however, since 1993, the board has the authority to reduce excessive prices and return the excess amount to the government, and to punish the manufacturer.

The PMPRB compares prices in Canada with those in seven industrialized nations (France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States) to ensure that Canadian prices are in line with those of comparable countries. There is some controversy that existing drug products are well-controlled regarding prices, but that such is not the case with newly introduced pharmaceuticals.

Further controls exist at the provincial level at which each province maintains a published formulary of drugs that are reimbursable along with the reimbursement level. Quebec, observers perceive, lists nearly all new drug products, whereas Ontario appears to be slow to list newly approved products. Each province has additional control mechanisms. Ontario requires the first generic drug to be at least 40% less costly than the branded originator product. Some components of the reference price system are seen in British Columbia and Newfoundland.

There is growing harmonization among the provinces; however, there is still no national, standardized, and interchangeable list of drugs for ambulatory care use. In hospitals, drugs that are administered are paid for by Medicare. Each province has interesting and different features in its drug benefit plan.

The Prince Edward Island plan pays for seniors; welfare recipients; nursing home patients; and those with rheumatic fever, diabetes, tuberculosis, multiple sclerosis, AIDS, and several other conditions. New Brunswick has an annual copayment cap for seniors and for organ transplant recipients and for selected other patient categories. A copayment is set at approximately $9 (Canadian) but is waived for some groups in Quebec, along with an annual copay ceiling of $750.

Other interesting features of the Canadian system include its 1998 mutual recognition agreement with the EU, prohibition of prescription drug advertising to consumers, a 20-year patent exclusivity period, and the establishment of the PMPRB to ensure fair pricing of medications (9, 10).

### Republic of South Africa

#### Organization

The Republic of South Africa (RSA) has a most diverse health care environment, with world-class practice and facilities in wealthy urban areas and some of the most primitive care in poor remote villages, with a vast array between these extremes. Primary care is now the focus of the ANC government in an effort to correct years of neglect and undemocratic practices under the earlier apartheid-oriented regimes. Public health services are being brought to the Black townships as rapidly as resources permit (11).

However, there are virtually no funds for new drugs against HIV infection in patients, a problem most prevalent in the RSA. To maximize the value of its drugs budget, the RSA has enacted legislation to create an Essential Drugs List for the public sector, along with generic substitution authority, the removal of some pharmacists' unique

professional privileges, and legislation permitting the parallel importation of pharmaceutical products already registered in the RSA. Obviously, this conserves resources, stretching them for more patients, but this angers the RSA and multinational pharma firms.

South Africa is still the wealthiest country in Africa, with a (1997) GDP at approximately $130 billion. It must be noted, though, that aggregate numbers hide massive racial differences. It is improving, but the standard of living for Blacks is yet only slightly better than it is in neighboring countries, whereas whites enjoy a standard of living similar to that found in North America or Western Europe. An unemployment rate of over 30% (mostly among Blacks) exacerbates the fiscal situation (12).

Routine immunizations for children, conforming to the World Health Organization (WHO) recommended schedule is the governmental policy, but it is not yet accomplished in all regions. Infectious diseases including HIV remain a serious challenge. Planning and budgeting for resource allocation are difficult because accurate census figures do not exist. Total health expenditures appear to be in the area of $300 per person per year, and it is estimated that the private sector accounts for greater than 50% of total expenditures.

Public-sector expenditures emphasize primary care, lately, at the expense of tertiary care facilities. Private-sector spending is primarily through private "medical schemes." These are nonprofit organizations supported by employer associations and employees. There are slightly fewer than 200 of these schemes, providing insurance and care payment for nearly 3 million workers and their 5 million dependents (of a total estimated RSA population of 40 million). The largest area of medical scheme expenditure is for medicines, which causes the pressures on pharmaceutical pricing addressed below. After drugs, the next largest expenditures are for private hospitals, medical specialists, general practitioners, and dentists (13).

The RSA Department of Health (DOH) has totally restructured the previous apartheid system of racial and provincial health systems into a coordinated national health program operated through health regions and local health districts. Still, there are major differences in knowledge, education, expectations, and wealth within different subpopulations (14, 15).

### Pharmaceuticals

Until recently, manufacturers were free to establish their desired price for a drug. Wholesalers and retailers added what they chose to reach the retail selling price for medications. In 1997, a proposed scheme of prices extending to the retailer was agreed on, but resistance was met from the Pharmaceutical Manufacturers Association(PMA). In the legislation, a pricing board composed of members selected by the Minister of Health would establish prices for each product and a maximum selling price. Public-sector primary care drugs are reimbursed 100% by the government. Hospital care outpatient drugs can have copayments. The Essential Drugs List would be the core of what is to be available at public facilities, but there appears to be a long way to go before most of these agents will be regularly available on a consistent basis at primary care centers or at public hospitals (13).

The parallel importation of RSA-registered drugs available at lower prices abroad is the basis for PMA litigation against the Drug Legislation of 1997. In addition to the price-setting committee, DOH efforts to encourage the use of generic drugs has proven to be a source of conflict. Other features of the new legislation bar dispensing samples or making bonus payments to dispensers of medicines; the creation of a Code of Ethics for pharmaceutical marketing; and a series of safety regulations, dealing primarily with limiting practice to fully qualified and licensed professionals.

There is a fast lane for new drug approvals if the product is already in at least one of the following jurisdictions: the United Kingdom, Canada, United States, Sweden, or Australia. Approxmately 85% (by value) of pharmaceuticals go through the nearly 3,000 community pharmacies. Yet, approxmately 80% of the population rely on the public sector for drugs, received through clinics, hospitals, primary care posts, or military facilities. Although there is a 20-year patent period of exclusivity/protection, the parallel imports option effectively defeats this protection.

It will be interesting to see how the access to drugs, price controls, and quality improvement forces will interact and what the actual situation will be in South Africa in the coming years, especially as the country complies with intellectual property and World Trade Organization policies and rules (16).

## Japan

### Organization

After North America and before Western Europe, Japan is the second largest pharmaceutical market in the world. Its population of 126 million spends $70 billion on pharmaceuticals each year. On average, each Japanese resident spends $2000 each year on health care with $550 of that on pharmaceuticals. Perhaps the primary single features of the Japanese market are the above-average proportion of elderly in the population and the higher than usual consumption of drugs. It has been estimated that by the year 2050, nearly 30% of the population will be older

than 65 years of age. The high consumption rate is attributed to drugs being injected and/or sold by the physician, a practice used, in part, to increase the total price of an office visit (17).

The primary funding source for health services in Japan is the Social Insurance System (SIS), made up of employee programs that pay for nearly 55% of care. The Medical Service for the Aged program covers another 35% of care. Private expenditures and a very small portion for public health promotion and disease prevention make up the difference. The Ministry of Health and Welfare (MHW) maintains overall responsibility for health care services and functions via a number of bureaus. Numerous sources comment that regulations are difficult to understand and interpret, often overlapping, and that this serves as a barrier to foreign firms desiring to enter a market. Physicians, for example, are authorized to own and operate hospitals, effectively excluding corporate owners or physicians not licensed in Japan (18).

Universal health insurance was established in 1961. Nearly the entire population is covered through the employer plans or through programs for the unemployed, retired, or self-employed. Employees pay 10% of the cost of treatments, up to an annual ceiling, and also pay a portion of their premiums, with their employers.

### Pharmaceuticals

The MHW sets prices for reimbursable drugs (those approved for the Social Insurance System). Physicians, clinics, and private hospitals are reimbursed at a price slightly higher than their actual acquisition cost. The government has scheduled annual reductions in the reimbursement prices to reduce this source of additional income to physicians. Patients make copayments of 20%, although for children and low-income elderly the copayment is waived, and recently a plan to eliminate copayments for persons 70 years of age and older was introduced.

The MHW reductions of 5–10% of the prices of existing drug products appear to have had the opposite of the intended impact. Doctors are prescribing more of the newest, high-priced pharmaceuticals that have not had their margins reduced yet, thereby earning a bigger amount from the wider difference between their actual cost and the listed reimbursement amount.

With regard to generic drugs, astute observers believe that the Japanese government wants its R&D-intensive firms to be successful. A regulation requires generics to be priced at not less than 40% of the innovator brand price. It is reasonable to assume that the margins (Yakkasa) for physicians are lower with generic drugs, and that these margins will continue into the future, as will the reference price scheme (19).

There is a Japanese pharmacopeia that sets official standards and diverse government agencies that perform tasks undertaken by an FDA. It is rumored that the Japanese will establish a Western-style FDA in the near future.

One of the most disliked regulations in the view of foreign and multinational pharmaceutical companies is the requirement for duplicative clinical trials with humans in Japan, because those carried out elsewhere are not recognized. Also of interest is the fact that Japan, like Korea and Taiwan, has no separation between prescriber and dispenser of drugs. Called "Bungyo," it is a major source of revenue for doctors and clinics. Fewer than 20% of prescriptions ever reach a pharmacy for dispensing (19).

Good post-marketing surveillance practices (GPMSP) rules have been in place since 1993. Postmarketing experience reports are to be sent to a government agency. Both GPMSP and periodic safety reporting requirements are in place that require a review of the product each year while it is in its re-examination period, immediately after marketing approval. Unlike in the United States, where a new drug application is approved for an indefinite period, in Japan, there is a periodic full reassessment. Such re-evaluations are conducted every 5 years once the initial re-examination period for a drug product has ended.

Drug products are distributed primarily via the 2000 wholesalers, and in addition, there exists a small second channel with drugs going directly to hospitals, GPs, and pharmacies. There are approximately 66,000 pharmacies, most of which are family-owned independents. There are chains as well. However, a growing market for OTCs is found in convenience stores.

Physicians administer and sell drugs to patients as a highly profitable sideline. The incentive is for the physician to use as much of the most costly drug products as possible. There is only a small OTC market, because physicians try to prescribe and dispense as much as is possible. Other than some concern about a drug lag, the pharmaceutical environment in Japan is robust. Periodically, there are calls to separate prescribing and dispensing; however, this is not likely in the near future given the powerful forces backing the status quo (20).

## United Kingdom

### Organization

With a population of more than 60 million and GDP per capita of more than US $22,000, the United Kingdom is one of the richest nations in the world. It is one of the G7 countries, a member of the European Union, and a member of the Organization for Economic Co-operation and Development (OECD).

In 1996, total health care expenditure in the United Kingdom was approximately 7.0% of the GDP. Public expenditure by the National Health Service (NHS) accounts for most of the health care costs. The NHS was set up after World War II, with the aim of unifying health care services by voluntary and local hospitals. The NHS offers free health services to all U.K. residents, funded through general taxation.

Two of the major characteristics of the U.K. health care system include health authorities responsible for hospital services and GP fundholders responsible for primary care. In 1996, 100 health authorities became operational in England, responsible for the provision of NHS hospital and community health services covering geographic boundaries with populations ranging from 125 thousand to over 1 million. There are four levels of hospital services. At the community level, community hospitals offer basic medical care for the treatment of acute cases and patients requiring convalescent and long-term/terminal care. General practitioners are the key staff here. At the district level, district general hospitals operate the key acute units, serving an average population of a quarter-million. At the regional level, major specialty services such as neurosurgery, open-heart surgery, and radiotherapy are provided. At the national level, highly specialized hospitals provide complex services for parts or for the entire country (21).

GPs are the gatekeepers and fundholders of the health care system. The principle of fundholding is that GPs manage their own budgets. They can obtain a defined range of services from hospitals and manage patients at the GP level whenever possible to reduce costs. In the late 1990s, GPs fundholders were organized into Primary Care Groups (PCGs). These networks of GPs cover wide geographic areas with an average population of 100,000. In 1999, there were 481 PCGs in England and Wales, and all have unified budgets (e.g., drugs, hospital care services). With a population of a small to medium-sized HMO in the United States, these PCGs have a very broad influence on patient health care and the selection of drugs through formularies.

## Pharmaceuticals

The regulatory authority in the United Kingdom is the Medicines Control Agency (MCA) under the Department of Health. The agency's responsibilities include drug licensing, clinical trials licensing, pharmacovigilance and drug safety, communication and provision of information on medicines, inspection of facilities and enforcement of regulations, and the *British Pharmacopoeia*. The United Kingdom is a reference member state for the European Union mutual recognition procedure. The European Union's pharmaceutical registration system came into effect for all member countries in 1995. The aim of the EU system is to harmonize pharmaceutical regulations throughout the EU. The centralized registration procedure is handled by the European Medicines Evaluation Agency (EMEA). Authorization through the central registration procedure is immediately valid in all EU member countries. The decentralized procedure relies on the principle of mutual recognition. After registration has been obtained in a member country under the centralized procedure, application may be made for registration in one or more other member countries via the decentralized procedure (21).

The majority of pharmaceuticals are distributed through wholesalers to retail pharmacies, with large pharmacy chains now dominating the market. There are approximately 11,000 community pharmacies in the United Kingdom (21). In recent years, pharmacy services are increasingly available in supermarkets at the expense of local independent pharmacies.

Total expenditure on pharmaceuticals in the United Kingdom amounted to approximately 8650 million pounds in 1999, accounting for approximately 17% of the total health expenditure (21). The NHS covers prescription drugs. However, the government does not reimburse for over-the-counter (OTC) products. The Department of Health indirectly controls pharmaceutical prices. Because the price control scheme is related to profit control, rather than to the prices of individual products, pharmaceuticals are relatively free-priced in the United Kingdom. The government operates a negative list for products that are not reimbursable. The cost of most licensed prescription products is fully reimbursed. However, cost constraints and prescribing budgets mean that GPs will often prescribe a generic when one is available. As a result, new prescription drugs usually have a slower penetration rate in the United Kingdom than in the United States. The recently introduced National Institute for Clinical Excellence (NICE) will add more barriers to the introduction of new pharmaceutical products in the United Kingdom.

## National Institute for Clinical Excellence

Funded by the government, the National Institute for Clinical Excellence (NICE) was set up as a Special Health Authority in the United Kingdom in 1999 and, as such, it is a part of the National Health Service (NHS). It was set up to "provide the NHS [patients, health professionals, and the public] with authoritative, robust and reliable guidance on current best practice." Its key functions are "to appraise the clinical benefits and the costs of those [health care] interventions and to make recommendations." Guidance is issued from each appraisal based on the clinical benefits, cost-effectiveness, and total economic impact on the

National Health Service. The government does not have to adhere to the recommendations by the NICE in its guidance and financial payment to health care providers. However, many believe that a negative recommendation from the NICE will have a detrimental impact on the pricing, reimbursement, and sales of the appraised product not only in the United Kingdom but also throughout Europe, Australia, and Canada.

The guidance covers both individual health technologies (including medicines, medical devices, diagnostic techniques, procedures, and health promotion) and the clinical management of specific conditions. The Institute may recommend a technology for general use, for specific indications, or for defined subgroups of patients. Based on the appraisal, a therapeutic intervention (e.g., drug) will be classified into one of three categories: category A, routine use in the NHS; category B, further trials needed; and category C, not recommended for routine use in the NHS.

The NICE has a board reflecting a range of expertise including the clinical professions, patients and user groups, NHS managers, and research bodies. The Board ensures that the NICE conducts its business on behalf of the NHS in the most effective manner. Details of the appraisal process and membership of the Appraisals Committee are available on the NICE Web site (www.nice.org.uk). Because the NICE was new at the time of completion of this article, its impact on the pharmaceutical industry is still not clear.

## Germany

### Organization

With a population of approximately 82 million in 1998 and a GDP per capita of more than $26,000, Germany is one of the world's largest economies and health care markets. The population enjoys a generally good standard of health with a high degree of public awareness about health-related issues. Life expectancy in Germany is among the highest in the world. In 1997, the life expectancy for males was 74 years and for females 80. Approximately 15.8% of the population were over 65 years in 1997, and it has been projected that by 2020, the number of German inhabitants aged over 60 years will be 28.2% (22).

In 1997, health expenditures in Germany totaled $298 billion, equal to 14.2% of the GDP. The health care system in Germany is decentralized, and health care expenditures are covered by a variety of sources/payers. The statutory insurance system (GKV) represents the biggest proportion of the total care coverage (for almost 50%). Employers, government budget, private households, private insurance, retirement insurance, and accident insurance cover the remaining 50% of the health care expenditures. The largest spending sector is hospital expenditure, representing 34.3% of the total GKV health care expenditures (22).

The federal government has little executive responsibility for the provision of health care in Germany. Its primary responsibility is to provide a regulatory framework within which the individual Länder have to operate. The health ministries of the individual Länder are responsible for implementing the federal legislation, enacting their own legislation, supervising subordinate authorities and the medical profession, hospital planning, and regional administration.

Hospitals in Germany can be classified into three major categories based on ownership: public, nonprofit, and private. In 1997, the public sector operated approximately 40% of general hospitals, and nonprofit organizations operated another 40%. However, the number of privately owned facilities has been increasing steadily over the past decade.

The number of practicing doctors has risen steadily for the past 10 years. More than 70% of the practicing doctors are specialists, with general medicine as the largest specialty. Fewer than 30% of doctors practice without any specialty.

### Pharmaceuticals

Germany is a reference member of the EU pharmaceutical registration system. The European Medicines Evaluation Agency (EMEA) handles the centralized registration and the decentralized registration procedures in individual countries. After marketing authorization of a product with a new active substance has been granted in one country, the mutual recognition procedure is compulsory in other member countries. The mutual recognition procedure is also compulsory for line extensions and generic products. Marketing authorization approvals in Germany are valid for 5 years and renewable thereafter in 5 year periods.

Germany is the home of some major multinational pharmaceutical companies such as Aventis, BASF, Bayer, Boehringer Ingelheim, Merck KGaA, and Schering AG. VFA is the research-based manufacturers' association, whereas the Bundesverband de Pharmazeutischen Industrie (BPI) represents small and medium-sized companies. Because North America is the largest pharmaceutical market in the world, many of the VFA pharmaceutical companies locate their key operations in the United States. Exports to Western European countries represent a major source of income for many of the German pharmaceutical companies.

The pharmaceutical market in Germany is one of the largest in the world. Based on drug use per capita, Germany is second only to Japan in the consumption of pharmaceuticals. The principal distribution channels for pharmaceuticals in Germany are public retail pharmacies and hospital

pharmacies. In 1998, there were 47,322 pharmacists in Germany, equal to 0.6 pharmacists per thousand population (22). Public (retail) pharmacies employed 96% of all pharmacists in 1998 and they obtained their supplies primarily from wholesalers. Prescribed drugs, including both branded and generic products, can only be dispensed in a pharmacy with a doctor's prescription. The generics market in Germany is one of largest and fastest-growing in Western Europe, representing approximately one-third of the European generics markets. OTC products can be divided into three overlapping categories: prescription OTC medicines, nonprescription OTC medicines, and freely available OTC products that can be sold freely through all retail outlets such as health food stores, supermarkets, and other retail outlets.

## Mexico

### Organization

Mexico is a federal republic of 31 states and a federal district. The population was officially estimated to be 97.7 million in 1997. GDP per capita was estimated at approximately US $4400 in 1998. As a developing nation, communicable diseases are still one of the major causes of mortality, although chronic and degenerative diseases have become the leading cause of death during the past decade.

One of the major challenges for the government is to address the inadequacies of the Mexican health care system. Approximately 10 million people have virtually no access to regular basic health care services, and another 20 million people have less than adequate access. In 1996, the total health care expenditure in Mexico was equivalent to approximately 4.6% of GDP. Spending by the public sector accounted for approximately 60% in 1996 (23).

There are three sectors in the Mexican health care system: public, social security, and private. The public sector is primarily directed and operated by the Secretariat of Health. The public sector of health services is under the Secretariat of Health and is coordinated by over 200 health districts. The Federal District Department provides health care services to some 3.2 million people in Mexico City. The Mexican Social Security Institute (IMSS) Solidarity program covers another 10 million people in rural areas.

The social security system covers health services for government employees, managed by the Social Insurance Institute of State Employees (ISSSTE), and for private-sector workers, managed by the Mexican Social Security Institute (IMSS). The two agencies operate their own networks of hospitals and clinics and provide similar benefits. Some other smaller social security agencies exist, providing medical services for special groups such as the army, navy, and state oil company personnel.

The private (commercial) sector includes private hospitals, doctor's offices, and practitioners of traditional medicine. Charity organizations such as the Red Cross also play a role in the Mexican health care system.



### Pharmaceuticals

The regulatory authority in Mexico is the Dirección General de Control de Insumos para la Salud (DIGECIS). The Health Secretariat issues pharmaceutical registration. Safety and efficacy must be proven by phase III clinical trials in Mexico to register drugs that are new to the Mexican market. All major pharmacopeia (*International Pharmacopoeia, US Pharmacopeia, British Pharmacopoeia, French Pharmacopoeia, Swiss Pharmacopoeia, European Pharmacopoeia*, and *Japanese Pharmacopoeia*) are acceptable in Mexico.

Most domestic producers in Mexico are wholly owned or licensed subsidiaries of multinational pharmaceutical firms. Exports have been growing fast, with other Latin American countries as the major destination markets. However, the United States is the major supplier of pharmaceutical imports in Mexico.

Pharmaceuticals in Mexico are subject to government price control. The private sector accounts for approximately 85% of the pharmaceutical market. Prescription drugs account for the majority of the pharmaceutical market, with antibiotics as one of the largest classes. Because the use of generics is still a relatively new phenomenon, most of the prescribed pharmaceuticals are branded products. OTC products represent approximately one-fifth of the total pharmaceuticals market.

## SUMMARY

As presented, these six representative countries use vastly different organizations, financing mechanisms, goals, and provision structures. In fact, few systems around the world are identical because the systems represent the values and priorities and political as well as economic leanings and traditions of that country. If there were one perfect system, we would be seeing migration toward that model. However, because this is not the case, it is reasonable to assume that most of the various systems encountered around the world are at least satisfactory in their foundations and macrolevel characteristics, even if some of the operating details are not always popular (24).

The world is full of interesting additional approaches that a serious student of this subject might wish to explore further. Some of these include the "need clause" used in Norway, where, for example, their FDA had the authority

to refuse to accept and review a new drug because Norway already had six benzodiazepines on the market. The FDA deemed that sufficient unless the sponsoring company knew of a new indication or other therapeutic breakthrough from its use. The Swedes bought all of the then-existing community pharmacies in the country in 1970 to rationalize distribution, and service level and to create a monopsonistic body for negotiating with manufacturers in price-setting. The French and others place new drugs into one of several reimbursement categories. Clearly, life-saving drugs are put in the 100% reimbursement (to the patient) category. Most others strive for the 70% reimbursement category; however, if the manufacturer cannot agree on a price satisfactory to the Social Security agency, the product will be placed in a lower reimbursement category, effectively hampering its market success. This is a powerful bargaining chip for the government to contain drug prices.

It will be interesting to watch the future in this area to see how medications previously requiring a doctor's prescription that move to OTC status are handled, and how nutraceuticals, herbals, homeopathic, and naturopathic drugs, without the benefit of rigorous, randomized clinical trial or outcome data are handled as well. Similarly, we can be certain that there will be excitement galore when the nations in Central America and the Middle East decide to control pharmaceuticals and to end the practice of lay-person purchases of virtually any product without the benefit of a physician's order. Separation of pharmacy and physician functions will occur in the Far East in the not too distant future, causing even more excitement or grief.

If logic dictates, we should expect to see in the future a trend to offer incentives for prescribers who use the most cost-beneficial products (bonuses) and disincentives for patients (reimbursement level co-payment differences) and physicians when less than optimal choices are made. Irrespective of whatever does actually occur, it will be most interesting to observe.

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# Health Care Systems: Within the United States

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## INTRODUCTION

A national health care system reflects the social, political, economic, and cultural character of a nation. A nation's historical roots and dominant values shape policies and directions for the organization, quality, financing, and access to health care services. These factors determine who gets what kind of care—at which locations, for what price, and paid by whom.

The distinctive historical antecedents of American cultural and social development have shaped the present health care system. These contexts have led to a health care system that is uniquely American in character and composition. Although the issues currently facing the American health care system bear some similarity to those in other developed, industrialized nations, many of the factors are unique to the United States.

Social values, that is, the collective societal beliefs about the nature of the human being and the structure of a society, play a strong role in the development of national policies. Political and economic decisions rest in large measure on the prevailing values held in a society. Hence, if a predominant social value rests on the notion that all societal members have a right to health care, political and economic policy developments will follow suit. One way of examining these contexts is to look at a spectrum of social values.

Donabedian (1) has proposed that such a spectrum might be considered from two polar positions: libertarianism versus egalitarianism. Dougherty (2) adds the dimensions of utilitarianism and contractarianism. The essence of these taxonomies of social values is that they characterize specific sets of beliefs and values held by a wide array of individuals.

Libertarian philosophical thought places major emphasis on personal achievement and freedom from political intervention. It holds that individuals should be free to exert their rational capacity to evaluate and determine what is good for them. They can then further act on these determinations for themselves from their own personal, fiscal, physical, and human resources. To this view, Dougherty (2) adds:

> Because they can think, persons can understand their circumstances and the alternatives available to them. Because they can choose, persons can act to affirm or change their circumstances. Because they can think and choose, persons are free to create their own life plans and the values of which they are made.

It follows then, that predominant libertarian values are deeply entrenched in the notion of the self-made person and that social rewards should only accrue if they are deserved and earned. The role of government is, therefore, limited to those functions that absolutely do not abridge the rights of the individual to exert his or her own will for what he or she believes to be best. Moreover, government's role would be limited to those functions and needs for which individuals could not provide (national defense, negotiation of treaties, etc.).

Egalitarian principles focus on the equal moral standing of all individuals regardless of achievement or station in life. This philosophy also centers on the right to equal opportunity and to the extent possible, to be free from need and want. Thus, egalitarianism (2) can be viewed as follows:

> Practically, this means an equal right to a reasonable share of those basic goods and services known to be necessary for a decent human life, including a right to a job, minimum income support, or provision in kind of the goods necessary for life, as well as a right to a range of social and health care services designed to prevent and minimize psychological and physical suffering, disabilities, and premature death.

Egalitarian values place specific demands on government and political policy to construct broad services and support systems so that all members of society are provided with equal opportunity designed to prevent and minimize psychological and physical suffering and disabilities, and to achieve one's life's aims. In this fashion, government would act on the entitlements due to all members of society. Such entitlements might be derived from legal or other forms of social consensus.

This range of social values from libertarianism to egalitarianism holds differing beliefs about equality,

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justice, opportunity, rights, and the functional responsibilities of government. When this spectrum of social values is held over health, health care, and the administration and financing of health care services, it is not surprising that a vastly different array of designs emerge. Because health and health care are so tightly wound into personal, cultural, and social beliefs, it is not surprising that such a vast array of health care systems and notions about health have emerged across the world.

America's historical foundations have leaned strongly to the libertarian philosophical viewpoint (3). The influence of the "Protestant ethic" from Europe, coupled with the opportunities that a fresh land provided to "become one's own person," are strongly borne out in American society. An unbridled, free-market economy and freedom from governmental intervention in the daily lives of the citizenry are strong values that have been integrated into the American lifestyle and American political economic thought. The notion of "pulling yourself up by your bootstraps" succinctly reflects these dominant social, political, and economic values. Such antecedents are reliable markers for characterizing America's health care system. Consequently, it is a fascinating mosaic of pluralistic approaches. It is a strongly market-driven, industrialized system, which, at the same time, may be described as one of the world's best and one of the world's most troubled systems.

The United States does not have a universal health insurance program characteristic of many developed nations. Nor does it have national health care services like that of the United Kingdom and other nations. Except for those persons in the United States who possess special legal entitlements, the American health care system is largely a private enterprise; in other words, an industrialized system. The providers, payers, and institutions of care represent a rich mixture of private agents, corporations, insurance systems, and governmental agencies. There is not a singular rationalizing source for setting broad-based national policy and direction for the health care system as a whole. Rather, the vast market place of ideas has a variety of options in order to implement any proposal for which someone will pay. Relman has termed this approach "the industrialization of health care" (4).

The role of the national and state governments in the health care system is limited to those entitlement programs that have been legislated into federal or state law or where there is a federal and state partnership. Federal involvement in the provision of health care services began with the U.S. Public Health Service (PHS), an agency of the U.S. government. The PHS was established in 1798 to provide essential health care services to merchant marine personnel and members of the U.S. armed forces. Subsequent federal involvement in the provision of and the payment for health care has incrementally increased to include care for individuals with special entitlements. The latter include veterans of the armed forces, the elderly, indigent people, Native Americans, persons with HIV/AIDS, certain disabled individuals, and qualifying persons with end-stage renal disease. For example, qualified veterans of the armed forces have access to a federal system of hospitals, clinics, and long-term care facilities under the Department of Veterans Affairs (a cabinet-level agency of the executive branch of the federal government). Since 1965, the federal government sponsors Medicare, a health insurance program for the elderly (65 years of age and over and later the disabled). The federal government also cost-shares with participating state governments to provide the Medicaid program (also enacted in 1965). The latter is an insurance program for health services directed toward qualifying indigent people. In Medicare and Medicaid, institutional and individual providers participate as contractors under a set of specific conditions for participation.

State and local (city and county) governments have limited roles in the provision of health care services. State, county, and city health departments are as differently organized and functioning, as there are states, counties, and cities in the United States. These agencies reflect and represent the special needs of the geographic areas and demographic compositions of their respective domains. Hence, the functioning and expanse of services offered by the New York City Department of Health is vastly different from a similar agency in rural Montana.

This unique approach to the application of a health care system must also be examined in light of the diversity of the demography and geography of the United States. Approximately 273 million people inhabit the United States across a geographic expanse of 3.5 million square miles of land. Ranging from the deserts of Nevada to the Rocky Mountains of Colorado and Wyoming to the tropics of Florida and the oceanic seaboards of the east, west, and southern coasts, American geography and topography is expansive (5). Hence, a substantial challenge to the delivery of health care services exists in this array of geographical areas.

The American population is equally diverse and expansive. There are almost 35 million people who are age 65 or older. African Americans constitute 12.8% of the population, Asian and Pacific Islanders 4%, American Indians 0.9%, and Caucasians make up 82% of the population (5). Because the United States is largely a nation of immigrants, there are literally hundreds of additional ethnic groups that are part of the American

social fabric. As of March 1997, 25.8 million individuals in the United States were foreign-born, which represents a 30% increase from 1990, when there were 19.8 million foreign-born individuals in the United States. Mexico was the place of origin for 7 million or 28% of the total foreign born population in 1997 (5). During 1996 and 1997, 1.3 million people moved to the United States from abroad, and 92% of those individuals moved to metropolitan areas. Additionally, during this time period, 3 million people left the central cities and 2.8 million moved to the suburbs (6). The health care system of the United States should then be viewed in the following context:

- A diverse spectrum of social values, which have historically pointed more toward libertarianism than egalitarianism
- Limited roles of the federal, state, and local governments in the provision of, and payment for, health care services
- A pluralistic, free-market approach to the provision of health care services
- A geographically diverse and substantive land mass
- A culturally diverse and numerically large population whose characteristics are changing toward more elderly and racial and ethnic heterogeneity

It is critical that the reader be sensitive to these contextual variables to understand the American health care system and how health care policy is shaped and implemented in the United States.

## THE ORGANIZATION OF U.S. HEALTH CARE SERVICES

Health care services in the United States are provided by a broad array of facilities, which are financed from a variety of payment sources. As of 1998, there were 6021 hospitals (7), 1,012,582 hospital beds, 33,765,940 admissions, and 241,574,380 inpatient days. In 1998, the average length of stay in community hospitals was 6 days, whereas it was 7.7 days in 1975 (7).

It is also notable that the numbers of hospitals in urban and rural settings are shrinking. In 1993, there were 3012 urban hospitals and 2249 rural, whereas in 1998, there were 2816 urban and 2199 rural hospitals (13). The numbers of public acute care hospitals decreased from 1390 in 1993 to 1260 in 1997 (8). Closure of hospitals and simultaneous reductions in hospital beds has occurred in inner city areas where care is provided for large numbers of indigent patients. Such closures are related to the high costs of care, which are not concomitantly reimbursed by state and federal sources either because the individuals are not eligible or because payment rates do not cover the costs incurred. Small, isolated rural hospitals are facing similar economic and, hence, survival difficulties. The plight of rural hospitals is of special significance because their survival is often linked to the economic and social survival of a rural community.

While the world's population grows at an annual rate of 1.7%, the population over 65 increases by 2.5% per year. There are just fewer than 600 million people over the age of 60 in the world. Approximately 360 million of the world's over 60 population lives in the developing world, in which 7.5% of the population is elderly. In contrast, 18.3% of the population is elderly in the developed world. The most rapid changes are occurring in some developing countries where an increase of 200–400% in the elderly population is predicted over the next 30 years (9). Because of the growth of the elderly population, there has been an increase in the demand for geriatric and long-term care facilities. Over the next several decades, the elderly's health care consumption in the United States will be approximately $25,000 per person (in 1995 dollars) compared to $9200 in 1995 (10). In this respect, the United States is following the trends exhibited in most developed industrialized countries.

The increased utilization of health care services by the elderly is expected to put additional strains on an already besieged health care system. Increasing the life span, either through preventive measures or through other acts of distributive justice, solves some problems while creating others. This astounding paradox will assuredly complicate the political and social processes of decision making. Equally likely will be the burdens these phenomena add to an already overburdened national economy.

In the last several years, it is the substitutability that has been emphasized, as more and more procedures are performed in outpatient settings. Many services previously performed in the hospital now take place in physician offices. In 1996, there were 734,493,000 visits to the physician, with an average of 3.4 per person (11), and the most frequent principal reason for a visit was a general medical examination, with a total of 54.7 million in 1996. Also in 1996, there were 67.2 million visits to outpatient departments, and 40.3 million inpatient surgery procedures were performed (11). This analysis points to the increasing importance of the ambulatory care setting as a place for rendering care. The relevance of outpatient care will continue to grow as more medical procedures are performed outside hospitals and greater emphasis is placed on preventive care. Outpatient visits in community hospitals alone have advanced from 263,631,000 in 1986 to 301,329,000 in 1990 to 474,193,000 in 1998 (7).

The National Association of Home Care estimates that more than 20,000 providers deliver home care services to approximately 8 million individuals each year (12). According to the Health Care Financing Administration (HCFA), the average number of home health visits a year per Medicaid beneficiary was 80, compared to 27 visits in 1989. Additionally, the number of home health agencies participating in Medicare has increased from almost 5000 in 1988 to over 10,000 in 1997 (13). Care of patients in home settings is likely to expand as data further suggest reduced cost for such care without compromising quality. Technological and scientific developments related to providing sophisticated treatments in the home will also stimulate growth in this sector of health services.

## TRENDS IN HEALTH INSURANCE COVERAGE

According to the President's Advisory Commission on Consumer Protection and Quality in the Health Care Industry, there are five trends that summarize the characteristics of health insurance plans of the late 1990s:

- Increased complexity and concentration of health plans
- Increased diversity of health insurance products
- Increased focus on network-based delivery
- Shifting financial structures and incentives between purchasers, health plans, and providers
- The development of clinical infrastructure for utilization management and quality improvement (14)

In response to rapidly increasing health care costs, private insurance companies and employers (who pay the premiums in whole or in part for their employees) have increased their part in implementing cost-containment strategies. A dramatic effort has been the application of business principles to purchasing and vendor selection and payment for and selection of health care providers and institutions of care.

Private employers, the federal government, and state and local governments invest significant financial resources in health care purchasing expenditures. In 1995, private employers contributed $183.8 billion to private health insurance premiums, whereas the federal government spent $11.3 billion on private health insurance premiums, and state and local government spent $47.1 billion (14). In 1995, more than 83% of the insured population was covered by private insurance, whereas about 31% was enrolled in a public program, such as Medicare or Medicaid.

Probably the most significant change in the American health care system in recent years is the development of managed care. In managed care settings, the covering company is responsible for providing services, whereas, at the same time, it is exposed to the financial risks of unanticipated services. Health Maintenance Organizations (HMOs) contract with hospitals and certain physician providers for services within a negotiated schedule of fees. HMOs and other such managed care organizations specify where and by whom care is to be given. The latter is a radical departure from the historically preeminent "freedom of choice" that patients and care providers enjoyed under the traditional indemnity and fee-for-service reimbursement programs. The traditional method of paying for medical services is fee-for-service when the provider charges a fee for each service provided, and the insurer pays all or part of that fee.

Managed care is an umbrella term for HMOs and all health plans that provide health care in return for preset monthly payments and coordinate care in a defined network of primary care physicians and hospitals. A network includes physicians, clinics, health centers, medical group practices, hospitals, and other providers that a health plan selects and contracts with to care for its members. An HMO is an organization that provides health care in return for preset monthly payments. Most HMOs provide care through a network of physicians, hospitals, and other medical professionals that their members must use in order to be covered for that care.

There are a number of different types of HMOs. A staff model HMO is an HMO in which the physicians and other medical professionals are salaried employees, and the clinics or health centers in which they practice are owned by the HMO. A group model HMO is made up of one or more physician group practices that are not owned by the HMO but operate as independent partnerships or professional corporations. The HMO pays the groups at a negotiated rate, and each group is responsible for paying its doctors and other staff as well as covering the cost of hospital care or care from outside specialists. An Independent Practice Association (IPA) generally includes large numbers of individual private practice physicians who are paid either a fee or a fixed amount per patient to take care of the IPA's members. A Preferred Provider Organization is a network of doctors and hospitals that provides care at a lower cost than through traditional insurance. PPO members have more health coverage when they use the PPO's network and pay higher out-of-pocket costs when they receive care outside the PPO network (15).

An integrated health system is a network that provides a coordinated continuum of services and is clinically and fiscally accountable for outcomes. There was a significant

growth of integrated health systems during the late 1990s. In 1997, there were 228 integrated systems and, in 1998, there were 266, representing an increase of almost 17% (16). Simultaneously, there has been a disintegration of systems when mergers fail and disassemble. Iglehart comments on how managed care has changed the face of health care:

> Before the emergence of managed care, it was largely physicians, acting individually on behalf of their patients, who decided how most health care dollars were spent. They billed for their services, and third-party insurers usually reimbursed them without asking any questions, because the ultimate payers—employers—demanded no greater accounting. Now, many employers have changed from passive payers to aggressive purchasers and are exerting more influence on payment rates, on where patients are cared for, and on the content of care. Through selective contracting with physicians, stringent review of the use of services, practice protocols, and payment on a fixed, per capita basis, managed-care plans have pressured doctors to furnish fewer services and to improve the coordination and management of care, thereby altering the way in which many physicians treat patients. In striving to balance the conflicts that arise in caring for patients within these constraints, physicians have become "double agents." The ideological tie that long linked many physicians and private executives—a belief in capitalism and free enterprise—has been weakened by the aggressive intervention of business into the practice of medicine through managed care (17).

There has been a recent challenge to the core tenet of managed care that centralized decision making could deliver improved care at a reduced cost. In November 1999, a large health care company decided to allow physicians to choose what care patients need without the insurance company's intervention or approval. This action opens the door to further discussions about how managed care principles are utilized. Regardless of managed care's future course, cost containment measures will be necessary to prevent an explosion of health care costs. The demand for cost containment will need to be weighed against the imperative to insure that patients have access to care. Paul Ellwood, often referred to as the "father of the HMO," believes that there will be a new era in which patients, not employers and government purchasers, will have power (18). Regardless, the weight of political and consumer pressures, along with experience and economic efficiency, will determine the future of managed care.

## HEALTH CARE FINANCING



The expenditures for health care in the United States have grown from $51 billion in 1967 (6.3% of GNP) to over $1 trillion in 1997 (14% of GDP).[a] In 1997, on a per capita basis, $4090 was spent on health care (19) and 0.64 per day/capita was spent on prescription drugs (20). This is substantially higher than that of other industrialized nations. When comparing health expenditures in the major industrialized countries comprising the Organization for Economic Cooperation and Development (OECD), for example, dramatic differences in per capita expenditures are noted (21). Such differences also exist in the percentage share of GDP spent on health care (21), and relative growth in health care expenditures over time varies greatly among these countries (21, 22).

The Health Care Finance Administration asserts that national health expenditures are projected to total $2.2 trillion and reach 16.2% of the GDP by 2008. The growth in health spending is projected to average 1.8 percentage points above the growth rate of the GDP for 1998–2008. This differential is higher than recent experience but remains below the historical average for 1960–1997, where growth in health spending exceeded growth in GDP by close to three percentage points. There are a number of factors that contribute to the projected acceleration, including:

- An increase in private health insurance underwriting cycle
- A slower growth in managed care enrollment
- A movement towards less restrictive forms of managed care
- A continued trend toward increased state and federal regulation of health plans

The growth of health care expenditures without a concomitant gain in health status of the population is receiving more and more attention on the governmental and corporate agenda. On the governmental level, an increasing proportion of federal and state budgets is being allocated to health care. In the private sector, corporations and individuals are bearing larger proportions of health care costs. Although no particular percentage of GDP has been determined to be an acceptable or unacceptable expenditure for health care services, the fact is that costs are increasing and the health care sector is gaining an increasing share of the economy. This follows several other interesting trends. During the period of 1961 to 1997,

[a] The GNP is the total annual flow of goods and services in a nation's economy. Most industrial countries now use GDP, which measures the value of all goods and services produced within a nation, regardless of the nationality of the procedure.

national health expenditures as a percentage of GNP rose from 5.4% to over 14%. In the same period, dramatic differences occurred in the source of revenues for health care expenditures. The pattern of spending these resources also changed significantly (13).

In 1960, 49% of health care revenues came from out-of-pocket payments from individuals. Out-of-pocket spending is defined as expenditures for coinsurance and deductibles required by insurers, as well as direct payments for services, which are covered by a third party. In 1990, individual consumers spent $144.4 billion directly for out-of-pocket payments for personal health services (23). This accounted for 38% of all personal health spending. In 1998, consumers spent $183.7 billion in out-of-pocket payments, which accounts for 33% of the $558.7 billion in personal health spending (23).

Consumers have spent and continue to spend less of their own personal money for health care services. This decrease in personal spending has been shifted largely to third parties, such as private health insurance, government programs, philanthropic organizations, and other sources. It is evident that the shift away from personal, out-of-pocket health spending has resulted in greater consumption of health care services. This transition reflects the general maxim in health care economics that the consumption of health care services is probably insatiable (24). Moreover, unlike other sectors of the economy and the laws of economics they obey, prices for health care services do not fall with increased consumption or purchasing.

According to Iglehart, the decline in personal spending is "attributed in large part to the growth in health maintenance organizations (HMOs), which traditionally offer broad benefits with only modest out-of-pocket payments. In the past few years, however, most HMO enrollees have had increased cost-sharing requirements, as employers and health plan managers have sought to constrain spending even further. Out-of-pocket payments are still considerably less in an HMO than with indemnity insurance (17)." However, "The overall declines in per capita out-of-pocket spending mask the financial difficulties of many poor people and families. A recent study estimated that Medicare beneficiaries over 65 years of age with incomes below the federal poverty level (in 1997 the level was $7755 for individuals and $9780 for couples) who were also eligible for Medicaid assistance still spent 35% of their incomes on out-of-pocket health care costs. Medicare beneficiaries with incomes below the federal poverty level who did not receive Medicaid assistance spent, on average, half their incomes on out-of-pocket health care costs (17)."

Historically, a lack of public insurance programs created obstacles to health care services. For those who could not afford to pay for private insurance, the costs associated with health care were larger than most could afford. After lengthy debate, the U.S. Congress passed legislation in 1965 that established Medicare and Medicaid. Medicare covers over 95% of the elderly in the United States as well as many individuals who are disabled. Coverage for the disabled began in 1973 and is divided in two parts: 1) hospital insurance and 2) supplementary medical insurance. The total disbursement for Medicare in 1997 was $213.575 billion, and there were 36,460,143 enrollees, of which 32,164,416 were elderly.

The total expenditure for the Medicaid program was $160 billion in 1996. Of the total amount spent in 1996, Medicaid payments for nursing facilities and home health care totaled $40.5 billion for more than 3.6 million recipients. The average cost per recipient in 1996 was $12,300, and almost 45% of the total cost of care for individuals using nursing homes and Medicaid was paid for home health care (13).

Since the enactment of Medicare and Medicaid, there have been various legislative and administrative changes. The Balanced Budget Act of 1997 enacted the most significant changes to Medicare and Medicaid since its inception, including a capped allocation of monetary resources to states and the addition of the Children's Health Insurance Program. The Children's Health Insurance Program set aside $24 billion over 5 years for states to provide health care to over 10 million children who are not eligible for Medicaid.

In 1960, public programs paid for one quarter (24.5%) of all health care spending; by 1988, this share had increased to 42.1%. Together Medicare and Medicaid financed $351 billion in health care services in 1996, which is more than one-third of the nation's total health care bill. Additionally, it represents three-quarters of all public spending on health care. There has been a significant increase in Medicare managed care enrollment—from 3.1 million at the end of 1995 to 6.3 million in 1999, leaving approximately 33 million beneficiaries in a traditional fee-for-service Medicare program.

An area of controversy is the limitation on coverage for prescription drugs. Spending on prescription drugs is the fastest-growing piece of personal health expenditures, amounting to $78.9 billion in 1997. Additionally, spending for prescription drugs has increased at double-digit rates: 10.6% in 1995, 13.2% in 1996, and 14.1% in 1997 (17). The reason for this rapid growth, according to Iglehart, includes: "Broader insurance coverage of prescription drugs, growth in the number of drugs dispensed, more approvals of expensive new drugs by the Food and Drug Administration, and direct advertising of pharmaceutical products to consumers. The use of some new drugs reduces

hospital costs, but not enough to offset the increase in expenditures for drugs (17)." In the year 2000, 86% of health care plans will have an annual limit on brand and generic drugs, and there will be increased use of copayments for prescription drugs (25).

The budget cuts imposed by Congress in 1997 to help balance the budget have restricted the fees that caregivers receive for the elderly and disabled. When federal health programs cut funding significantly, as occurred in the Balanced Budget Act of 1997, the resulting cutbacks at the institutional and health-system level trickled down to providers' abilities to provide an acceptable level of service designed to protect patient safety and foster appropriate medication use. Partial restoration of the Balanced Budget Act in 1999 addressed the transition to an outpatient prospective payment system for hospitals, payments to skilled nursing facilities and home health agencies, payments for indirect medical education, and a number of rural health care provisions.

The dramatic shift of third parties (government, private health insurance) toward paying for a greater and greater proportion of personal health care services has led to a paradigm shift in attitudes and actions toward health care financing and cost control. Several approaches have been adopted in the governmental sector to slow the increases in costs and expenditures. The most dramatic of these has been the introduction in 1983 of the prospective payment system (PPS) to curb the growth in hospital costs and expenditures. By imposing prospective limits on Medicare payments to hospitals through a system of reimbursing average costs of specific diagnoses, hospital utilization has decreased dramatically. The average length of stay and admission rates in community hospitals of elderly patients (those covered by Medicare) dropped sharply after the introduction of PPS (13).

Because of cost-containment strategies of both the private and governmental sectors, hospital utilization has declined. This has resulted in a decline in the number of patient beds, the average length of stay, and patient bed census (7). The present predominant view is that hospitalization of any patient, regardless of revenue source, is to be avoided wherever possible. Only those patients for whom hospitalization can be fully justified are admitted.

As much as the financing of America's health care system is a major issue on the policy agenda of the nation, so too is the continuous question about the relationship between the costs and the outcomes of care. As costs increase, the numbers of policy analysts, organizations, and governmental agencies calling for a better definition of the cost-outcome relationship has sharply risen.

Cost-effectiveness and cost-benefit analyses are frequently mentioned in academic and policy-analysis circles. These notions center on careful examination of the costs and their corresponding outputs. Eisenberg (26) defines cost-effectiveness analysis as the measure of the net cost of providing service (expenditures minus savings) as well as the results obtained (e.g., clinical results measured singly or a series of results measured on some scale). Cost–benefit analysis determines whether the cost is worth the benefits by measuring both in the same units (26). Such analyses will be critical, as future policy decisions are made with regard to the collection, allocation, and utilization of finite resources in the health care system for the enhancement of health status of the American people.

Private-sector strategies and governmental plans to curb health care costs have not escaped criticism. Ginsberg, for example, argues that the notion of "for profit" hospital chains has severe limitations with respect to garnering large proportions of market share and, consequently, greater profits (27). He bases this view on the limited amount of private funding available for hospital care. On the other hand, he sees this sector as being able to grow in the area of nursing homes and other businesses related to the care of the elderly.

## ACCESS TO HEALTH CARE SERVICES IN THE UNITED STATES

There are three classes of individuals who have open access to and can derive some form of services from America's health care system:

- Those who receive support from governmental sources because of specific entitlements (indigents, elderly, and veterans)
- Those who are provided with basic health insurance coverage from their employers
- Those who choose to cover their expenses from out-of-pocket payments

There are, however, those who have no specific financial support or capacity to pay for health care services and who are not eligible for any type of entitlements. These individuals must rely on some form of charity care or services. In addition, there are those who, for reasons of geographic remoteness or total inability to gain access, have no access to health care services. This group represents a complex, resource-based demand model, which also has an equally complex pattern of health care system and services-utilization requirements.

With increasing health care costs and consequent increases in insurance premium costs, gaining access to

health care services without incurring personal costs has become more difficult. Not all services are covered for individuals in the federal Medicare and Medicaid programs. Moreover, there are strict limitations on the extent of services offered in these programs. A similar set of restrictions may be found in private-sector health care coverage strategies. Because few insurance programs and none of the federal programs provide coverage for unlimited long-term care, all but the very rich are at risk of financial ruin.

The health care lexicon includes two new terms to reflect these problems: underinsured and uninsured. The underinsured may include the "working poor," those individuals who have jobs and may be covered by a very limited, if any, health insurance program by their employers. They are likely low wage earners and those receiving incomes at, or slightly above, the poverty level. Typically, they do not qualify for Medicaid entitlements, do not have employer-paid health insurance benefits, and cannot afford (or choose not to purchase) third-party coverage for payment of health care services.

There are no specific policy plans available to finance uninsured and underinsured care. Whether planned as charity care or unplanned as financial loss, the "price tag" for uncompensated care in the United States was $18.5 billion in 1997, which is 6% of the total of hospital expenses (28). This percentage has remained constant since 1984, when the percentage of total expenses for uncompensated care was also 6% (8).

Reduced payments and high levels of uncompensated care have led to the closing of hospital facilities in both urban and rural blighted areas, making access to care even more difficult for some. Whiteis and Salmon (29) refer to this phenomenon as "disinvestment in the public goods." Because privately owned and not-for-profit hospitals and private clinics, pharmacies, and physician's offices must rely on their own financial soundness, any threat to that foundation may lead to closure.

The amount of uncompensated care is magnified in areas where serious social problems exist because health status is directly related to social status. Health status should be examined in broad terms by reviewing morbidity and mortality data available for the whole population. The life expectancy of people who live in the United States has grown by almost 10 years, from 68.5 years in 1936 to 76.1 years in 1996. Women were expected to live to 79.1 years in 1996, whereas the average for men was 73.1 years (11). The leading causes of death in 1996 among people living in the United States were (11):

1. Heart disease (733,361 deaths)
2. Cancer (539,533 deaths)
3. Stroke (169,942 deaths)
4. Pulmonary diseases (108,027 deaths)
5. Accidents (94,948 deaths)
6. Pneumonia and flu (63,727 deaths)
7. Diabetes (61,787 deaths)
8. AIDS (31,130 deaths)
9. Suicide (30,903 deaths)
10. Liver disease (25,047 deaths)

Infant mortality, another measure of the health status of a nation, stated as the number of deaths per live births, was 7.2 per 1000 live births in 1997 compared to 9.9 per 1000 live births for 1988. Overall, these figures are comparable to those of the major, industrialized nations of the world.

Major morbidity in the United States is currently centered on diseases of life style. These morbidities contrast sharply with disease patterns prevalent during the early part of the 20th century. Outside of AIDS and other sexually transmitted diseases, infectious diseases represent a small proportion of prevalent morbidity. Rather, life-style diseases, associated with smoking, poor nutrition, a sedentary life style, alcohol and other chemical consumption, homicides, suicides, and accidents, represent the majority of morbidity in the United States. Significant preventive strategies can markedly reduce the incidence, prevalence, and mortality associated with these health care problems.

Not surprising, in areas with high concentrations of indigent people, there are similarly high concentrations of uninsured individuals requiring intense health care services. These areas exist in both rural and urban settings. Emergency rooms have become a major resource for primary health care services in areas where physician office services or other service providers (clinics) are not available because of location, cost, or quality. Emergency rooms have also become providers of high-intensity care for victims of gun shot wounds, drug overdoses, communicable diseases, and other trauma associated with poor social conditions. Much of the care in emergency rooms is uncompensated because the quality and amount exceed the allowable reimbursement. Some trauma centers in economically blighted areas have been closed (30).

Hospitals in inner cities and blighted rural areas also care for a higher proportion of "at-risk" patients than hospitals in the for-profit sector generally located in more affluent areas (29). In fact, affluent hospitals sometimes "dump" their uncovered patients on charity care and other public hospitals in order to reduce their financial risks. This, however, increases the financial risks of public or charity hospitals. Again, the reimbursement levels under present schemes for large numbers of "at-risk" patients simply do not cover costs; thus, the United States has

witnessed hospital closings, particularly in those areas where such loss is most noticeable (30).

American health policy continues to grapple with these issues related to the underinsured and the uninsured (31). A multiple-tiered health care system based on social class and ability to pay is unacceptable in a nation that boasts incomparable riches and political agendas of democracy and rights. Ginsberg (27) notes:

> Despite all our efforts of recent years, then, health care costs continue to increase.... There is undoubtedly waste in the health care system, but no solid proposals have been advanced to recapture the $100 billion, plus or minus, that some believe can be saved. I believe that we will not reshape our national health policy agenda unless and until we achieve a broad consensus on the key issues. Do the American people, for example, desire to ensure access to health care for the entire population? In that case they must agree to pick up a sizable additional tab, which they have thus far avoided.

The issue of quality health care has become an increasing issue of concern in the face of cost constraints and limited access to health care. The *President's Advisory Commission on Consumer Protection and Quality in the Health Care Industry* (32) states that "the purpose of the health care system must be to continuously reduce the impact and burden of illness, injury and disability and to improve the health and functioning of the people of the U.S." According to the Commission, there are basic characteristics of health care that, as a nation, we should strive to achieve. The Commission has created "Guiding Principles for the Consumer Bill of Rights and Responsibilities" for the health care of people in the United States. These include the following:

- All consumers are created equal.
- Quality comes first.
- Preserve what works.
- Costs matter.

## THE FUTURE OF HEALTH CARE

Suggestions for broad reform, which address the financial, access, and quality of care issues for America's health care system, have emerged during the past decade. Iglehart emphasizes the irony of the American health care system. He writes (17):

> By many technical standards, U.S. medical care is the best in the world, but leaders in the field declared recently at a national round table that there is an "urgent need to improve health care quality." The stringency of managed care and a low inflation rate have slowed the growth of medical spending appreciably, but a new government study projects that health care expenditures will soon begin escalating again and will double over the next decade. In short, the American system is a work in progress, driven by a disparate array of interests with two goals that are often in conflict: providing health care to the sick, and generating income for the persons and organizations that assume the financial risk.

The President's Commission (32) outlines areas in which the American health care system could be improved in light of the reality that many individuals receive substandard care and 44.3 million individuals are without health insurance coverage. This commission outlines several types of quality problems including avoidable errors, underutilization of services, overuse of services, and variation in services. Based on the reality of these quality problems, the Commission recommended that the initial set of national aims should include (32):

- Reducing the underlying causes of illness, injury and disability
- Expanding research on new treatments and evidence on effectiveness
- Ensuring the appropriate use of health care services
- Reducing health care errors
- Addressing oversupply and undersupply of health care resources
- Increasing a patient's participation in his or her care

The President's Commission engages a broad consumer advocacy movement in public and private sectors calling for a major reform of the U.S. health care system to improve access to care for more individuals living in America. Consistent with previous patterns, however, these calls have only led to incremental adjustments in policy and slight quality changes in direction. The major problems, for the most part, remain unaffected. Although broad based health care reform efforts have been unsuccessful, market forces and more targeted legislation and regulatory efforts have changed the face of health in the 1990s.

The 1993–94 Clinton health care reform plan, in its ideology, provided an ambitious plan to eliminate the enormous problem of lack of access to health care. It proposed to guarantee comprehensive health benefits for all American citizens and legal residents, regardless of health or employment status. The proposal was unsuccessful due to a number of factors, including its vast scope, the complicated nature of the plan, and an underestimation of

the politics involved with radically reforming health care. The failure of the Clinton administration health care reform agenda and the subsequent events to revise the American health care system are important lessons of health-care-system related politics.

Unfortunately, since the failure of the Clinton Administration plan in 1994, the number of uninsured individuals in America has grown. According to the Census Bureau, 44.3 million people are uninsured, comprising about 16.3% of the population. Of those uninsured, 15.4% are under 18 years of age, and the largest percentage is among individuals between 18 and 24 years of age. People of Hispanic origin make up 35.3% of those uninsured and 43% of the total uninsured population are not citizens of the United States (6).

The number of uninsured persons is expected to continue to grow. Proposals for health care reform to combat this problem include President Clinton's proposal for Medicare buy-in proposals for "middle aged" adults and House Majority Leader Dick Armey's (R-TX) proposal for a refundable tax credit to pay for insurance for the uninsured. The 2000 presidential campaign opened the debate for legislation that will improve health care coverage for the uninsured. This public debate on how to enhance access to care will stimulate creative ways to improve the U.S. health care system. However, rhetoric is not enough; it needs to be translated into programs that attack the problem.

The essence of the health care financing dilemma is related to how much a nation wishes to spend, on whom these funds are to be expended, and by what methods a relationship among cost, quality, and outcomes might be determined. In a time when advancing science and technology is flourishing in the health care field, "high tech" medicine will continue to evolve with an ever-increasing price tag. Furthermore, the costs of unanticipated and complex disease problems (e.g., HIV/AIDS) add to the unpredictability of health care system costs. This is all to say that most policy makers understand what needs to be done. They are in a quandary, however, in finding the appropriate and acceptable solution. Hence, it is likely that costs and expenditures will continue to rise (and, thereby, increase the percentage of GNP that will be spent for health care) and that solutions may become even more elusive.

Although some might argue that the available resources for expenditures on health care are ultimately limited, few are able to say exactly where that limit is or should be. In the United States, there has been an expansion of technologies and procedures based on scientific advancements without a concomitant development of a moral and ethical policy for determining who might be best served by such advancements. Rationing of health care services or otherwise limiting access to high cost services, for example, has resulted from political policy rather than from deliberated public policy and rational decision making. This is most notably evidenced in the Medicaid component of the U.S. health care system.

As cost pressures continue to mount, there will likely be a return to having patients pay more of the health care expenditure dollar from their own resources. This will take the form of higher deductibles and co-insurance payments. Perhaps returning the burden of health care financing to the individual will raise the collective consciousness of American society that "there is no such thing as a free lunch" insofar as using and paying for health care services is concerned. Certainly, this phenomenon has occurred in social welfare "reform" in which the programs that have had mixed success have been restructured to "roll" participants off of welfare to work.

On the other hand, there are perhaps no solutions forthcoming on some of the problems represented in the arena of health care financing. As Hardin suggests, there is indeed a class of human problems that have no technical solution (33). In using Hardin's analogies, Hiatt (34) suggests that "nobody would quarrel with the proposition that there is a limit to the resources any society can devote to medical care, and few would question the suggestion that we are approaching such a limit. The dilemma confronting us is how we can place additional stress on the medical commons without bringing ourselves closer to ruin."

## CONCLUSION

These are the principal contemporary features of the U.S. health care system. A massive societal structure is at once saviour, behemoth, juggernaut, and question mark. It certainly will be in a constant state of flux and gradual change. It therefore bears constant vigilance and careful guidance by those who derive their livelihoods from it and those who are the beneficiaries of its caring. Most importantly, it will require significant pressure from those who are disenfranchised from it.

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PROFESSIONAL DEVELOPMENT

# Health Services Research

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## INTRODUCTION

Health services research (HSR) is a relatively new and evolving field. As the organization and financing of healthcare has changed, the need for information about the type and level of care and the effectiveness and quality of care provided in the healthcare system has increased. This chapter provides a definition of HSR, a historical perspective of the development of the field and the relationship between HSR and public health policy, and a discussion of the profession of pharmacy and its relationship to HSR. The chapter concludes by highlighting some of the institutions that commonly fund HSR and journals that publish manuscripts on HSR topics.

## DEFINITION OF HEALTH SERVICES RESEARCH

Most fields of research can be identified by the academic degree of the investigators in that area of research. However, health services researchers are identified more by the work than by the particular degree of the investigator. This diversity of degrees reflects the many disciplines that work in the field. As seen in Fig. 1, many disciplines may be involved in a given HSR project, making it difficult to succinctly define the field of HSR. In 1995, the Institute of Medicine (IOM) developed a comprehensive definition that characterized HSR as a

> multidisciplinary field of inquiry, both basic and applied, that examines the use, costs, quality, accessibility, organization, delivery, financing, and outcomes of health care services to increase knowledge and understanding of the structure, processes, and effects of health services for individuals and populations.[1]

One way to understand HSR is to examine the differences between HSR and clinical research. Although the two areas are certainly related as described here, there are differences that distinguish the two. For the purposes of this discussion, comparisons are made using three categories: 1) study setting, 2) subject selection and sampling, and 3) data sources and measures.

### Study Setting

In general, clinical trials study the efficacy of a medication or other treatment under defined conditions. HSR studies evaluate the effectiveness of care under usual conditions. Clinical trials are generally conducted in some type of clinical laboratory. That is, the intervention takes place in a controlled clinical setting where the process of care is dictated by the protocol (i.e., how often patient is followed, how often and which tests are performed at each visit). Any additional healthcare is provided external to the study setting. In contrast, data in a HSR study are gathered from the setting where routine clinical care is provided. Subject sampling and data collection follow a strict protocol, but the process of care continues according to the usual clinical practice in that setting.

### Subject Selection and Sampling

Subject selection for clinical trials generally consists of a convenience sample of a specified number of subjects that exhibit the particular syndrome or disease of interest. There are generally very strict inclusion and exclusion criteria that determine eligibility for the study. However, HSR uses population-based sampling such that all the subjects who meet a set of criteria are identified and then a sampling plan is developed to enroll a study sample that is representative of the population of interest. The population to be studied may be defined by a specific geographic location (e.g., people living in the Mississippi delta), by a specific disease (e.g., veterans with schizophrenia), or by the health care payer (e.g., Medicare recipients). It is imperative that sampling occurs in a way that allows for comorbid diseases, differences in demographic variables, and other natural variations among



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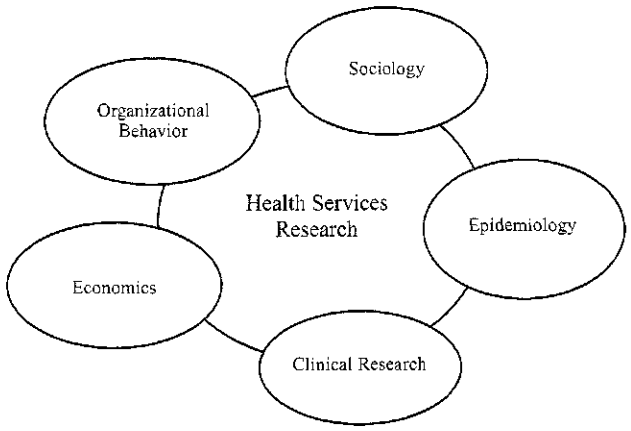


Fig. 1

subjects. Due to the extensive sampling strategies required by HSR, these projects generally require much larger sample sizes than those used in clinical research.

### Data Sources and Measures

Data for clinical trials are generally collected directly from the patient and include detailed clinical information collected by trained clinicians. These data are often lengthy and disease specific, and are designed to detect small variations among subjects. In HSR projects, lay interviewers may collect data or they may be gathered by self-report. Secondary data sources such as pharmacy refill records, paid claims data, or secondary analyses of data from national surveys are used to address HSR questions. Given the large samples in HSR data collection, instruments for primary data collection tend to be shorter and do not detect small clinical differences. Instead, they offer a broad assessment of the patients health, level of function, and well-being. Some instruments are rather "generic" and are designed for use in any population (SF-36). Others may be designed for a specific disease or population (e.g., asthma quality-of-life questionnaire, toddler quality-of-life survey).

## RELATIONSHIP BETWEEN HSR AND HEALTH POLICY

Ginzberg provides an excellent review of the history of HSR and health policy.[2] The IOM 1995 report, "Health Services Research: Work Force and Educational Issues," also provides an excellent summary of HSR and health policy.[1] Because the funding and conduct of HSR has been driven by changes in health policy, a brief overview is provided.

Using a very broad definition, HSR activities can be found as far back as the late 1800s, consisting primarily of descriptive surveys of the prevalence of disease and the number and type of health care personnel and services. Federal and state government funded most projects, although professional organizations such as the American Medical Society also paid for and conducted some studies. One of the earliest true HSR projects began in the 1920s. Between 1928 and 1932, this landmark study, known as the Committee on the Cost of Medical Care (CCMC), produced 27 field studies and final reports that provided recommendations on many aspects of health care, including hospital planning, enhancing public health, and improving professional medical education. One report suggested the use of group medical practice in association with hospitals as a means to provide comprehensive health care. Some CCMC members strongly supported a system using a federally funded health care program, although most favored a system of voluntary health insurance. A significant minority, mostly physicians, firmly opposed any insurance initiative.

Despite the recommendations of the CCMC, the federal government did not intervene in the health care system until the end of World War II (WWII).[2] During WWII, most of the United States' resources were diverted to the war effort. By the time the war was over, it was clear that U.S. hospitals had suffered due to a lack of resources. Not only were the hospitals lacking modern amenities, but also as the nation moved into suburban areas, the number and location of hospital beds were inadequate. In the late 1940s, the federal government began to enact subsidies that encouraged the expansion of the stock of technology and biomedical knowledge, hospitals, and health care personnel. This was accomplished through funding for the National Institutes of Health (NIH) and programs to increase education of nurses, ancillary personnel, and physicians. In 1946, the Hill-Burton Act provided funding for construction of many new hospitals and renovation of old ones. This was the first federally mandated health planning initiative and one of the first efforts to reduce or eliminate shortages of health care facilities in rural and relatively poor regions of the United States.

From the 1940s to the 1960s, federal healthcare initiatives focused primarily on supply issues with limited efforts to improve funding of healthcare. The 1960s marked some of the most significant changes in organization and financing of health care and, therefore, in the development and funding of HSR. In 1965, the legislation that funded Medicare and Medicaid was passed, and in 1966, the Office of Economic Opportun-

ity (OEO) was funded. The OEO opened several large community health centers throughout the United States. The federal governments new responsibility for funding and providing healthcare focused attention on the need to evaluate strengths, weaknesses, and consequences of these programs. In 1967, Congress enacted a bill that made it possible for the Secretary of the Department of Health Education and Welfare (DHEW) to establish the National Center for Health Services Research and Development (NCHSR). This new center consolidated a variety of research activities in the DHEW, and established other centers for health services research through contractual arrangements with academic institutions and other organizations. At about this same time, other federal organizations began funding HSR projects. These included the Health Care Financing Administration (HCFA) and the Department of Veterans Affairs. Ultimately, NCHSR was absorbed into the Agency for Health Care Policy and Research (AHCPR), which has been renamed the Agency for Healthcare Research and Quality (AHRQ).

By the 1970s, it was clear that costs for both Medicaid and Medicare were increasing more rapidly that anyone expected. Of particular concern was the scope of coverage provided by the Medicaid program and the cost-based reimbursement policies for Medicare. Despite only limited evidence that health maintenance organizations (HMOs) decreased costs of health care, support was increasing for use of HMOs in both the public and private sectors. During the mid-1970s, Congress passed a variety of legislation that made changes to both Medicaid and Medicare, but was unable to enact any proposal for a national healthcare program. The concern over costs for these national programs and the increasing healthcare costs in the private sector were the basis of several HSR projects to examine many aspects of health insurance and the costs incurred in these plans. However, there were problems in most of the studies, so no definitive answer was available. Because of the need for better information in this area, the OEO agreed to sponsor an extensive experiment in health insurance.

This controlled trial in healthcare financing, known as the Health Insurance Experiment (HIE), was one of the largest and longest running HSR projects ever conducted. Enrollment of a pilot sample began in 1973, and the last families completed participation in the project in 1982. The HIE randomly assigned families to four health insurance plans that varied the amount of copayment incurred by the family from 0–95% or to a staff-model HMO. One of the most notable findings of the HIE was that free care did not decrease total health care costs, as some proposed. Rather, plans in which patients received essentially free care resulted in higher total costs and higher costs for hospitalization. The HIE also suggested that cost-sharing and enrollment in HMOs was most likely to have a deleterious effect on the health of the poorest and sickest groups of patients who were enrolled. As the results of the HIE were published, many private medical insurance plans were changed to increase the amount of out-of-pocket expenses incurred by patients.

Despite the changes in the design of healthcare plans in the 1980s, the costs of medicaid and medicare and the costs to employers for private health insurance plans increased steadily. By the 1990s, there was growing interest in healthcare reform. Despite considerable effort by the Clinton Administration to propose these types of reforms, opposition in Congress prevented anything except further tweaking of federally funded plans. In both the public and private sectors, payers began to emphasize the value obtained for the dollars spent for healthcare. This emphasis on cost versus value of services is the focus of many current HSR efforts.

## ROLE OF THE PHARMACY PROFESSION IN HEALTH SERVICES RESEARCH

The pharmacy profession can offer considerable expertise to the field of HSR. Furthermore, recent changes in the healthcare system mandate that, as a profession, pharmacy must broaden its focus from individual clinical interventions to include population and system-level interventions and evaluations. The techniques used in HSR provide vital tools for pharmacy to influence health policy and, ultimately, delivery of care. Furthermore, because of their unique skills and perspectives, pharmacists can offer a distinctive knowledge base that can inform HSR.

When thinking about pharmacy's involvement in HSR, it is helpful to use seven areas of HSR outlined in the IOM's 1995 report.[1] These are 1) organization and financing of health services; 2) access to health care; 3) quality of care; 4) clinical evaluation and outcomes research; 5) informatics and clinical decision making; 6) practitioner, patient, and consumer behavior; and 7) health professions work force. By thinking about the type of research questions considered in each of these categories, it is possible to better understand both the contribution pharmacists can make to HSR and what HSR has to offer the profession of pharmacy.

### Organization and Financing of Healthcare

HSR has contributed to many proposals for healthcare reform since the 1960s. These include managed care,

consumer choice, and outcomes and performance monitoring. The field has devised tools and techniques that have facilitated the development of alternative methods of paying for health services, such as resource-based relative value scales for physician services. The recent emphasis on the provision of clinical pharmacy services has spurred an increase in studies evaluating the effect of these services on the costs of care.[3–6] McCombs and colleagues conducted an extensive study of the impact of pharmacists services on costs of care.[7] This study compared the effects of three models of pharmacy consultation services on hospital admissions, total healthcare costs, and medication costs. When compared with usual care, the consultations were associated with a lower likelihood of hospital admission and with lower total healthcare costs for high-risk patients. The consultations that focused on high-risk patients were associated with lower costs for office visits but with higher costs for medication.[7] This study is an excellent example of using HSR tools to provide the kind of evidence necessary to improve both the organization and financing of pharmaceutical care.

## Access to Healthcare

Projects that study access to healthcare evaluate factors that influence the timely receipt of appropriate care. In the pharmacy profession, access to care implies access to both dispensing and clinical pharmacy services. Examining access can highlight the effects of changes in payments for prescription medications on access to dispensing services. For example, in 1999, Straub and Straub[8] studied access to retail pharmacies in rural Illinois. This survey showed that, although current access to pharmacies was good, changes in reimbursement from third-party payers, demands of managed care, and expanded competition provided threats to access in rural pharmacies. This type of information is vital to develop health policy that will maintain access to retail pharmacy services throughout the United States.

Access to clinical pharmacy services is a somewhat more difficult issue because barriers to these services are both geographic and financial. Because pharmacists cannot obtain a provider number to directly bill for clinical pharmacy services, it is difficult for them to receive the financial incentives necessary to make this service widely available. Furthermore, because financial incentives exist only for dispensing services, patients may have access to clinical pharmacists only in special environments such as inpatient hospitalization or in systems such as the Veterans Healthcare Administration (VHA) or HMOs.

## Quality of Care

Donabedian describes quality of care in terms of the structure, process, and outcomes of the healthcare system.[9] Structure refers to the availability, organization, and financing of health care programs and the characteristics of the targeted populations. Process encompasses the transactions between patients and providers during actual care delivery. Equity, efficiency, and effectiveness serve as intermediate outcomes of the medical care delivery process, which has the ultimate goal of enhancing the populations' health and well-being. Major quality initiatives have adopted this approach. These include the National Committee on Quality Assurances, Health Plan Employer Data and Information Set, the Foundation for Accountability, the Medical Outcomes Trust, the Health Outcomes Institute, and the Joint Commission for Accreditation of Healthcare Organizations ORYX system. Relatively little work has explicitly addressed the interactive effects of organizational factors on care delivery and client outcomes. Most HSR has focused on broad structural organizational variables without studying the mechanisms that may account for differences in outcomes.

Measurement of quality is an area in which pharmacists could play a key role. Pharmacists in hospitals and other institutions are often charged with the task of evaluating quality of medication use in the form of drug use evaluation. Furthermore, many efforts at assessing quality of care rely on use of computerized prescription records.[10,11] Because of pharmacists' knowledge of clinical aspects of care along with the details of dispensing of medications and, therefore, the development of prescription records, pharmacists are poised to offer insight and leadership in quality assessment efforts in a variety of settings, particularly as it pertains to use of medication.

## Clinical Evaluation and Outcomes Research

Ellwood described outcomes management as a way to help patients, payers, and providers make rational medical choices based on better insight into the effect of these choices on a patient's life.[12] Clinical evaluation and outcomes research studies include evaluation of the impact of severity of illness on clinical and economic outcomes, the effect of patient participation in care, the role of patient preferences in medication adherence, and the relationship between quality of life and satisfaction. Many studies address the impact of pharmacist activities on economic outcomes.[4,13] Some studies also evaluate pharmacists impact on clinical outcomes.[14–16] However, in a literature review of studies that examined the impact

of pharmacists in ambulatory care or community practice, Tully and Seston found few studies that clearly demonstrated improvement of economic outcomes.[17] Only a minority of the literature reviewed included assessment of quality of life, patient satisfaction, or functional outcomes and, when assessed, these parameters were rarely significantly different after the pharmacists intervention. The authors believed these results were due, in part, to small sample sizes and problems with research design. It is imperative that studies evaluating the impact of pharmacists activity pay particular attention to study design, sample size, and outcomes measurement.

### Informatics and Clinical Decision Making

Studies of informatics and clinical decision making concentrate on the benefits of using computerized decision support systems in clinical practice and in research to measure outcomes, efficiency, and effectiveness of care. Decision analysis in clinical research employs probability analysis to express uncertainty and utility theory to express patient preferences for health outcomes.

Computers have been used as a routine part of pharmacy practice for many years. Pharmacists use this technology in many ways. For example, computers can be used to interact with physician colleagues, track patient behaviors, or as tools to evaluate cost and effectiveness of medication regimens.[18,19] Pharmacists have also investigated concordance between traditional and computerized patient records, and are now incorporating computers into patient assessment and educational activities.[20,21] This familiarity with the technology positions pharmacists to provide leadership in using informatics to examine and improve health services.

### Practitioner, Patient, and Consumer Behavior

Many HSR studies focus on the behaviors of practitioners, patients, and consumers, and the relationship between behaviors and the outcomes of care. The study of practitioner behavior includes identifying and understanding the impact of factors that influence the way providers make decisions. These factors can include training, experience, confidence level, peer pressure, patient preferences, financial incentives, and organization constraints. Strategies for changing practitioner behavior are also examined in this type of study. Investigation of patient behaviors includes treatment and medication adherence, preferences for types and delivery of services, and perceived barriers to receipt of health care services. The goal is to provide information to many types of consumers (e.g., patients, policy makers, payers, etc.) with scientifically based, understandable information that will guide decisions about many aspects of healthcare.

Clinical pharmacy has a long history of influencing provider behavior through medication formularies, clinical recommendations, drug utilization review, and provision of drug information. Pharmacists influence consumer behavior through patient education and clinical management strategies designed to optimize clinical outcomes. This experience provides a knowledge base that can be used to enhance HSR studies that seek to understand and influence patient, provider, and consumer behaviors. Pharmacists can also use the information gained by researchers in this area to improve the effectiveness of pharmacy practice.

### Health Professions Work Force

HSR also asks questions about the education and supply of health care workers. For example, a project evaluating care for rural patients with cancer identified both a shortage of pharmacists to deliver pharmaceutical care and raised questions about how well pharmacy curricula prepare pharmacists to meet the needs of rural patients.[22] Other studies evaluate the number of professionals needed to optimize costs of care or evaluate the supply and demand of health care workers.[23–25] Unfortunately, these efforts have not proven particularly successful.[1,26–28] Given the increasing concern over shortages of pharmacists, it is important for the profession to work with health service researchers to develop models to better address this issue and to study the consequences of personnel shortages.[29–32]

## FUNDING

Funding for HSR projects can be divided into four broad categories: 1) self-funding, 2) consultation, 3) contracts, and 4) grants.[33] Self-funding is fairly self-explanatory in that the project is conducted by using resources already available to the researcher. Data processing and library services are common examples of this type of resource. Some institutions may also allow junior researchers to use datasets already in existence at that institution. An important issue in self-funded projects is that the researchers time is already paid for, usually by an academic institution. Consultation provides funds that pay for the professional expertise of the researcher. The researcher combines this expertise with research activities to address the client's specific question or problem. Rand Corporation in Los Angeles, California, is one of the most prominent examples of this type of activity. Grants and

contracts provide funds to conduct a specific research proposal. Both may be funded by public or private institutions. The major difference between contracts and grants has to do with control of the project and the project funds. In a grant, the principal investigator generally controls all aspects of the project including study design, project implementation, disbursement of funds, and modifications to the original protocol. In a contract, the funding entity has much more input into all aspects of the project.

Among federal programs, the Agency for Healthcare Research and Quality (AHRQ), formerly the Agency for Healthcare Policy and Research (AHCPR), is the leader in research to improve quality of care. However, others such as the Government Accounting Office, Health Resources Service Administration, HCFA, Office of the Assistant Secretary for Planning and Evaluation, and Centers for Disease Control and Prevention also perform HSR. Individual institutes within the NIH also support services research. For example, there is a Services Research and Clinical Epidemiology Branch within the National Institute of Mental Health (NIMH) that funds services research.

The VHA has had a department of Health Services Research and Development (HSR&D) since 1976.[34] Since the mid-1980s, this department has emphasized use of health services research as a tool to improve the health of veterans. Funding from HSR&D is primarily for investigators in the Veterans Administration system, and consists of both investigator initiated research proposals and solicited proposals for specific research.

A number of large centers in the private sector are now offering grant funding for HSR. These institutions may also conduct HSR. These include the Center for Studying Health Systems Change, funded by the Robert Wood Johnson Foundation, and affiliated with Mathematica Policy Research Inc., RAND Health, the Health and Policy Center of the Urban Institute, and Emergency Care Research Institute. Key HSR academic centers include the Cecil G. Sheps Center For Health Services Research at the University of North Carolina at Chapel Hill, the Center for Health Services Research and Policy in the George Washington University Medical Center School of Public Health and Health Services, and Michigan Health Services Research at the University of Michigan.

There are also resources for identifying funding sources. The Federal Information Exchange provides an electronic service that uses e-mail to send grant information to researchers. The Directory of Research Grants and The Foundation Directory are also excellent sources for information regarding federal, state, and private funding institutions. A more complete listing is available in *Health Services Research Methods* written by Leiyu Shi.[33]



## HSR PUBLICATIONS

The specific educational disciplines of health service researchers are reflected in the wide variety of journals that now publish health research manuscripts. Journals that are devoted entirely to HSR include *Medical Care*, published by the American Public Health Association; *Health Services Research*, the official journal of the Academy for Health Services Research and Health Policy (formerly known as the Association for Health Services Research); and the *Journal of Health Services Research and Policy*, published by the Royal Society of Medicine, Ltd. Many specialized journals are beginning to publish work based on health services research. For example, *Journal of Health Economics*, *American Journal of Public Health*, *American Journal of Medical Quality*, and *American Journal of Epidemiology* will accept manuscripts based on HSR projects. Prominent clinical journals such as the *New England Journal of Medicine* and *Journal of the American Medical Association* are also increasing the number of publications of HSR projects. Pharmacy journals also contain some HSR articles, including the *American Journal of Health-System Pharmacy*, *Annals of Pharmacotherapy*, and *Pharmacotherapy*.

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# Health Status Assessment

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## INTRODUCTION

For many pharmacists, their first encounter with the terminology "quality of life" was in the 1986 New England Journal of Medicine article by Croog et al.[1] entitled "The effects of hypertensive therapy on the quality of life." The authors found that antihypertensive agents had different effects on the quality of life and that these differences can be meaningfully assessed with available psychosocial measures. Currently, the clinical community is more aware of patient-based measures and the potential uses of health status assessments. Curriculum of many schools of pharmacy now includes some information on outcomes of patient care beyond just the traditional biological measures.

This article discusses selected milestones in the evolution of health status assessments, the health status/quality of life conceptual framework(s), an introduction to the scientific basis and evaluation of patient health status self-assessment questions, and potential future research and application of health status measures to patient care, with special emphasis on its role in clinical pharmacy practice.

## DISCUSSION

> The act of measurement is an essential component of scientific research, whether in the natural, social, or health sciences.[2]

Although measurement has always played an essential role in health sciences, measurement in laboratory disciplines rarely presented difficulty. As with other natural sciences, measurement was a fundamental part of the discipline and was approached through the development of appropriate instrumentation. Subjective judgment played a minor role in the measurement process; any issue of reproducibility or validity was therefore amenable to a technological solution.

Since the 1990s, the situation in clinical research has become more complex. The effects of new drugs or surgical procedures on quantity of life are likely to be marginal.[2] Conversely, there is an increased awareness of the impact of health care on the quality of human life. Therapeutic efforts in many disciplines of medicine, especially those increasing numbers who care for patients with chronic, long-term disease states, are directed equally if not primarily to improvement of the quality of life,[3] not the quantity of life.

With therapeutic efforts focusing more on improving patient function and well-being, the need increases to understand the relationships between traditional clinical and health-related quality of life (HRQOL[a]), especially because it is increasingly used as an outcome in clinical trials, effectiveness research, and research on the quality of care. Factors that have facilitated this increased usage include the accumulating evidence that measures of health status are valid and reliable. In an effort to promote a better understanding of linking clinical variables to HRQOL, Drs. Wilson and Cleary[4] published a valuable distinction between basic clinical medicine and social science approaches to patients' health. They also propose a model to link both, which is discussed later in this article.

> In the clinical paradigm, the "biomedical" model, the focus is on etiologic agents, pathological processes, and biological, physiological, and clinical outcomes. The principal goal is to understand causation to guide diagnosis and treatment. Controlled experiments are its principal methodology, and current biomedical research is directed at fundamental molecular, genetic, and cellular mechanisms of disease. Its intellectual roots are in biology, biochemistry, and physiology.

> In contrast, the social science paradigm, or quality of life model, focuses on dimensions of functioning and overall well-being, and current research examines ways to accu-

[a]Because quality of life represents the broadest range of human experiences, use of this general term in the health field has led to considerable confusion, particularly because of the overlap with the more specific concept, health status. To make the meaning more specific and retain the important aspects of life quality, the term "health-related quality of life" is both useful and important.


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rately measure complex behaviors and feelings. Experimental research designs are rarely possible[5] because the focus of social science is on the way that numerous social structures and institutions influence individuals. These models have their foundation in sociology, psychology, and economics, and use concepts and methods often foreign to clinicians and clinical researchers.[4]

## EVOLUTION OF HEALTH STATUS OUTCOME MEASURES

During the 1940s, physicians first began to measure patient functioning; the Karnofsky Functional Status for Patients with Cancer[6] and the New York Heart Association Classification[7] were among the instruments developed during that period. The first health status measures distinguished among functional states and included symptoms, anatomic findings, occupational status, and daily living activities. Studies began in the 1950s when clinicians examined the functional status of patients with severe disabilities. When social science methods and clinical expertise came together in the 1970s, the first modern health status questionnaires emerged. Typical measures of this period include the Quality of Well Being Scale,[8] the Sickness Impact Profile,[9] the Health Perceptions Questionnaire,[10] and the OARS[11] for use in health services and clinical research as outcome measures. The next generation of measures developed in the 1980s and 1990s were the Health Insurance Experiment (HIE) health surveys,[12] the Duke–UNC Health Profiles,[13] the Nottingham Health Profile,[14] and the Medical Outcomes Study health surveys,[15] including the SF-36 Health Survey.[16]

For a more detailed discussion of the history and development of health status assessment, see Refs. [17–19]. Also, for a more exhaustive list of questionnaires, readers are directed to Spilker.[17,18,20–22]

### Variations in Medical Care in Small Areas

The impetus for research on rationality of processes in health care delivery, an issue that the field of outcomes research and guidelines development are meant to address, is typically traced to the work of John Wennberg,[23] who uncovered a phenomenon known as small area variation. In brief, Wennberg and colleagues noticed large disparities in the rates of various medical procedures in different geographic areas. The differences could not be attributed to differences in the populations, but instead appeared to indicate differences in physician cultures of different regions, where certain treatment strategies became the norm. For example, a 10-fold difference in rates of tonsillectomy was observed just within the six New England states.

### The Rand HIE

In 1990, when it became apparent in the United States that health expenditures accounted for 12.4% of the gross national product, whereas that proportion was 4% in 1980 and that the rate of growth of health care expenditures was exceeding the rate of inflation as well as growth in our economy,[25] questions surfaced. Does spending more buy better health? In individual cases, the answer may be an obvious yes or no, but in the population as a whole as of 1983, the point of diminishing (or absent) returns was difficult to identify.[12] This quandary prompted the federal government to support a large-scale controlled trial, now known as the Rand HIE.[24]

One purpose of the HIE was to learn whether the direct cost of medical care, when borne by consumers, affects their health. First, the researchers found that the more people had to pay for medical care, the less of it they used. Free care had no effect on major health habits associated with cardiovascular disease and some types of cancer. Second, the study detected no effects of free care for the average enrollee on any of the five general self-assessed health measures.

In addition to these remarkable findings, the HIE presented one of the first major challenges for measuring health status. A consequence of this challenge resulted in one of the most extensive applications of psychometric theory and methods (long used in educational testing) to the development and refinement of health status surveys. Researchers developed or adapted measures to evaluate the effect of cost sharing on health status. At that time, the comprehensive set included four distinct categories—general health, health habits, physiological health, and the risk of dying from any cause related to risk factors. General health was operationally defined as physical functioning, role functioning, mental health, social contacts, and health perceptions.[24]

The measurement goal in the HIE was to construct the best possible scales for measuring a broad array of functioning and well-being concepts; it demonstrated the potential of scales, constructed from self-administered surveys, as reliable and valid tools for assessing changes in health status. It, however, left two questions unanswered: Can methods of data collection and scale construction work in sick and elderly populations? In addition, could scales that are more efficient be constructed? The answer to these questions was the challenge

accepted by the Medical Outcomes Study (MOS) investigators.[26]

## MOS

The MOS was a 2-year observational study designed to help understand how specific components of the health care system affected the outcomes of care. One of the two original purposes of the MOS was to develop more practical tools for monitoring patient outcomes, and their determinants, in routine practice using state-of-the-art psychometric techniques. The study and its many implications and conclusions are discussed in detail elsewhere[15] and mentioned here for completeness.

## Agency for Health Care Policy and Research (AHCPR)/Agency for Healthcare Research and Quality (AHRQ)

To enhance the quality, appropriateness, and effectiveness of health care services, and access to these services the federal government in the Omnibus Budget Reconciliation Act of 1989 (Public Law 101-239)[27] established the AHCPR. The act, sometimes referred to as the Patient Outcome Research Act,[28] called for the establishment of a broad-based, patient-centered outcomes research program. In addition to the traditional measures of survival, clinical endpoints and disease- and treatment-specific symptoms and problems, the law mandated measures of "functional status and well-being and patient satisfaction." In 1999, then President Clinton signed the Healthcare Research and Quality Act, reauthorizing AHCPR as the AHRQ until the end of fiscal year 2005. Presently, its mission is to improve the outcomes and quality of health care, reduce its costs, address patient safety and medical errors, broaden access to effective services, and improve the quality of health care services.

## Summary

Now that we briefly reviewed the history of some of the origins of health status assessment research and a few of the important stimuli, we proceed with a brief discussion of some of the underlying theories and assumptions.

The design of health surveys, consisting of scales measuring attributes of a person or a population's health, are supported by underlying theory known as psychometric theory.[29] Health status scales development can also be viewed as a unique application of the design and theory that support the creation of educational measurements (e.g., Standardized Achievement Tests). A person who studies these theories and conducts research or measurement of such attributes as intelligence, pain, mental well-being, or functioning is usually a doctorate-level research psychologist and can be known as a psychometrician.

# PSYCHOMETRIC THEORY

Any type of measurement can be boiled down to two fairly simple concepts: "measurement" consists of rules for assigning numbers to objects so as to 1) represent quantities of attributes numerically (scaling) or 2) define whether objects fall into categories with respect to a given attribute (classification). The objects from a psychological perspective are usually people. The rules indicate that the assignment of numbers must be explicitly stated. The term "attribute" in the definition indicates that measurement always concerns some particular feature of the objects.

Scales can be created based on a number of different theories or models. Three commonly referenced scales are the Guttman scale, Thurstone scale, and Likert-type scale. Developing questions and scales using any of these theories requires some assumptions be made. To reduce error, one measures the extent that the assumptions[30] are met. For example, with the Likert-type scales, one needs to test that summated rating assumptions are met, or that the scale achieves maximum reliability and validity with a minimum number of questions.[31] Other examples of assumptions are that each item can discriminate itself from a different concept (measured by a different scale) and that its properties converge with other like scale items with its own concept. One might also address the reliability of the scale scores and the features of the scale distributions. For a much more extensive discussion, see Nunnaly (1994)[29] and for examples see papers written by Bayliss et al.,[30] Mc Horney et al.,[32] and Wagner.[33]

## Basic Concepts of Measurement

One readily apparent feature of health sciences literature devoted to measuring health status is the daunting array of already available scales. Paradoxically, if you proceed a little further to find an instrument for your intended purpose, you may conclude that none of the existing scales is quite right. Many researchers tend to magnify the deficiencies of existing measures and underestimate the effort required to develop an adequate new measure. Perhaps the most common error committed by clinical researchers is to dismiss the existing scales too lightly, and embark on the development of a new instrument with an unjustifiably optimistic and naïve expectation that they can do better. The development of scales requires considerable investment of both mental and fiscal re-

sources. A comprehensive set of standards, widely used in the assessment of psychology and education, is the manual called Standards for Educational and Psychological Tests, published by the American Psychological Association (1974).[34] In addition to these standards, there are a number of compendia of measuring scales.[2]

### Face and Content Validity

These terms are technical descriptions of the judgment that a scale looks reasonable. Face validity simply indicates whether, on the face of it, the instrument appears to be assessing the desired qualities. Content validity is a closely related concept, consisting of a judgment as to whether the instrument samples all the relevant or important content of domains. Nevertheless, a researcher should be cautions not to dismiss existing measures based on a judgment of face validity—for example, if they did not like some of the questions or the scale was too long. This judgment of face and content validity comprises only one of several used to decide on the usefulness, and will need to be balanced with other evaluations of the measure.

### Reliability[b]

On the surface, the concept of reliability is deceptively simple. Before one can obtain evidence that an instrument is measuring what it is intended (validity); it is first necessary to gather evidence that the scale is measuring something in a reproducible fashion. The basic idea behind the concept is an index of the extent to which measurements of individuals obtained under different circumstances yield similar results.

### Validity

Reliability assesses that a test is measuring something reproducibly; it says nothing about what is being measured; it is necessary, but it is not sufficient, to establish the usefulness of measures. To determine that the test is measuring what was intended requires some evidence of validity. Many variables in health sciences are physical quantities, such as height, serum cholesterol level, or potassium. As such, they are readily observable, either directly or with the correct instruments. The situation is different when it changes to range of motion or responsibility of a physician.

[b]For more in-depth information on this topic, the reader is directed to Refs. [2] and [29].

Presently, validity is represented as a process whereby we determine the degree of confidence we can place on inferences we make about people based on their scores from that scale. Some different types of validity, a discussion of which is beyond the scope of this chapter, are called content validity, criterion validity, and construct validity.

## DEFINITIONS

### Health

Defining health is vital to developing a strategy for measuring it. Concepts of health[35] can lack clarity yet commonly hold their dimensionality as a fundamental feature. Terms used to define health include positive states—wellness and normal—and negative states—disability and illness.[35] Clues to what dimensions comprise health are found in the definition of health offered by the World Health Organization (WHO). The WHO defines health as a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[36] Dictionaries also identify both physical and mental dimensions of health. Two features of these definitions are crucial; namely, the many dimensions of health and the range of health states from disease to well-being.

### Quality of Life

Quality of life is a global concept with many meanings. It is generally advisable to understand the domains included when the term is used. Quality of life, it has been suggested, involves highly subjective value judgments and is equated with "profound satisfactions from the activities of daily life."[37] Research and measurement of quality of life have encompassed both objective and subjective indicators involving a wide array of experiences, states, and perceptions. Cultural, psychological, interpersonal, spiritual, financial, political, temporal, and philosophical dimensions may be incorporated into various definitions.[35] In 1981, Campbell[38] defined 12 dimensions or domains of quality of life: community, education, family life, friendships, health, housing, marriage, nation, neighborhood, self, standard of living, and work. Health is but one domain or one aspect of life or the quality of one's life.

### Health-Related Quality of Life

Because quality of life represents the broadest range of human experiences, use of this general term in the health

field has led to considerable confusion, particularly because of the overlap with the more specific concept, health status. To make the meaning more specific and to retain the important aspects of life quality, HRQOL is both a useful and important term.

## MEASURING HEALTH

### Conceptual Framework/Models

Researchers have proposed a number of conceptual models of the relationships among the components of HRQOL.[15,16,39–44] Wilson and Cleary, who proposed a model linking clinical variables with HRQOL, argued that "the ultimate promise of the ability to measure HRQOL will not be fulfilled until it has clear applications to clinical care."[4] Their pursuit of this goal sets their model apart from previously published models. Their model includes five levels or subdivisions: biological and physiological variables, symptom status, functional status, general health perceptions, and overall quality of life (Fig. 1).

A comparison of different conceptual models is beyond the scope of this chapter. Because the conceptual model informs the measurement, each may be slightly different although some commonly agreed upon and frequently measured general health concepts can be identified and discussed. These concepts are: 1) physical functioning, 2) mental functioning, 3) social and role functioning, and 4) general health perceptions. By denoting a measure as a general health status measure, it is understood that the questions are not disease or disorder specific, and that they cover a range of health states from life-threatening conditions to an overall sense of well-being. General measures evaluate aspects of health relevant to all ages, races, genders, and socioeconomic backgrounds. The measures also permit the examination of the benefits of treatments in comparable units.

Using general health measures, Stewart et al.[45] compared the functional status and well-being of patients with chronic conditions. They reported the usefulness of generic (non-disease-specific) health measures for monitoring progress and for use as outcomes in studies of patients with chronic conditions. The authors maintained that there are several advantages of general measures of functional status and well-being over disease-specific measures. Among these, they noted, first, they are useful for monitoring patients with more than one condition, and second, for comparing patients with different conditions by providing a common yardstick. Last, the same measures can be appropriately applied to both general (well) and patient (sick) populations, with the advantage of comparing patient groups (sicker) with the healthy standard of a general population (Fig. 2).

### Commonly Measured Domains of Health: General Health Status Assessment

#### Physical function

Physical health is commonly measured in terms of limitations in the performance of or ability to perform self-care activities (e.g., eating, bathing, dressing), mobility, moderate or more strenuous physical activities, and bodily pain. Responses to questionnaire items in this category

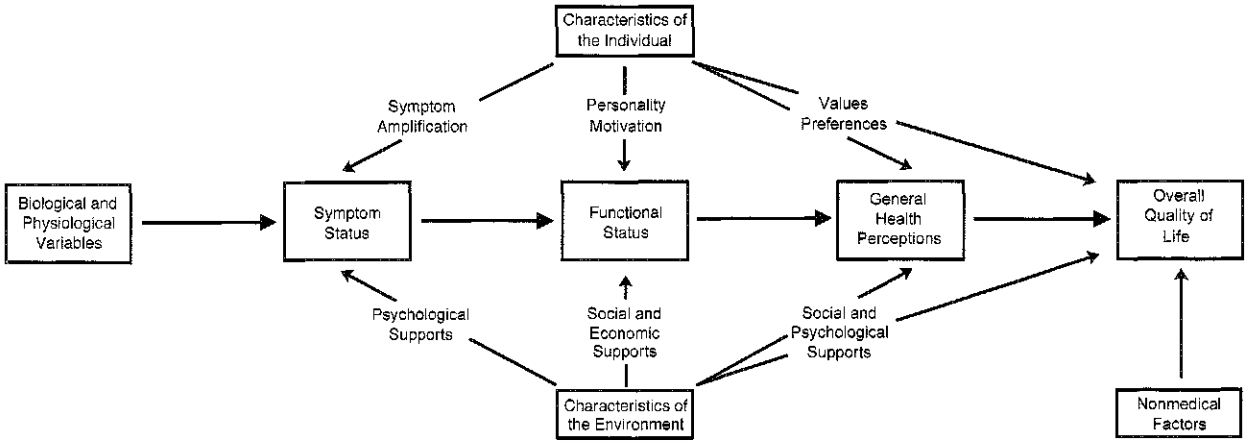


**Fig. 1** Relationships among measures of patient outcome in a HRQOL conceptual model. (From Ref. [4].)

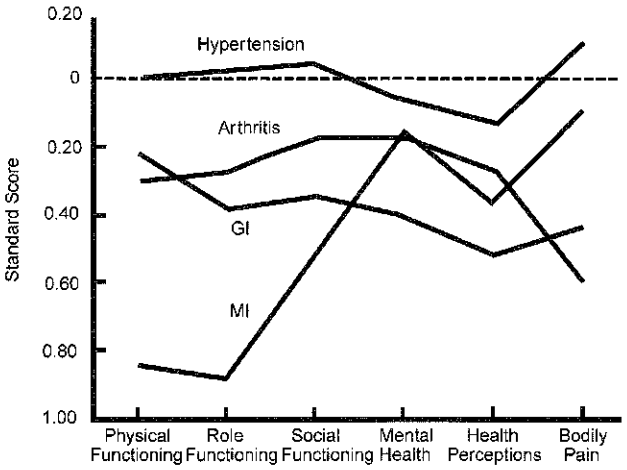


**Fig. 2** Health profiles for patients with four conditions. Dotted line indicates patients with no chronic conditions. GI, gastrointestinal disorder; MI, myocardial infarction. (From Ref. [45].)

generally focus on limitations due to physical health as opposed to some other cause.

Assessments of physical health often vary in the range of functioning. Questionnaires that assess self-care often concentrate on the negative end of the continuum of physical functioning; some determine different physical health states, and others determine individual differences in the level of effort, pain, difficulty, or need for assistance in performing physical activities.[46,47] Thus, individual patient responses to question may be identical or may different substantially from one test to another. To be comprehensive as measures of physical health status for a population, measures for general use are recommended[46] to elicit information concerning activities of daily living, energy level, satisfaction with physical shape or condition, and ability to perform vigorous activities. Questions in those areas are sometimes phrased positively to extend the measurement scale into the positive range (how we feel as opposed to the limitations we experience). This allows measurement only of differences in physical well-being among those free of limitations.

## Mental health

These measures often focus on the frequency and intensity of psychological distress (e.g., anxiety or depression), and include the individual's perception of psychological well-being and life satisfaction and an assessment of cognitive functioning.[48] Measures of this domain also cover the broad range of differences possible in the mental health continuum. Health disturbances commonly manifest themselves on behavioral and physical levels; however, mental health can change long before observable changes in behavior. Furthermore, clinical and social changes in mental health do not always manifest as distress or cognitive dysfunction. Disease or illness may cause a loss of zest for life or the feeling that life is less enjoyable. Capturing such a change requires the presence of questions that assess psychological well-being; therefore, general measures should encompass the full range of states in the continuum.[49]

## Social and role functioning

Functioning in interpersonal relationships and in role and other daily activities are commonly lumped together as measures of social functioning. However, for evaluating HRQOL it is better to consider them separately.

Social functioning is defined as the ability to develop, maintain, and nurture mature social relationships. Our group has concluded that measures of social functioning 1) reflect physical and mental health status, 2) serve to indicate the need for health care, and 3) reflect appropriate outcomes of health care.

Usually, social well-being is separated into two areas: 1) whether and with what frequency social contacts are occurring and 2) the nature of the person's social network or community. The frequency and number of contacts, as well as personal satisfaction with those contacts, vary a great deal amount individuals. Depending on the person, quantitative data may offer no insight or may offer the wrong insight. A person's evaluation of the adequacy of the social network to which he or she belongs may be more valuable. People who consider themselves part of a community, family, or neighborhood often have a strong sense of being wanted, loved, or valued.[50] Measures of personal resources often overlap the mental dimension of health. The feeling that one is loved or cared for may assess mental health even more than it measures social well-being. Some research reviewed by Wortman[51] suggested that social circumstances are linked to both physical and mental health outcomes.[52]

Role functioning describes whether a person can meet the demands of their normal role in life (e.g., formal employment, schoolwork, housework). Persons not working in outcomes research often use the terms role function and social function interchangeably; however, in terms of measuring HRQOL, they are distinct. A role function measure seeks to identify situations in which an individual's health problem directly interferes with the performance of their everyday role, in contrast to participation in the social interaction and network to which they belong. For example, arthritis strikes a professional organist who has a loving and supportive family and a

network of friends. He may not feel isolated or unloved, and his relationships with his wife and children continue to be positive. However, to the man for whom music is fuel for mental, financial, and spiritual well-being, the loss of his professional role may be devastating. That devastation is a role function loss. If he then lost the friendships he developed and maintained through his music, then that would be loss of social function.

For many people, physical health problems limit role performance. Occasionally, mental disruption can impinge on role functioning, but measures of this health dimension seldom detect mental or emotional problems because patients seldom consider role limitations unless they are asked about them explicitly. Some questionnaires ask specifically about limitations of role function due specifically to personal or emotional problems, in addition to those due to physical health problems.

Measurement of the impact of health on role activities has grown, owing in part to legislation and information provided by the passage of the Americans with Disabilities Act.[53] Approximately 55 million working-age individuals (18–65 years of age) have chronic illnesses and/or impairments. Disabilities are a potential consequence of health problems and signify a partial or total inability to perform social roles in a manner consistent with norms or expectations.[53] National survey data suggest that 32% of employed adults have ongoing health problems that interfere with their ability to perform their job demands.[54] Historically, although limited, studies have used outcomes of "work loss" or amount of time missed from work due to illness or treatment.

Role functioning scales usually measure global, role-level disability indicators to capture disability in paid work and/or other activities. However, for some applications, these may be relatively course, distinguishing a limited range of disability levels. Recently, researchers introduced a more detailed measure of work productivity assessing on-the-job impact of chronic conditions and treatment.[54]

### General health perceptions

The beliefs and evaluations of a person's over health in general, rather than a particular mental or physical aspect, constitute their general health perceptions. Questions in this area reflect each person's own health preferences, values, needs, and attitudes, and thereby discriminate between individuals whose objective levels of physical and mental health, as defined by other measures, appear identical. Such self-perceptions are important for two reasons: 1) reports of behavioral performance do not capture important subject manifestations of differences in health such as pain, difficulty, level of effort required, or worry and concern about health; and 2) questions in this domain inquire about positive feelings or a positive frame of reference, for example, a favorable health outlook in contrast to questions from other domains that focus on measures of limitation, pain, or dysfunction, and are usually stated in a negative way. Responses in the general health perception domain are subjective and evaluative. They are typically ratings rather than reports, for example, a rating of health from "excellent" to "poor."

## Disease-Specific Health Status Instruments

Often, it is necessary to focus on the particular impact that a certain disease has on patients. In such cases, general health status tools are inadequate for providing the information needed. To overcome this limitation, condition- or disease-specific measures are often used instead of or along with a general health status instrument. The more narrowly focused disease-specific measure requests detailed information on the patient's perspective on the impact of a disease and its treatment. In addition, using disease-specific measures allows inclusion of domains of specific interest for the disease under study and the patients it affects. Among the specific areas previously investigated with disease-specific questionnaires are sexual and emotional functioning, nausea and vomiting, chronic pain, anxiety and depression, chronic obstructive pulmonary disease, cardiovascular disorders, hypertension, epilepsy, benign prostatic hypertrophy, end-stage renal disease, diabetes, cancers, AIDS, HIV infection, and migraine.[20,55–57] The reader is directed to Refs. [20] and [22] for a more comprehensive listing of disease-specific questionnaires.

The argument in favor of disease-specific questionnaires is twofold. The first consideration is that, if an instrument has to cover a wide range of disorders, many of the questions may be inappropriate or irrelevant for any one specific problem. The second reason is to keep the length of the questionnaire manageable. Thus, there will be fewer, relevant questions to detect real changes within patients or to detect differences among them.

On the opposite side of the argument, the cost of a greater degree of specificity is a reduction in generalizability.[58,59] That is, generic scales allow comparisons across groups of patients with different disorders, severities of disease, interventions, and perhaps even demographic and cultural groups,[60] as well as being able to measure the burden of illness of populations suffering from chronic medical and psychiatric conditions,[32] as compared with a healthy population. This is much harder to do when each study uses a different scale.

Furthermore, because any one generic scale tends to be used more frequently than a given disease-specific instrument, there are usually more data available regarding its reliability and validity.

## THE INTERNATIONAL QUALITY OF LIFE ASSESSMENT (IQOLA) PROJECT

As the integration of patient-based outcome measures into all sectors of health care expands, the need arises for instruments capable of capturing data across cultures. In recent years, a rapid increase in the number of available translations of both generic and condition-specific instruments has occurred throughout the world.[61] The rise in demand for translated instruments is partially driven from the need to aggregate data from two or more cultures in clinical trials.

The IQOLA Project is translating, validating, and preparing norms for the SF-36 Health Survey for use in multinational clinical trials and for other international studies.[62–66] Based at the Health Assessment Laboratory at New England Medical Center, the project began in 1991, with sponsored investigators from 14 countries.[c] In addition, researchers from more than 30 other countries are translating and validating the SF-36 using IQOLA Project methods.[d]

The general process of translating an instrument is very complex, and is oversimplified here to give the reader a brief introduction only. The instrument is translated from the source (original) language to the target language (forward translation). Several forward translations are conducted by translators residing in the target country who are familiar with the tenets of the field of health outcomes. Then a consensus meeting with experts is convened to evaluate the efforts. A quality control step exists to ensure that the target version is equivalent to the source version, both conceptually and linguistically. This usually includes a backward translation from the target language to the source (original) language. The instrument is then pretested, which marks the final stages of the translation process.

[c]Australia, Belgium, Canada, Denmark, France, Germany, Italy, Japan, The Netherlands, Norway, Spain, Sweden, United Kingdom (English version), and United States (English and Spanish versions).

[d]Argentina, Bangladesh, Brazil, Bulgaria, Cambodia, China, Croatia, Czech Republic, Estonia, Finland, Greece, Hong Kong, Hungary, Iceland, Indonesia, Israel, Korea, Mexico, New Zealand, Poland, Portugal, Romania, Russia, Singapore, Slovak Republic, South Africa, Taiwan, Tanzania, Turkey, United Kingdom (Welsh), United States (Chinese, Japanese, Vietnamese), and Yugoslavia.

## USING HRQOL ASSESSMENTS IN CLINICAL PRACTICE

When you ask a patient or any person, "how are you?", what type of information do you expect in response? Do you direct the patient in what units to answer? For example, how are you? ... I am fine. If prompted, the respondent could produce a rating of how they think they are doing ... "On a scale of 1 to 10, I am a 2." Likewise, the answer could include a reference to the time span on which they are reflecting when answering your question. Such as, "At this moment, I am just fine, in general my life is a bit unsettled."

This example underscores and oversimplifies developers' thought processes when developing items to measure the domains of health. A measurement strategy can be defined to obtain as little or as much information. Ultimately, the amount of detail in the answers depends on what one plans to do with the information. The first, "I am fine," is a global assessment. The second "I am a 2," is an example of a rating scale. The third gives you and example of what one might call a recall period, or more practically, what time frame do you want the information from, yesterday, in the past 4 weeks, or in the last year. To obtain breadth in the answer to your question, you need to identify the potential extent of the answer, such as "including both the physical and mental dimensions of health." Last, how much depth do you want in the reply? Parameters such as rating, breadth, depth, quantity, and frequency are the details with which measurement experts' struggle when developing patient self-administered health status questions.

Fig. 3 is an example of a mental health status subscale from the SF-36 Health Survey,[4,16,67] a popular general health status measure or instrument. The subscale is commonly referred to as the Mental Health Inventory, or the MHI-5. The five questions are each called an item stem. The balance of the item consists of the response choices; which are designed to be the same for many different items, thus making it less burdensome to the respondent.

The respondent is instructed to answer each question "about the past 4 weeks" (the recall period) and indicate "how much of the time" (quantity in amount of time). The response choices are: 1) all of the time, 2) most of the time, 3) a good bit of the time, 4) some of the time, 5) a little bit of the time, and 6) none of the time. Each of the patients' answers to the five questions are assigned a number between 1 and 6, summed and averaged, and then converted to a score between 0 and 100, with 100 being best health and 0 being worst.

Some of the questions require an endorsement such as how often have you been a happy person. In that case, the

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks?

| | [1] All of the time | [2] Most of the time | [3] A good bit of the time | [4] Some of the time | [5] A little of the time | [6] None of the time |
|---|---|---|---|---|---|---|
| Have you been a very nervous person? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Have you felt so down in the dumps that nothing could cheer you up? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Have you felt calm and peaceful? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Have you felt downhearted and blue? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Have you been a happy person? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

**Fig. 3** Example of a mental health scale from the SF-36. (From Ref. [5].)

response "all of the time" indicates better health. However, other items are stated so that "none of the time" indicates a better health. Such items are reversed before scoring. An example is "how often have you felt so down in the dumps that nothing could cheer you." Persons answering "none of the time" need to be assigned a scoring indicating better health, or the opposite direction of the endorsed items.

## Advantage of Health Status Assessment Information to a Health Care Professional

Self-administered surveys allow the patient to have a voice in their care. It permits the patient to communicate to the health care professionals who are caring for them about what matters most. This may be information that you need to know but do not have time to elicit. Analogously to providing a common language for patients and health professionals, the general HRQOL information can also provide a standard or common language for different disciplines of health care professionals. For example, a nephrologist and a psychiatrist can use a common metric to discuss a dialysis patient's emotional health. A standardized method of asking patients about their functioning and well-being can be efficiently used in treatment decisions and as a monitoring parameter for efficacy and toxicity. The information may also be a tool or indicator for compliance assessments.

In addition, HRQOL can be used to add important information to the evaluation of the effectiveness of an intervention, in terms that matter most to the patient. For example, does the 34-year-old otherwise healthy woman diagnosed with depression who just started an antidepressant feel better or worse? One could just simply ask her that question when you see her 4 weeks after the start of her therapy. As pharmacists, we commonly use the question, "Are you having any side effects?" If the patient tells you she has diarrhea, you may form an impression of that diarrhea—seems like a mild side effect. However, having her answer survey questions about her functioning can reveal how trivial or nontrivial the impact of her diarrhea is to her everyday activities. What would happen if her diarrhea limits her ability to function as the checkout person in the grocery store? She cannot leave her post frequently to go to the bathroom and, if she does, she could be fired and not be able to provide for her two young children that she is raising alone. The patient sees the limitation imposed by diarrhea as considerable, and knowing more about her functioning conveys a different message to us than just knowing she is having diarrhea. A discussion employing information from a patient self-administered health status survey could also lead to the patient revealing that she has decided to stop taking her medication. She did not think it was working and the diarrhea was not worth the hassle.

## Pharmacists Use of Health Status Assessment Information

As pharmacists, we can use evidence from patient self-administered health status surveys in caring for patients.[68] A common model used in teaching students to monitor therapy is to first create a problem list and, for every problem on the list, develop an assessment and plan. The diagram in Fig. 4 breaks down the assessment process. It requires one to write a potential inventory of all monitoring parameters. It reminds and guides us to monitor both the efficacy and the toxicity using subjective and objective parameters appropriate for the disease and the treatment.

We can easily incorporate the information from health status surveys in any of these boxes. Examples are bolded in Fig. 4. Now, instead of just monitoring clinical parameters of efficacy and toxicity, we can extend our

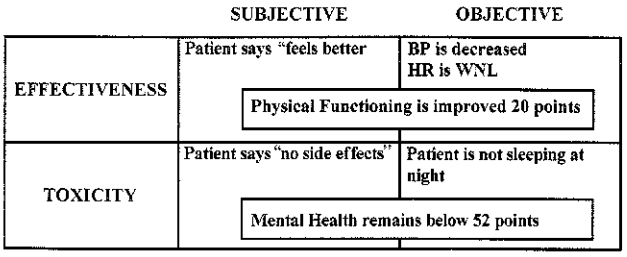


**Fig. 4** Pharmacist assessment and monitoring therapy with health status assessment information included into typical paradigm.

monitoring parameters to include how a patient is functioning and feeling. For instance, is the patient able to go to the store and buy food? Do the patient's medications allow them or prevent them from socializing? Is their role in life supported by the therapy, or is it harder to do what they normally consider their job, whether home with kids or in the office.

Imagine that you get a number back just as you would a laboratory test from a scored survey. Where would you place it in the existing paradigm? What will do with it? If the patient's physical functioning after cardiac surgery and a new medication regimen is up 20 points, that could be a quantifiable part of your subjective information, or it could be considered in the objective category of effectiveness. However, if that same person still had a mental health score below 52, thus indicating a high probability of depression, then that could be reported as toxicity. Although it could be a consequence of the seriousness of his treatment (45-year-old man who just suffered a myocardial infarction), it could also be related to his medications. This is just a start; there is much more to be done to develop the use of these measures in the care of individual patients. However, it seems that the information on patients' functioning and well-being at a minimum can help pharmacists to better assess compliance and reasons for noncompliance. It also presents an opportunity to be better informed about the patient and tailor education strategies to fit the individual.

## Controversies in Using Health Status Assessments for Individual Patient Care Decisions

Standardized measures capturing patient perspectives on their physical functioning, social and role functioning, mental health, and general health perceptions are likely to become more acceptable as an additional piece of evidence on which providers and their patients can make decisions about treatment and the treatment's efficacy. Mature theoretical models,[4,69] sophisticated measurement techniques,[70,71] and enhanced technology for use in measurement make the routine use of individual patient results in their own care more promising than ever before.

Two practical concerns of the critics of use of HRQOL assessments in individual patient care are: 1) respondent burden and 2) reliability of scores obtained from shorter questionnaires. Current researchers struggle with the competing demands invoked by everyday use requiring shorter forms and the reliability of a result obtained from fewer questions. Specifically, concerns are raised about the reliability of the result and the interpretation. With popular outcomes measures, the standard error around a single person estimate is large and not satisfying enough to ensure stable conclusions.

Modern test theory offers the potential for individualized, comparable assessments for the careful examination and application of different health status measures.[69] One such theory is item response theory (IRT). Researchers report that IRT has a number of potential advantages over the currently employed classical test theory in assessing self-reported health outcomes. Applications of the IRT models are ideally suited for implementing computer adaptive testing.[55] IRT methods are also reported to be helpful in developing better health outcome measures and in assessing change over time.[70]

Patients increasingly have more access to computer technology. It is becoming more practical to employ assessments using a computer. Patients answering questions about a health status concept using dynamic assessment technology are requested only to complete the number of questions needed (minimizes response burden) to establish a reliable estimate. The resulting scores for an individual are estimated to meet the clinical measures of precision.

## CONCLUSION

The study of HRQOL requires a multidimensional approach. Assessments must include components that evaluate, at a minimum, the health concepts of physical functioning, social and role functioning, mental health, and perception of general health. In addition, the full continuum of these concepts must be included, from the most limited to the healthiest. Approaches to capture HRQOL data include the self-administered questionnaire, personal interview, telephone interview, observation, and postal survey. The assessment instruments must possess acceptable reliability, validity, and sensitivity, and the investigators and the participants must accept them. Psychometrics

is an essential part of HRQOL research, especially in today's research environment that requires shorter, more focused measures.

Existing health outcomes measures drawn from classic test theory and emerging approaches based on item response theory offer exciting opportunities for appreciably expanded applications in biomedical and health services research, clinical practice and decision making, and policy development. The research agenda of measurement scientists includes challenges to: 1) refine and expand measurement techniques that rely on IRT; 2) improve measurement tools to make them more culturally appropriate for diverse populations, and more conceptually and psychometrically equivalent across such groups; 3) address long-standing issues in preference- and utility-based approaches, particularly in the elicitation of preference responses and scoring instruments; and 4) enhance the ways in which data from outcomes measurement tools are calibrated against commonly understood clinical and lay metrics, are interpreted, and are made useable for different decision makers.[19]

With the advances in measurement that promise to continue, knowledgeable clinicians will become the transportation for these measures to inclusion in patient care. Interpretation, it is suggested, is partially an issue of familiarity and repeated applications of the measures would lead to a better understanding. Ideally, a better understanding of what a patient tells their provider about their health status can be used for decision making that requires the patient to more actively and routinely participate in their own care.

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PROFESSIONAL DEVELOPMENT

# Health-Systems, Clinical Pharmacy Careers in

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## INTRODUCTION

Health systems evolved from a hospital into multiple facilities and levels of care during the 1980s and 1990s in the United States. A health system can include more than one hospital, ambulatory care clinics, physician office buildings, long-term care facilities, and home care services. The economic forces, both internal and external to the hospital, led to the development of health systems. From a pharmacy perspective, the scope (range) of pharmacy services expanded from acute care to ambulatory care, to home care, to long-term care, and to other diversified pharmacy services. Consequently, positions for clinical pharmacists expanded from acute care to the other care settings within the health system.

## RANGE OF CAREER ACTIVITIES WITHIN THIS FIELD

A simple description of the range of career activities within health system pharmacy would be acute care, ambulatory care, and home care to administrative pharmacist positions. A more detailed description of pharmacist positions within the health system is as follows.

### Acute Care

Acute care relates to hospitalized patients. Patient care areas within a hospital include internal medicine, general surgery, pediatrics, obstetrics and gynecology, critical care, cardiac care, pulmonary critical care, psychiatry, oncology, and geriatrics.

### Ambulatory Care

A health system can own and operate its own ambulatory clinics and physician offices. The physician component can be either by staff physicians employed by the health system or by contract for physician services.

### Community Pharmacy

A health system can own and operate its own licensed community pharmacies. Prescription services and clinical services can be provided.

### Geriatrics and/or Long-Term Care

A health system can own and operate its own licensed long-term care facilities or license beds within the hospital for long-term care.

### Home Care Services

A health system can own and operate its own home care services for nursing care, prescription drug products, and pharmacist services.

### Drug Information Service

A health system can own and operate its own drug information service (DIS) to serve the drug information needs of pharmacists, physicians, nurses, and other professional staffs within the system. In addition to drug information, the DIS focuses on drug formulary and pharmacoeconomic issues of drug products and drug use within the system.

### Therapeutic Drug Monitoring Service

A health system can own and operate a centralized therapeutic drug monitoring service (TDMS) to focus on the application of clinical pharmacokinetics to the care of patients within the system.

### Management of Pharmacy Services

Depending on the size and complexity of the health system, pharmacy management positions will range from the



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director of pharmacy services to supervisor of a segment of the pharmacy services within the health system. Some examples of pharmacy manager positions include supervisor of the drug information service, supervisor of the therapeutic drug monitoring service, supervisor of ambulatory care services, supervisor of community pharmacies, supervisor of clinical services, and assistant director of pharmacy services.

## WORK SETTINGS AND JOB ACTIVITIES

The typical work settings for clinical pharmacists in a health system include acute care hospital, ambulatory clinic, outpatient pharmacy, home care pharmacy, and community pharmacy.

Clinical practice in the hospital could be in the central hospital pharmacy, a satellite pharmacy, a pharmacist's office, or a patient care area. The hospital pharmacy is usually located on a lower floor of the facility, which places the pharmacist physically remote from the patient, physician, nurse, and other personnel. Communications are often by telephone, fax, or information technology rather than in person. A satellite pharmacy is a pharmacy area located in the patient care area where drug distribution and clinical services are provided. A satellite pharmacy places the pharmacist in the patient care area where drug distribution and clinical services are provided. A satellite pharmacy facilitates the placement of pharmacists in close proximity to the patients, physicians, and nurses. A pharmacist's office space is often provided as a location for the pharmacist to provide clinical services that is in close proximity to patients, physicians, and nurses. Clinical services can be provided in a drug information center, often located in the hospital pharmacy, but it may be located in the medical library. Therapeutic drug-monitoring services may be provided from a pharmacist's office location.

Clinical practice in an ambulatory clinic may be provided from an office area within the clinic. The patient, patient medical record, physician, nurse, and other practitioners are in close proximity to the pharmacist's office area. Examples of clinics in which pharmacists have provided clinical services include family practice, OB-GYN, anticoagulation, prescription refill, pain therapy, nutrition, and internal medicine.

### Outpatient Pharmacy

The health system may own one or more community pharmacies. Clinical services can be provided relating to patient drug therapy counseling for prescription and nonprescription medications, management of drug therapy via physician-approved guidelines, monitoring of drug therapy, and screening tests for hypertension, diabetes, and hypercholesterolemia.

### General Clinical Practice Model

The following list of pharmacist practice activities describes a general clinical practice model:

- Clarify prescription orders.
- Question inappropriate prescription orders.
- Answer drug information requests from patients.
- Answer drug information requests from physicians, nurses, and other health professionals.
- Monitor patient drug therapy for safety and efficacy using a comprehensive patient medication record:
  - Drug–drug interactions.
  - Concomitant drug therapies.
  - Appropriate drug, dose, and dosage form.
  - Patient allergies.
  - Drug–laboratory test interactions.
  - Drug–food interactions.
  - Abnormal laboratory tests that are drug induced.
  - Clinical pharmacokinetics.
- Provide patient medication counseling.
- Provide screening tests.
- Participate in collaborative practice agreements for managing drug therapy.
- Participate in clinical research.

## EDUCATION, TRAINING, AND EXPERIENCE

The preferred education for a health system pharmacist is the doctor of pharmacy degree. A general practice residency is also preferred. Some clinical pharmacist practices prefer pharmacists with a specialty residency. The American Society of Health System Pharmacists for the past 25 years has adopted policies and provided programs to support these preferred education and training programs. When the criteria can be met for board certification, many health systems support clinical pharmacists in becoming board certified.

Pharmacist clinical expertise requires practice, practice, and more practice. Years, usually three to five, are often acceptable to health systems in lieu of some residency training. The challenge is to get appropriate clinical practice experience without a residency.

For supervisory positions, three to five years of practice experience is often required. During the practice experience, the pharmacist should demonstrate the ability to achieve results, complete objectives on a timely basis, possess good communication skills, and demonstrate good working relationships with coworkers, physicians, and nurses.

For director of pharmacy services, five to seven years of experience are often required in a similar health system. Additional education and training, such as an advanced residency in pharmacy management or a masters degree in business administration, are often preferred or required. Ability to manage resources, personnel, planning, financial, and interprofessional relationships with good communication skills are often required.

## CAREER LADDERS AND GROWTH

Career ladders and growth within a health system can be viewed as longitudinal and/or lateral. Longitudinal would be from staff pharmacist to director of pharmacy services. Lateral would be clinical pharmacist from acute to home care.

The usual longitudinal path is staff pharmacist to clinical pharmacist, to supervisor of clinical services, to assistant or director of pharmacy services. Each practice along this path requires demonstrating knowledge, skill, and the ability to learn more; assuming new responsibilities; and successfully performing the duties and responsibilities of each position. Additional education and training often will speed the time line for the longitudinal career path.

The lateral career path relates to clinical practice at different patient care levels or settings. Acute care to ambulatory and/or home care was often required in the 1990s as health systems expanded ambulatory and home care services and reduced acute care services.

Directors of pharmacy may be asked to assume the management of other departments and programs within the health system. The pharmacy director may continue as director or may give up the management responsibility for pharmacy services.

## SITES OF PHARMACIST CLINICAL PRACTICE

Pharmacist clinical services can be provided at any site or location of patient care. These services are provided directly to patients or indirectly to patients through the nurse and/or physician.

The following sites are examples within health systems where pharmacist clinical services are provided:

- Acute care hospital in the patient care area(s).
- Critical care unit.
- Pediatrics hospital.
- Neonatal intensive care unit.
- Long-term care facility.
- Family practice physician office.
- Ambulatory care clinic.
- Home care services pharmacy.
- Community pharmacy.
- Outpatient pharmacy.
- Drug information services.
- Therapeutic drug monitoring service.
- Oncology.
- Hospice.

## ADVANTAGES OF WORKING IN THE HEALTH-SYSTEM ENVIRONMENT

Several of the obvious advantages for working as a pharmacist in a health system include:

- Direct access to patients and patient information.
- Availability of physicians and nurses.
- Patient care environment.
- Levels of care—primary, secondary, tertiary.
- Resources to support pharmacist clinical services.
- Patient care quality assurance activities for pharmacist participation.
- Hospital and medical staff committees for pharmacist participation.
- Opportunities for clinical research.
- Opportunities for participation in education programs for physicians, nurses, and patients.
- Provision of drug information on a daily basis.
- Participation in therapeutic drug-monitoring services.
- Collaboration with pharmacist colleagues in clinical practice.
- Participation in teaching programs for pharmacy students and residents.
- Demand to know acute care pharmacotherapy.

These examples translate into a demand for the pharmacist to know pharmacotherapy and a requirement to update clinical therapeutics knowledge and expertise; to collaborate and work effectively and efficiently with physicians, nurses, and pharmacist colleagues in providing services and care to patients; and to participate in the

many varied activities to provide quality care to patients at different levels of care.

## DIFFERENT TYPES OF HOSPITALS AND PHARMACY SERVICES

A broad categorization of hospitals is government and nongovernment. Government hospitals are federal, state, and local. Nongovernment hospitals can be categorized into nonprofit and proprietary (for-profit). A teaching hospital is one that provides a postgraduate education program for physicians. All hospitals exist to provide services and care to the patients being served. Some of the key differences between hospitals include the management decision-making process, type of medical staff, scope of patient services to be provided, size, and financial objectives and strength of each hospital. There is not an existing method to determine which types of hospitals provide more pharmacy and pharmacist clinical services as there are too many variables that determine the existing scope of pharmacist services. In general, every hospital needs more clinical services from the pharmacy department and staff than currently exist.

Some questions to consider when looking at a health system for possible employment include the following:

- What is the existing scope of pharmacist clinical services? What types of services? How long have they been provided?
- Is the hospital a teaching hospital?
- Does the pharmacy have an affiliation with a school of pharmacy?
- Does the health system provide pharmacy residencies?
- What is the pharmacy director's philosophy regarding pharmacist clinical services?
- How does the pharmacy facilities look regarding to size, organization, cleanliness, automation, and drug information resources?
- Does the medical staff and health-system administration support pharmacy services and pharmacist clinical practice activities?
- What is the job satisfaction and morale of the pharmacist staff?
- How are pharmacy technicians used in the pharmacy operations?
- What is the compensation and benefit package?
- What is the strategic plan for the health system and for the pharmacy services?

The answers to these and similar questions should convey whether the health system being considered will provide an environment for clinical practice, job satisfaction, and opportunities for growth and career advancement.

## WHY SEEK EMPLOYMENT IN A HEALTH SYSTEM?

Some key factors for seeking pharmacist employment in a health system relate to the opportunities to provide clinical services directly to patients, to collaborate with physicians and nurses, to cope with the personal challenge to maintain and expand clinical pharmacotherapy knowledge and expertise, to change practice settings for the different levels of care and job satisfaction, and to be viewed as an essential health care practitioner by the institution, physician, and nurse colleagues. The personal satisfaction from providing clinical services that benefit patients is the best reward for working in a health-system environment.

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# Healthy People 2010: Objectives for Improving Health

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## INTRODUCTION

Healthy People 2010 is a national health promotion and disease prevention program aimed at improving the health of all Americans. Progress in reaching these goals will be measured using 467 objectives organized under 28 focus areas. Healthy People 2010 is important to pharmacists because many of the objectives involve the use, or the need for proper use, of medications. This article provides a short history of this program. Using diabetes as an example, it explains the content of the focus areas, then reviews the goals and how progress toward them is assessed. Finally, the implications for pharmacists are presented. (All of the information in this article is from the Healthy People 2010 Web site, http://www.health.gov.healthypeople/.)

## HISTORY OF HEALTHY PEOPLE 2010

*Healthy People 2010: Objectives for Improving Health*, the third decade-long national initiative, builds on the achievements of the past two decades. In 1979, the first report, *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention*, put forth national goals for preserving independence for the elderly and reducing premature deaths. A second report, in 1980, *Promoting Health/Preventing Disease: Objectives for the Nation*, provided more than 200 health objectives for the United States to achieve over the next 10 years. *Healthy People 2000: National Health Promotion and Disease Prevention Objectives*, released in 1990, continued this program and identified health improvement goals and objectives to be attained by the year 2000. The Healthy People 2010 initiative continues in this tradition as a tool to improve our nation's health into the first decade of the 21st century.

One of the most encouraging lessons learned from the Healthy People 2000 program was that we, as a nation, can make dramatic progress in improving the nation's health in a relatively short period of time. For example, during the last decade, significant reductions were achieved in infant mortality. "Childhood vaccinations are at the highest levels ever recorded in the United States. Fewer teenagers are becoming parents. Overall, alcohol, tobacco, and illicit drug use is leveling off. Death rates for coronary heart disease and stroke have declined." Significant advances have been made in the diagnosis and treatment of cancer and in reducing unintentional injuries.

But there is still much progress to be made. "Diabetes and other chronic conditions continue to present a serious obstacle to public health. Violence and abusive behavior continue to ravage homes and communities across the country. Mental disorders continue to go undiagnosed and untreated. Obesity in adults has increased 50% over the past two decades. Nearly 40% of adults engage in no leisure time physical activity. Smoking among adolescents has increased in the past decade. And HIV/AIDS remains a serious health problem, now disproportionately affecting women and communities of color." The development and implementation of Healthy People 2010 will be the guiding instrument for addressing these health issues, reversing unfavorable trends, and expanding on past achievements.

## DEVELOPING OBJECTIVES

Suggestions for Healthy People 2010 objectives were gathered from a variety of diverse organizations and people using a series of national and regional meetings. On two different occasions in the late 1990s, the American public was given the opportunity to express its views and opinions. More than 11,000 comments were received from every state in the Union, plus the District of Columbia and Puerto Rico. Using this input, the final Healthy People 2010 objectives were developed by teams of experts from various federal agencies under the direction of Health and Human Services Secretary Donna Shalala, Assistant Secretary for Health and Surgeon General David Satcher, and former Assistant Secretaries for Health. The Office of Disease Prevention and Health



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Promotion, U.S. Department of Health and Human Services, coordinated and oversaw the entire process.

## GOALS AND ASSESSMENT

The two overarching goals of Healthy People 2010 are the elimination of disparities in health status among racial and ethnic groups and the improvement in the years and the quality of life for people of all ages. Progress in attaining these goals will be measured using the 467 objectives in the 28 Focus Areas (Table 1). Each focus area contains its own overarching goal. For example, the goal of the diabetes section states, "Through prevention programs, reduce the disease and economic burden of diabetes, and improve the quality of life for all persons who have or are at risk for diabetes." After listing the goal, an overview of the issues, trends, disparities, and opportunities for action is presented. If the topic was included in the previous program, Healthy People 2000, interim progress toward the objectives is detailed. Using the diabetes example, there are five objectives in the previous initiative. As Healthy People 2000 draws to a close, one objective is trending toward the goal, while the other four are trending away from the goal.

Next, the focus area objectives for 2010 are presented. Each focus area contains varying numbers of objectives. Many of the objectives are aimed at "interventions designed to reduce or eliminate illness, disability, and premature death among individuals and communities. Others focus on broader issues, such as improving access to quality health care, strengthening public health services, and improving the availability and dissemination of health-related information." In the diabetes example, the number of objectives was increased from 5 in the 2000 program to 17 for the current program. Each objective (e.g., increase the proportion of persons with diabetes who receive formal diabetes education.) lists a target (e.g., 60%) for the year 2010, the rationale behind its focus, and the national data tables from which the measurements will be extracted. Each focus area ends with a listing of related objectives from other focus areas, an explanation of the terminology used, and the references employed.

**Table 1** Focus areas for Healthy People 2010

| |
|---|
| Access to quality health services |
| Arthritis, osteoporosis, and chronic back conditions |
| Cancer |
| Chronic kidney disease |
| Diabetes |
| Disability and secondary conditions |
| Educational and community-based programs |
| Environmental health |
| Family planning |
| Food safety |
| Health communication |
| Heart disease and stroke |
| HIV |
| Immunization and infectious disease |
| Injury and violence prevention |
| Maternal, infant, and child health |
| Medical product safety |
| Mental health and mental disorders |
| Nutrition and overweight |
| Occupational safety and health |
| Oral health |
| Physical activity and fitness |
| Public health infrastructure |
| Respiratory diseases |
| Sexually transmitted diseases |
| Substance abuse |
| Tobacco use |
| Vision and hearing |

(Ref. http://www.health.gov.healthypeople/.)

## LEADING HEALTH INDICATORS

In order to periodically assess the health of the nation, a set of leading health indicators was developed for the first time (Table 2). These indicators, which address major public health concerns, "were chosen based on their ability to motivate action, the availability of data to measure progress, and their relevance as broad public health issues." For each of the leading health indicators, specific objectives from Healthy People 2010 were selected and will be used to track progress. This small subset of measures will provide a snapshot of the health of the nation. Even though the leading health indicator may have the same name as a focus area, the indicator may

**Table 2** Leading health indicators for Healthy People 2010

| |
|---|
| Access to health care |
| Environmental quality |
| Immunization |
| Injury and violence |
| Mental health |
| Overweight and obesity |
| Physical activity |
| Responsible sexual behavior |
| Substance abuse |
| Tobacco use |

(Ref. http://www.health.gov.healthypeople/.)

contain only a few of the focus area's objectives and may even contain objectives from a related focus area. For example, the tobacco use focus area has 21 objectives, while the tobacco use leading indicator follows only 2 of the objectives. The indicators will highlight achievements and challenges throughout the next decade while serving as a link to the 467 objectives of the Healthy People 2010 program. The leading health indicators are intended to help the populace more easily understand the importance of health promotion and disease prevention. They are also aimed at encouraging wide participation in improving health in the next decade.

## IMPLICATIONS FOR PHARMACISTS

Healthy People 2010 is important to pharmacists in all areas of practice. The focus areas and their objectives address not only clinical issues but also social issues. As pharmacists push forward into true pharmaceutical care, the entire patient must be considered, not just the medical management. Healthy People 2010 provides the information needed to help pharmacists develop services that are aligned with national goals.

For detailed information, the full text of *Healthy People 2010 Conference Edition* (Volumes 1 and 2) is available online at http://www.health.gov.healthypeople/. A CD-ROM version (B0071) can be purchased from ODPHP Communication Support Center, P.O. Box 37366, Washington, D.C. 20013–7366, (301) 468–5960. Limited numbers of the print version (B0074) are also available from the ODPHP Communication Support Center.

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PROFESSIONAL DEVELOPMENT

# Home Care, Clinical Pharmacy Careers in

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## INTRODUCTION

The practice of clinical pharmacy in the home care/home infusion setting is a challenging, but rewarding practice site. The pharmacist is a vital member of the home care team, which includes the patient and/or their caregiver, the physician, the home care nurse, and various other support personnel (e.g., pharmacy technicians, customer service personnel, billing personnel). The practice sites vary greatly, and many clinical, operational, and marketing opportunities exist.

## BACKGROUND INFORMATION

Home infusion therapy involves the administration of medications using the intravenous, subcutaneous, or epidural routes. Therapies administered at home include antiinfectives, chemotherapy, pain management, parenteral or enteral nutrition, and immunologic or biological agents. Many different diagnoses are treated at home, including many infectious diseases (bacterial, fungal, or viral), gastrointestinal diseases, immunologic disorders, and cardiac diseases (e.g., congestive heart failure).[1–7]

Home infusion therapy has proven to be a safe and effective alternative to patients receiving care in hospital settings. For most patients, receiving treatment in the home (or in an outpatient clinical setting) is preferable to being kept in a hospital.

Whenever a patient starts on home infusion therapy, a prescription from a qualified physician responsible for the care of the patient is needed. Home nursing services are also generally provided to ensure that the proper patient education and training occurs, and to provide ongoing clinical monitoring of the patient in the home, along with the pharmacist's clinical interventions.

From a business perspective, the home infusion market is projected to have annual revenues approaching $4.5 billion (year ending 2000). The market continues to experience cost-containment pressures (as does the entire healthcare market); however, the future for providing care at home looks good, as it is approximately one-third as costly as providing care in the hospital.

As an alternative, some infusion pharmacies also provide infusion therapies in an ambulatory cliniclike setting. This arrangement has the advantage of providing services to patients in a supervised setting. It allows several patients to receive their infusions concurrently, therefore making more efficient use of the organization's staff, particularly nursing.

## THE PHARMACIST IN HOME CARE

The staff pharmacist may or may not have an advanced degree (i.e., Doctor of Pharmacy degree). Although a PharmD degree is not required, it does ensure that the pharmacist has a good, sound clinical education. More important is the person's ability to think quickly when asked difficult questions or when in difficult situations; to interact professionally with a wide range of individuals (both clinical and nonclinical); and to be able to work with little supervision in an often unstructured environment.

As a manager, when hiring, the person's previous work history should be evaluated for these abilities. However, experience working in the home care environment is not an absolute requirement. There are pros and cons to hiring someone with experience. The person must be licensed in the state in which they are practicing and must meet all continuing education requirements.

## WORK ENVIRONMENTS

Typical work environments are office-type settings where the pharmacist is working alongside many different individuals. The sites may be free standing (located in light industrial or suburban office parks) or located on a health system campus. Many health systems provide home care/home infusion services as part of the for-profit arm of the system. In those cases, the home infusion provider pro-


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vides service for only those patients being discharged from the hospital.

For-profit home infusion providers range from single-site, private companies to multiple-site, million-dollar companies. All home care providers are licensed by the state and can chose to become accredited by several accrediting bodies (e.g., Joint Commission on Accreditation of Healthcare Organizations (JCAHO), Accreditation Commission for Health Care, Inc. (ACHC), Community Healthcare Accreditation Program (CHAP)). Accreditation is a requirement for many insurance companies to serve as a provider for their members.

An advantage of working in home care is the flexibility in hours and activities that the home care environment offers. Positions are available that range from PRN or, to as needed, to part and full time. As needed positions are often used to help cover vacations and scheduled time off or on-call activities. Part-time positions can range from 1 or 2 days per week to 4 or 5. Average hours per day are 8 or 10 depending on the home care company.

Because home care personnel must be available 24 hours per day, on-call related activity may be required. Depending on the organization and workload activities, afternoon, evening, or weekend shifts may be used.

## ACTIVITIES OF THE HOME CARE PHARMACIST

Activities vary greatly, depending on the services provided and the size of the operation. In small offices, the pharmacist may wear many different hats. In large offices, the pharmacist may do only one task on a given day.

**Table 1** Home care preadmission criteria

- Patient/caregiver agrees to receive services in the home.
- Patient/caregiver are willing to learn the necessary steps to administer their drug(s) in the home.
- The home environment is acceptable (clean, access to telephone and running water).
- The patient is readily accessible to the home care provider.
- The patient has adequate family support, both physically and psychologically.
- A physician is readily available in the event of an emergency, ongoing clinical updates, and/or order changes.
- The medication ordered is appropriate to be given in the home environment.
- The indication, dosage, and route of administration of the medication(s) ordered is appropriate.
- Labs etc., are ordered to access the effectiveness of the therapy ordered.

**Table 2** Home care patient database

- Patient's name, address, phone number, date of birth.
- Alternate contact information in the event of an emergency.
- Information on the status of any advance directive.
- Height, weight, gender.
- Diagnoses.
- Location and type of intravenous access and date of placement.
- Pertinent laboratory test results.
- Pertinent medical history and physical findings.
- Accurate history of allergies.
- A detailed medication profile, including all prescription and nonprescription medications, home remedies, and investigational and nontraditional therapies.
- Other agencies involved in patient care.
- Prescriber's name, address, phone number, etc.
- A plan of care.
- Patient education activities.
- Any functional limitations.
- Any pertinent social history.

Tasks include dispensing-related functions; technician oversight; obtaining orders from physicians and then assessing the orders for appropriateness; assessing the patient and caregiver for the appropriateness of providing care in the home; patient and/or caregiver education; providing education for nursing agencies, discharge planners, etc; answering drug information questions; sales support; and so on. No one day is ever the same. The following explains these activities in greater detail.

One of the primary roles of the pharmacist is the preadmission assessment. This role ensures that each patient is assessed for appropriateness using predetermined admission criteria. Common criteria are outlined in Table 1.

In conjunction with other members of the home care team and with the patient's physician, a decision is made to either accept the patient for home care services or refer them back to the hospital discharge planner or referral source. Once accepted, an assessment is completed and an initial patient database established. Table 2 lists some of the items that are part of this database. Again, the pharmacist is an integral part of this process. Much of this information is obtained via the telephone in conversations with the physician, hospital personnel, or patient. Information may also be received via fax or from the home care agency nurse. Pharmacists working in a hospital-based home care pharmacy may be able to go up to the floor and obtain this information directly from the medical record, floor nurse, and/or patient.

One of the documents that is part of this patient database is the care plan or plan or care. The plan of care should indicate the treatment goals and indicators of de-

sired outcomes, any interventions that need to be done, and the frequency of those interventions. Any drug-related problems that occur or have the potential to occur should be addressed by the pharmacist, along with other members of the patient care team. When multiple providers are involved with the patient, the pharmacist is in an ideal position to coordinate the information flow and care of the patient.

The plan of care should be developed initially and updated as needed. Based on the drug(s) used and the potential for side effects and adverse drug reactions, the pharmacist should determine what type of monitoring is needed (e.g., labs, physical findings) and the frequency at which it is to occur. The pharmacist must communicate this plan to others involved and provide updates as needed.

Another role of the pharmacist is the selection of products, infusion devices (i.e., pump), and ancillary supplies. Many factors need to be considered when choosing the administration method, infusion device to use, and what ancillary supplies are needed.

The stability, compatibility of the drug, and volume of the drug are important considerations when determining what method (IVPB, IV push, continuous infusion) or infusion device (elastomeric, electronic infusion device, etc.) will be used. Nursing agency knowledge and ability of the patient to learn the methodology are all important considerations. Patient convenience, prescriber preference, and cost must also be considered. Again, the pharmacist is able to weigh the pros and cons of any method and help the patient care team make appropriate decisions.

The ongoing clinical monitoring is the hallmark of the pharmacist's involvement. By having regular, ongoing conversations with the patient/caregiver, physician, and home care nurse, the pharmacist is able to make an objective evaluation of the therapy(ies), make appropriate recommendations for changes, and effectively communicate those changes to the patient/caregiver and all involved health care providers.

On an initial and ongoing basis, the pharmacist should be providing education to the patient and/or caregiver. Some of this information may be provided verbally, although most is provided in writing. Table 3 lists some of these education-related issues. The pharmacist should be involved in the development of all educational material.

**Table 3** Education-related issues

- Medication related, including dose, route of administration, dosage interval, duration, side effects, adverse reactions (and their management).
- Proper aseptic technique.
- Precautions and directions for administering the medication.
- Equipment use, maintenance, and troubleshooting techniques.
- Proper care of the vascular access device and site (if applicable).
- Home inventory management, how to contact help, emergency issues (what to do if something goes wrong).
- Special precautions and directions for the preparation, storage, handling, and disposal of drugs, supplies, and biomedical waste.

## CAREER OPTIONS

The range of careers is very diverse. Pharmacists may choose to remain clinically focused, providing hands-on care to the patient. Opportunities exist to do research on the delivery and use of drugs in the home environment. Extended stability studies are one area where the pharmacist can become involved. If the pharmacist gets involved in clinical research, they should ensure that all appropriate policies and procedures are followed, that the patient and health care providers have appropriate information concerning the drug(s), and that all required record-keeping requirements are met.

Many sites offer clinical clerkships for undergraduate pharmacy students and several post-PharmD residencies in home care exist.

From an operational perspective, pharmacists who have a business background can progress from a staff-level position to branch, regional, or corporate management positions. It is not unusual for a mid- to high-level manager to have started out as a staff pharmacist.

The pharmacist should be actively involved in the organization's performance improvement activities.[8] Aspects of care that can be monitored include, but are not limited to, patient satisfaction, unscheduled admissions, medication errors, adverse drug reactions, infection control-related issues (e.g., line infections), unscheduled deliveries, and so on.

The pharmacist must also take an active role in the development, implementation, and review of an organization's policies, procedures, and protocols. The pharmacist should ensure that all aspects of care are addressed, including patient care, drug preparation and dispensing, quality control, infection control, and equipment maintenance. Involvement in such activities can have far-reaching effects on efficiency and financial outcomes.

As a manager, the pharmacist's responsibilities include: 1) setting the goals (both short- and long-term) of the pharmacy, based on the needs of the patients and

mission/goals of the organization; 2) developing plans to achieve those goals; 3) implementing those plans; 4) assessing whether the goals are being met; and 5) instituting corrective actions when necessary.

The pharmacy manager will have multiple areas of responsibility, such as managing the pharmacy (including compliance with laws, regulations, and accreditation standards), financial resources (drugs, budgets, reimbursement), and pharmaceutical care and human resources (scheduling, hiring, education and training, staffing needs).

Pharmacists that have a sales/marketing nature can pursue this career tract if so desired. As mentioned previously, positions range from branch sales/marketing to corporatewide strategic sales management.

## CONCLUSION

The practice of pharmacy in the home care environment presents many opportunities for professional and personal growth. The practice continues to evolve and will continue to offer pharmacists multiple opportunities (both clinically and management related), as well as continuing to provide sound pharmaceutical care to the patients receiving home care services.

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# Home Care Pharmacy Practice (Spain)

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## INTRODUCTION

The introduction of home care is unavoidably bound to the changes that have been taking place in most health systems over the last 30 years. The financial pressure to reduce the hospital length of stay has a direct relationship on the acceptance of home care, and on the growth of other activities such as nursing homes and outpatient clinics.

*Home care* or *hospital at home* is defined as a service that provides active treatment by healthcare professionals in the patient's home of a condition that otherwise would require acute hospital in-patient care, always for a limited time period.[1]

This definition is the same for all models of health systems but the application and focus of care differ. However, in most systems home care implies the application of high technology in the patient's home for a limited period, rather than care for chronic patients. For this reason, in most systems, the referral centers are the hospitals.

The concept of home care originated in the university hospitals in the forties. In 1947 the Montefiori Hospital in New York planned to extend the hospital to the patient's home. But home care was in fact first applied in the sixties with "Hospitalisation a Domicile" in France in 1961.[2] It has been implemented in a number of other countries, including the United States,[3] Canada, and the Netherlands.[4] Home care coverage within the Medicare program in the United States was implemented in 1966.

The acceptance of home care has been faster in North America than in European countries where there is no direct cost to the patient or an insurer when a patient is admitted to a hospital.[5]

## ADVANTAGES OF HOME CARE

The advantages of home care are:

- *Reduction in hospital length of stay.*[1] This is reflected in the decrease in costs [from 30 to 85% according to different studies][1,6–8] without loss of effectiveness of treatment. A meta-analysis carried out by Hughes et al.[9] studied the impact of home care hospital days (22 studies) and demonstrated a significant reduction in hospitalization days across studies due to home care, with a cumulative effect size of $-0.38$ (CI, $-0.42$ to $-0.34$, $p=0.001$).
- *The patient's maintenance in his/her family environment.* This implies an improvement in the quality of life[10] and patient satisfaction.[11]
- *The patient's involvement in his/her own care.* This is not typical in conventional health care and should be considered to improve the effectiveness of treatment. At the same time it breaks the bonds of nonpositive dependence that sometimes exist between the patient and the hospital.
- *Avoidance of the risk of nosocomial infections.* Patient care in a nonhospital environment avoids contact with hospital organisms, which are usually more resistant to antibiotic treatment.
- *Development of health models which integrate the different areas (basically hospital and community care).* The separation between the different areas of patient care is artificial, while integration implies a higher quality and more individualized care.

## ORGANIZATION

The way home care is organized depends more on the type of care within each country than on the kind of care provided. Home care can be classified according to the type of reference center or according to the type of structure.

### Classification According to the Type of Reference Center

#### Hospital-based home care services

The hospital is responsible for the patients and is the decision-making center. A hospital team organizes,


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stimulates, and assumes the leadership of the inclusion of patients in home care. High technology such as long-term ventilation,[12] intravenous antibiotics administration,[13] chemotherapy administration,[14] or parenteral nutrition[15] is included. The length of hospital stay is reduced by early discharge of patients following elective surgery with a home-based rehabilitation program.[16–19]

### Community-based home care services

These usually include patients with chronic diseases requiring low technology. The community center medical team visits the patient at home. Examples of programs applying such schemes are home care programs for diabetes, hypertension, terminally ill patients, physiotherapy at home, and care of elderly.

Programs may also consist of mixed care with collaboration between the different areas of the health system.[20]

## Classification According to the Type of Structure

- *External provider.* The health care team (physicians, nurses, and pharmacists) and the drugs and ancillary supplies proceed from a commercial provider who has a contract with hospital or the reference center.
- *A mixed structure of external provider and the reference center.* The hospital may provide the medical team and pharmacy services, for example, and the external provider supplies the nurses and drugs.
- *Reference center structure.* The physicians, nurses and the pharmacy services depend on the reference center, hospital or community centers.

# PATIENT SELECTION

## Selection Criteria

Selection criteria for patients who are candidates for home care are adapted to each environment, geographical area, and type of patient. These criteria can be divided into medical condition and psychosocial and family support. They will be described in each protocol of patients' inclusion defined for each diagnosis. But some general environments should be evaluated in all cases: home and family environment.

### Home environment

A series of home requirements must be met and in all cases assessment of the following is needed:

- Geographic access to the reference center that each home care team will define according to the characteristics of the area.
- A telephone is imperative for continued contact between the patient and the home care team.
- The home should be clean and have electricity and running water. Based on this information, the pharmacist, in conjunction with the other team members, will assess the patient's appropriateness. Other requirements such as a refrigerator will also be necessary in some cases if the patient requires medication that has to be stored at low temperatures.

### Family environment

The presence of a caregiver is mandatory in most of the home care protocols, although this will depend on the therapy administered and also on the medical situation. The home care team should assess the patient's or caregiver's capacity to be involved in the care.

## Patient's Origin

Patients evaluated for inclusion in a home care program may proceed to a hospital, emergency room, or community care center.

## Procedure for the Patient's Admission

The whole home care team is involved in patient inclusion and care planning although each member will play a specific role in the activities.

The steps in the admission procedure are:

1. The physician in charge of the patient considers whether he/she will be a candidate for home care according to the clinical assessment described in the previously defined protocol. In the detection of patient candidates, the pharmacist and the nurse who are working in the home care team can also participate.
2. Family support and home environment are evaluated by the social worker or by the nurse together with the pharmacist, also according to the previously defined protocols.
3. The entire home care team plans the care.

**Table 1** Infections most frequently included in home care programs

| |
|---|
| Skin and soft-tissue infections |
| Cellulitis |
| Abscess |
| Postoperative wound infection |
| Posttrauma wound infection |
| Diabetic foot |
| Decubitus ulcer |
| Bone and joint infections |
| Acute and chronic osteomyelitis |
| Septic arthritis/bursitis |
| Prosthetic joint infections |
| IV line infection |
| Infective endocarditis |
| Ear and sinus infections (sinusitis/otitis/mastoiditis) |
| Acute exacerbation of pulmonary symptoms in cystic fibrosis |
| Lung infection (hospital- or community-acquired pneumonia) |
| Gastrointestinal infections (abscess/peritonitis) |
| Kidney, bladder, and prostate infections (pyelonephritis/ perinephric abscess) |
| Systemic febrile syndromes |
| Cytomegalovirus infection |
| Febrile neutropenia |
| Brain abscess |

4. The patient or the caregiver is trained in and informed about the therapy to be carried out in the home. The information has to be oral and in writing and the pharmacist and the nurse can provide it.
5. The patient goes home and therapy begins.

One option to facilitate the coordination among the different steps is periodic meetings to discuss the cases with the participation of all the members of the home care team.

## TYPE OF INTERVENTIONS

### Home Parenteral Antibiotics

In general, all types of infection and all organisms are susceptible to home IV antibiotic therapy. The treatment of patients with bone and joint infections has proven highly effective and is now well accepted.[21] Other bacterial infections that have been studied extensively are skin and soft tissue infections and lung infections. The reason is that these infections fulfill two important criteria: patients are clinically stable and require prolonged IV antibiotic therapy (>7 days).[22] But home care can be extended to great number of infections: bacterial, viral, and fungal (Table 1). The patient's admission to home care should be considered from the beginning of the infection or should be wait until the patient is clinically stable, depending on the infection.

A large number of cost-effectiveness studies have been carried out (Table 2), all with positive results.

### AIDS

The maintenance therapies of opportunistic disease in acquired immune deficiency syndrome (AIDS) are an-

**Table 2** Studies of cost savings from home IV antibiotic therapy

| Study | *n* | Infection | Average savings/day/ patient ($) | Average savings/day/ patient (Euros) |
|---|---|---|---|---|
| Antoniskis A 1978[38] | 20 | NA | 165 | 196 |
| Stiver 1978[39] | 23 | NA | 97 | 115 |
| Kind 1979[40] | 15 | NA | 95 | 113 |
| Swenson 1981[41] | 8 | Osteomyelitis, pyelonephritis and others | 148 | 176 |
| Poretz 1982[42] | 150 | Osteomyelitis | 142 | 169 |
| Stiver 1982[43] | 95 | NA | 135 | 160 |
| Rehm 1983[44] | 48 | Bone and joint infections | 305 | 362 |
| Kind 1985[45] | 315 | NA | 350 | 416 |
| Corby 1986[46] | 36 | NA | 345 | 410 |
| Chamberlain 1988[47] | 6 | Osteomyelitis | 265 | 316 |
| Kane 1988[48] | 27 | Cystic fibrosis | 618 | 735 |
| Tice 1991[49] | 290 | Osteomyelitis | 303 | 360 |
| Williams 1993[50] | 56 | Cellulitis, osteomyelitis and others | 262 | 312 |
| Williams 1994[51] | 58 | Pneumonia | 252 | 300 |
| Clopes 1998[29] | 13 | Several | 152 | 180 |

**Table 3** Opportunistic disease in AIDS candidates for home care

| Infection | Antimicrobial therapy |
|---|---|
| Cytomegalovirus infection | Maintenance and induction therapies:<br>Ganciclovir IV<br>Foscarnet<br>Cidofovir |
| Acyclovir-resistant *Herpes simplex* | Foscarnet |
| Acyclovir-resistant *Herpes zoster* | Foscarnet |
| *Pneumocystis carinii* pneumonia | Pentamidine IV<br>Pentamidine aerosol |
| Cryptococcosis | Amphotericin B |
| Histoplasmosis | Amphotericin B |
| Coccidiomycosis | Amphotericin B |
| Drug-resistant mycobacterium Pneumonia | Amikacin<br>3rd Generation Cephalosporins<br>Aminoglycosides |

tibiotic therapy candidates for home care. The reasons are that the patient is clinically stable and requires long-term therapy. In some cases the induction can also be considered to be treated at home. These infections and treatments are described in Table 3.

Other support therapies for AIDS patients that can be given at home are nutrition support, parenteral and enteral, IV immunoglobulins, chemotherapy in lymphoma or Kaposi's sarcoma, and care of terminally ill patients.

## Cystic Fibrosis

The majority of antibiotics needed for the treatment of infectious complications of cystic fibrosis have to be administered intravenously for several weeks; until recently these treatments were given on an in-patient basis. As the lung disease progresses, patients may require more frequent hospitalizations. This greatly increases health care costs and adversely affects the patient's quality of life.[23]

Home intravenous therapy in cystic fibrosis may also cut costs by avoiding hospital admissions and may improve family life and psychological well-being.

## Palliative Care

Some trials have evaluated the effectiveness of hospital at home for terminally ill patients.[20,24] Patients and caregivers receiving hospital-at-home care reported greater satisfaction than those in the hospital group.

One of the fundamental pharmacological treatments in this group of patients is the opioid continuous infusion with devices adapted to outpatient treatments as patient-controlled analgesia pump.

## Oncology Patients

The administration of chemotherapy at home has demonstrated that it is feasible and that it produces a decrease of adverse effects and an improvement of the quality of life and a monetary savings.[25]

However, home care can also give support to the patient with cancer in other areas: parenteral antibiotics in febrile neutropenia, nutrition and fluid support, or pain support.

## Hematology Patients

In the support of hematology patients, the therapy candidates for home care may be chemotherapy, IV antibiotics in febrile neutropenia, blood products, IV immunoglobulins, fluid/electrolyte replacement, central line maintenance, and specific treatments such as deferoxamine administration.

In the support of hematopoietic stem cell transplantation there are programs developed to permit treatment with chemotherapy at home and treatment of complications.[26]

## Cardiology Patients

In cardiology patients some home-based interventions have been published on the treatment of heart failure patients and heart transplant patients. In our center we also have experience with patients with pulmonary hypertension.

Increased survival of cardiovascular disease has resulted in a significant rise in the number of patients with chronic, refractory heart failure requiring intensive medical management and follow-up. In a controlled study,[27] among a cohort of high-risk patients with congestive heart failure, beneficial effects of a postdischarge home-based intervention were sustained for at least 18 months, with a significant reduction in unplanned readmissions, total hospital stay, hospital-based costs, and mortality.

Cardiac patients receiving inotropic therapy can be successfully treated in the home using specific admission criteria and monitoring guidelines,[28] and home dobutamine infusions can improve functional status and quality of life of patients with severe heart failure.

Home care can also give support to heart transplant patients. In our center we have the experience of a program for organ rejection therapy, antilymphocyte immunoglobulin, and high dosage of methylprednisolone at home. After the experience, we can say that it is feasible to carry out this treatment at home and the satisfaction of the patients is high.[29]

There are experiences of ambulatory treatment of patients with pulmonary hypertension, with inhaled nitric oxide and with prostaglandins, in both cases using an ambulatory delivery system. In our center we have an outpatient treatment program of pulmonary hypertension with inhaled iloprost leading in some patients to significant improvement in pulmonary hypertension and in the quality of life with no adverse effects.

## Nutrition Support

The candidates for home nutrition support should be clinically stable patients that require enteral or parenteral nutrition for a long term. Before initiation of home nutrition support, a nutrition assessment and a care plan should be performed and after initiation nutrition status should be monitored on a regular basis.[30]

The indications included in a study of incidence of home nutrition support made by the American Society for Parenteral and Enteral Nutrition were:

*Pareteral nutrition:*

- Short bowel disease.
- Crohn's disease and ulcerative colitis.
- Gastric or duodenal fistula.
- Radiotherapy damage.
- Congenital disorders.
- Disorder of the GI motility.

*Enteral nutrition:*

- Neuromuscular diseases:
  - Amyotrophic lateral sclerosis
  - Myasthenia gravis
  - Parkinson's disease
  - Alzheimer's disease
  - Cerebral palsy
  - Cerebral vascular accident
  - Brain tumors
- Oral and GI diseases:
  - Secondary to surgical procedure:
    - Head and neck
    - Esophagus or stomach
  - Malabsorption
  - Disorder of GI motility
  - Crohn's disease and ulcerative colitis

## Elderly Patients

Home care in elderly patients can help with the geriatric assessment of disability and functional status and the prevention of complications related or not related to drugs. Stuck et al. conducted a three-year, randomized, controlled trial of the effect of annual in-home comprehensive geriatric assessment and follow-up for people who were 75 years of age or older.[31] The results showed that this intervention can delay the development of disability and can reduce permanent nursing home stays among elderly people living at home.

## Pediatric Patients

Some programs of home care have been applied to pediatric patients. Home care for cystic fibrosis and oncology patients is previously described. Other examples of home care programs in children are patients with asthma that require high technology at home,[32] children with newly diagnosed diabetes,[33] and infants who require neonatal special care and a family support program.[34]

## Surgery and Obstetric Patients

Because of developments in surgery, early discharge after surgery is becoming popular. These programs sometimes need support at home, for example, with rehabilitation.[35,36] In obstetric patients there have been experiences of home care giving support to the woman before or after childbirth.[37]

## Others

Other home care programs with smaller pharmacist implications are long-term mechanical ventilation and renal dialysis.

# PHARMACIST'S ROLE

The pharmacist's role in home care should include the following functions:

1. Development of protocols or practice guidelines for each diagnosis candidate for inclusion in the home care program in collaboration with other home care team members.
2. Preadmission assessment. The pharmacist, together with the other team members, should assess

the patient's suitability for home care on the basis of criteria described in the protocol (home environment, psychosocial factors, and clinical condition).

3. Coordination of preparation and delivery of drugs to the patient or caregiver. Together with the medication, the pharmacist should provide the ancillary supplies and drug delivery systems. The pharmacist should also ensure appropriate disposal of cytotoxic products.
4. Planning home treatment and care, also with an interdisciplinary approach, involving the patient and in collaboration with other team members. This home treatment and care plan should be reviewed and updated periodically and outcome should be assessed.
5. Therapy monitoring using parameters previously defined in the protocol. The pharmacist should carry out this monitoring from the medical records and verbal exchange with the patient and/or the caregiver, nurse, physician, and other family members.
6. Patient and caregiver education about the treatment. The information should be both oral and written and include:

   - Description of the therapy (drug, dose, route of administration).
   - Goal of the therapy.
   - Administration technique.
   - Special precautions regarding storage, handling, and disposal of drugs.
   - Emergency procedure.

7. Information for home care team members regarding:

   - Drug stability and compatibility.
   - Adverse effects.
   - Administration technique.

8. Early detection and reporting of adverse drug effects.
9. Monitoring pharmacokinetic laboratory data for evaluation of efficacy and prevention of adverse effects of the specific drugs (vancomicyn, aminoglycosides, cyclosporin, etc.).
10. Selection of drug delivery systems for parenteral and inhaled drugs. This selection should be carried out in cooperation with the physician and nurse taking into account safety features, ease in handling, and cost. It should be individualized according to the patient's characteristics.
11. Participation in performance improvement activities. Patient satisfaction and outcome should be monitored to detect and resolve problems. Quality of life should also be considered.

## WEB SITES OF INTEREST

- Section of Home Care Practitioners of American Society of Health-System Pharmacists (ASHP)(USA): www.ashp.org/homecare.
- Home Care Highlights of American Society of Health-System Pharmacists (USA): www.ashp.org/public/news/newsletters/homecare/index.html.
- ASHP Guidelines (USA): www.ashp.org/bestpractices.
- American Society of Parenteral and Enteral Nutrition (with the Standards of Practice for Home Nutrition Support)(USA): www.clinnutr.org.
- Joint Comission on Accreditation of Healthcare Organizations (USA): www.jcaho.org.
- American Academy of Hospice and Palliative Medicina (USA): www.aahpm.org.
- Edmonton Palliative Care Program (Canada): www.palliative.org.
- National Council for Hospice and Specialist Palliative Care Services (United Kingdom): www.hospice-spc-council.org.uk.
- Agence Nationale d'Accreditation d'Evaluation en Sante, France (with the recommendations for the medical records of the home care patients for ambulatory nursing professionals) (France): www.anaes.fr.
- American College of Chest Physicians (ACCP) (Patient Education Guides: Mechanical Ventilation at Home) (USA): www.chestnet.org/health.science.policy.

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# Hospice and Palliative Care

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## INTRODUCTION

Hospice programs have existed in the United States for more than 25 years, providing symptom control-based palliative care for patients with advanced, life-limiting disease. In fact, more than 3000 hospice programs are now operating or are in formation in the United States. The World Health Organization (WHO) defines and comments on palliative care as follows: "Palliative care is active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care is achievement of the best possible quality of life for patients and their families."[1] Pharmacists often serve as key members of hospice interdisciplinary teams, and many opportunities for pharmacists to provide valuable clinical services exist in hospice programs. Most hospice care is provided in the patients' homes. Palliative care units are increasingly being integrated into hospitals and long-term care facilities.

## OVERVIEW

The explosive growth of interdisciplinary hospice and palliative care programs for patients with terminal illnesses has created excellent opportunities for pharmaceutical care. In the United States, the number of hospice programs has grown from 1 less than 30 years ago to approximately 3000 today. The importance of pharmacists providing care to terminally ill patients appeared in the American pharmaceutical literature over 25 years ago.[2] In addition, rapidly expanding opportunities for pharmacists in hospice care were defined in the 1990s.[3] All pharmacists should know about the availability and quality of hospice care in their communities, and should be able to refer patients to programs appropriate for their needs.

In the 1970s and 1980s, hospices provided care primarily for patients with advanced cancer. Today, hospice care is common for patients with cancer; acquired immunodeficiency syndrome (AIDS); degenerative neurological diseases, such as multiple sclerosis and amyotrophic lateral sclerosis; end-stage organ system failure, including congestive heart failure, hepatic disease, pulmonary disease, and renal disease; and patients with dementia and other progressive, irreversible disorders.

The word "hospice" is derived from a medieval French term for resting places established for Crusaders on their journeys to the Holy Land. It was revived in the last century by a Catholic order that provided resting places for terminally ill patients in Ireland and England. By the mid-1900s, several such hospice programs existed in the United Kingdom. However, the modern hospice movement based on comprehensive symptom control only began in 1967, with the opening of St. Christopher's Hospice in London. The first American hospice—originally called simply Hospice, Inc., now The Connecticut Hospice—was started in the early 1970s in New Haven, CT. That program became the National Cancer Institute Demonstration Project of Hospice Care from 1974 to 1977. More than 1000 American pharmacists are now estimated to provide hospice pharmaceutical care as integral parts of their practices. Many more are needed.

A hospice is a program of care, not necessarily a facility, per se. In the United States, most hospice care is provided in patients' homes. Some dedicated inpatient hospice facilities exist, as do hospice wings of long-term care facilities and hospice beds in hospitals. These inpatient hospices commonly provide support for the home care programs, respite care (admission of patients to allow their families to rest so that they can resume home care), admissions for difficult symptom control problems, and admissions for care in the last hours or days, when necessary.

The term "palliative care" was used initially to define the provision of symptom relief for patients who were no longer considered to be candidates for cure or remission. Today, the need for palliative care throughout the course of life-threatening disease, including patients for whom cure will be achieved, is becoming more widely accepted. Palliative medicine is a recognized medical specialty in the United Kingdom and several other countries. In 1997,

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the report of the Committee on Care at the End of Life of the Institute of Medicine of the National Academy of Sciences concluded that "palliative care should become, if not a medical specialty, at least a defined area of expertise, education and research."[4] Hospice and palliative care are often used interchangeably.

Hospices provide care for patients with advanced, irreversible disease and a life expectancy measurable in weeks to months as opposed to years. The defined unit of care is the patient and their family. The focus of care spans physical, psychological, social, and spiritual domains. This requires an interdisciplinary team. Nurses usually coordinate home visits and serve as team leaders. The patient's primary care physician normally continues to provide care, often in consultation with the hospice medical director. Other key members of the team are social workers, nursing assistants/home health aides, chaplains, volunteers, and pharmacists. Persons from several other disciplines support the hospice team (Fig. 1). As shown in Fig. 1, the central focus of care is the patient, family, and primary care person(s), who is usually a family member. They continue to work with their primary physician. The interdisciplinary hospice team listed in the next concentric circle from the center provides direct support. This team may include both health care professionals and other persons who are equipped to deal with issues that are complicating the lives of the patients/families (e.g., financial counselors). The third concentric circle from the center includes persons who support the team. Pharmacists have both direct patient care and supportive roles in hospice teams as described in the following paragraphs.

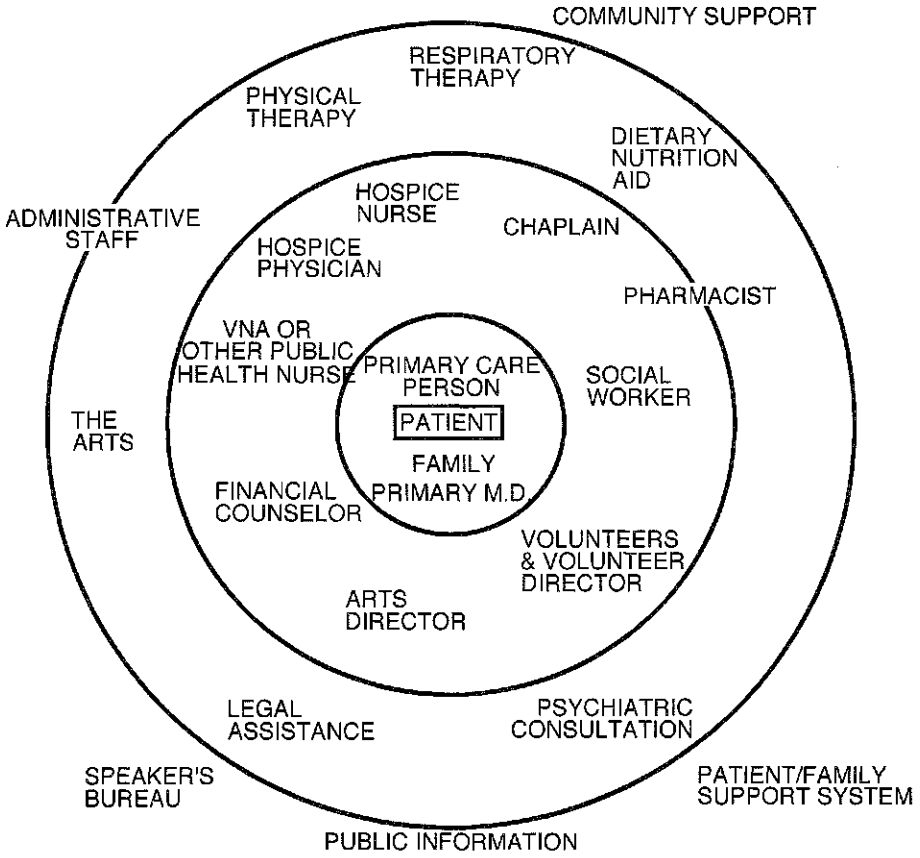


**Fig. 1** The hospice interdisciplinary team. The patient, primary caregiver, and family are the focus of the hospice team's efforts in collaboration with the patient's primary physician. The core team is represented by the next circle away from the center. The support team is indicated by the outer circle. Community resources that support hospice care are listed outside that circle. Pharmacists serve on both the core team (second circle from the center) by providing direct pharmaceutical care to patients and families, and on the support level (next circle out from the center) by providing professional and public education about drug therapy in the care of terminally ill patients. (From Lipman AG, Berry JI. Pharmaceutical care of terminally ill patients. *Journal of Pharmaceutical Care Pain and Symptom Control*, 1996; 3(2):31–56.)

There is a need for elimination of artificial barriers between the time when a cure is sought and the inevitability of death is accepted. This barrier exists, at least in part, due to the requirement for documenting life expectancy by the Medicare Hospice Benefit. The U.S. Congress defined this benefit in the 1980s through which Medicare beneficiaries can assign their medicare part B benefits to any Medicare-certified hospice program. That program then receives a daily fee from Medicare in return for assuming responsibility for the patient's total care, including drugs and pharmaceutical care. To be eligible for this benefit, the patient's physician must certify a probable life expectancy of 6 months or less. This arbitrary time limit has created psychological barriers for physicians, patients, and their families, resulting in many patients not being referred, seeking, or receiving the hospice care to which they are entitled. Because pharmacists commonly have long-standing relationships with families they serve and enjoy their patients' trust, pharmacists are often in the best position to advise patients about the importance of developing relationships with a hospice program as soon as possible after determination that the disease has a probability of being life ending.

Hospice and palliative care are becoming much more widely recognized by healthcare providers. The American Academy of Hospice and Palliative Medicine (founded in 1988 as the Academy of Hospice Physicians) and the Association of Hospice Nurses are respected national organizations of health care professionals who provide palliative care. The National Hospice and Palliative Care Organization (NHPCO, formerly known as the National Hospice Organization [NHO]) includes the National Council of Hospice Professionals (NCHP). The 15 membership sections of the NCHP include an active pharmacist section.

## PHARMACEUTICAL CARE OPPORTUNITIES

It is unfortunate that many physicians and families remain unaware of the benefits that modern hospice care provides. As a result, referrals to hospice programs often do not occur, or occur when the patient has only days to live. Hospice care is most efficacious and cost effective when referrals are made early, while the patient still has months to live and is reasonably active. Relationships between the hospice team and the patient/family that are established before crises occur are most effective. Such relatively early relationships permit the hospice team to provide more effective and efficient care when it is actively needed. As the most accessible and trusted healthcare professionals (Gallup surveys), pharmacists are often in an excellent position to recommend hospice care and to refer families to appropriate programs.

Services provided by pharmacists in American hospices have only been qualitatively and quantitatively documented twice, in 1979[5] and 1991.[6] Many more pharmacists provide these services today than when the latter survey was completed, but the observed types and mix of services do not appear to have changed much since the 1990s.

Although many pharmacists serve as hospice volunteers, about three-fourths are paid for their services. The majority of pharmacists who provide services to hospice programs are not employed directly by the hospices, but by a provider of pharmaceutical services such as a home health pharmacy or hospital. Many are employees of pharmacies that have contracts with hospices to provide drugs and services. In recent years, specialized hospice pharmacy service providers have been developed in several parts of the United States.

The 1991 survey[6] reported that dispensing fees accounted for about one-half of the reimbursement received by pharmacists. In the past few years, payment for cognitive services has become more common. Some pharmacists provide only consulting or dispensing services, but many provide drug products, home health supplies and equipment, and pharmaceutical care. Pharmaceutical services other than prescription dispensing services are not usually required by licensing or certifying agencies. Payment for cognitive services is at the discretion of the hospice administration. The experience of many hospices has been that integration of pharmacists directly into planning and provision of patient care both improves the quality of symptom control and lowers costs. In many hospices, pharmacists are now active participants in weekly or biweekly interdisciplinary team (IDT) meetings at which patients' progress is discussed and care plans are refined.

## HOW TO GET STARTED

Most pharmacists possess many of the skills needed to provide pharmaceutical care to terminally ill patients. In the last few years, pharmacy curricula have placed increased emphasis on pain management and symptom control.[7]

Many pharmacists increase their knowledge of drugs and dosing regimens for symptom control in seriously ill patients through consultation and visits with experienced hospice pharmacists. Pharmacists can gain a valuable perspective on hospice care by taking hospice volunteer training. Continuing pharmaceutical education directly

**Table 1** Selected palliative care resources

**Journals**

*Journal of Pain and Palliative Care Pharmacotherapy* (incorporating the former *Journal of Pharmaceutical Care in Pain and Symptom Control* and *The Hospice Journal*)
Pharmaceutical Products Press, an imprint of The Haworth Press, 10 Alice Street, Binghamton, New York; (800) HAWORTH; e-mail: getinfo@haworth.com

*Journal of Pain and Symptom Management*
Elsevier Science, Inc.; (888) 437-4636

*Pain*
Journal of the International Association for the Study of Pain (IASP); (206) 547-6409

*The Journal of Pain*
Official Journal of the American Pain Society; (800) 654-2452; e-mail: info@ampainsoc.org

**Newsletters**

*IASP (International Association for the Study of Pain) Newsletter*
(206) 547-6409

*American Pain Society Bulletin*
American Pain Society; (847) 375-4715; e-mail: info@ampainsoc.org

**Texts**

Berger AM, Portenoy RK, Weissman DE. *Principles and Practice of Supportive Oncology*. Philadelphia, Lippincott-Raven, 1998. Doyle D, Hanks GWC, MacDonald N, editors. *Oxford Textbook of Palliative Medicine*, 2nd edition. New York and Oxford, Oxford University Press, 1997. Berger AM, Portenoy RK, Weissman DE. *Principles and Practice of Supportive Oncology*, 2nd Ed.; Philadelphia, Lippincott-Raven, in press 2002.

**Web sites**

*National Hospice and Palliative Care Organization*
www.nho.org

*PDQ (Physician Data Query)*
www.cancernet@icii.nci.nih.gov/

*Talarian Map Cancer Pain*
www.stat.washington.edu/TALARIA/TALARIA.html

*Open Society Institute: Project Death in America*
www.cyberspy.com/~webster/death.html

*The Palliative Medicine Program*
www.mcw.edu/pallmed

*Hospice Foundation of America*
www.hospicefoundation.org

*Information about hopsice with links*
www.hopsiceweb.com

*Hospice Hands web site*
http://hospice-cares.com

*Purdue Pharma Pain and Palliative Care Information*
http://www.partnersagainstpain.com

Additional web references can be found in Ref. [9].

relevant to hospice care and symptom control is often provided at meetings of the American Society of Consultant Pharmacists, American Society of Health-System (previously Hospital) Pharmacists, American Pharmaceutical Association, the National Hospice and Palliative Care Organization, and at some state and local professional associations. Several journals, newsletters, and web sites focus on pain and symptom control. Examples are listed in Table 1. Because hospice care is interdisciplinary by definition, most programs are open to suggestions of additional ways in which any discipline can contribute to the program's overall objectives.

Hospice programs are always recruiting and training new volunteers. Therefore, most readily welcome calls from persons in the community interested in learning more about the program or becoming involved in patient care. Any pharmacist can simply call a local hospice and make an appointment to meet with the staff to discuss unmet pharmaceutical care needs. These include a range of activities, including administrative responsibilities, provision of medications, and outcome-oriented pharmaceutical care.

Common administrative functions include the following:

- Managing program or facility (if applicable)
- Serving on the hospice board or professional advisory committee
- Negotiating contracts with provider pharmacies
- Reviewing and ensuring compliance with state and federal laws and regulations that relate to the provision of hospice pharmaceutical care and services
- Developing drug-related policies and procedures
- Participating in continuous quality improvement and quality assurance activities, including drug-use evaluations and cost-avoidance and cost-effectiveness studies
- Procuring medications for indigent patients through pharmaceutical industry patient assistance programs
- Managing the hospice formulary

Common clinical functions include the following:

- Developing pharmaceutical care plans, including assessment and monitoring for therapeutic and toxic outcomes
- Participating in hospice interdisciplinary team meetings (chart rounds)
- Performing drug regimen reviews
- Providing pain and symptom management consultations to team members and to patients' primary physicians
- Preparing routine admission orders
- Developing drug-use protocols
- Making home visits as needed to assess medication needs and use, and to educate patients/families about medication use

Common educational functions include:

- Providing staff education in drug therapy for symptom control and other indications
- Providing education to patients and their families on medication use
- Providing physician education to hospice patient primary physicians
- Providing public education on drug use in terminal care
- Educating hospice volunteers about desired and achievable outcomes from medication use
- Providing clerkships for pharmacy students

Common dispensing functions include the following:

- Dispensing prescription and over-the-counter medications, including therapeutic interchange
- Providing for delivery of medications to patients' homes
- Extemporaneous compounding of dosage forms that are not commercially available
- Providing home infusion service
- Maintaining patient medication profiles

## MARKETING PHARMACEUTICAL CARE SKILLS

The broad range of relevant pharmaceutical services needed by a progressive hospice program nearly always requires more than one provider. Simple, informal needs assessments of programs with which pharmacists want to affiliate is an effective way to market their services. Hospice Medicare payments and most other insurance reimbursement is capitated (i.e., a flat daily fee is paid to the program for all aspects of care). Therefore, the full range of care must be provided within a defined cost structure. Efficient formulary management, including generic and therapeutic interchange and elimination of unneeded drug therapy, can improve both patient care and the fiscal health of the program. Patient and family satisfaction are also important considerations for every hospice program. Medication-related education provided by a pharmacist can markedly increase satisfaction. Hospice nurses often work relatively independently from

their patients' physicians. Therefore, by providing nursing education and consultation about patient assessment for responses to therapy and about drug use, pharmacists can increase their perceived need on the hospice team.

## DOCUMENTATION FROM CARE PROVIDERS

Most hospice referrals come to the programs from patients' primary physicians. Some come directly from families who have heard about hospice from other families that used the service or from presentations made in the community. Most hospice programs send a nurse to the patient's home (hospital or nursing home) to assess the patient and to perform an intake evaluation. This evaluation requires a detailed history, including a medication history.

Pharmacists need to know patients' prescription and nonprescription medication intake; use of nutritional supplements that may be pharmacologically active, physical, and psychiatric diagnoses; and relevant laboratory test data when they are available. Usually, that information is available from the primary physician's referral and the documentation from the intake interview. Frequently, laboratory test data are not available because of the hospice philosophy of only doing tests that will directly affect patient outcomes. Renal function often can be estimated from the quantity and quality of the patient's urinary output balanced against intake. Careful dose titration is often needed in the absence of laboratory test data as patients' metabolic and elimination capabilities decline. Sometimes, pharmacists make home visits to get more complete medication histories, and to ascertain the family's understanding of medications and ability to administer them correctly.

## CONCLUSION

Most pharmacists will interact with terminally ill patients or their family members at some time. Many pharmacists will provide services to dying patients and hospice programs. An increasing number of pharmacists will work with hospice programs as a substantial part of their practices.

Effective management of pain and other symptoms associated with life-threatening disease is usually attainable with the proper combination of pharmacological and nonpharmacological interventions.[8] Pharmacists can, and should, play an important role in ensuring that their patients receive this care when it is needed.

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# Hospital Pharmacy Practice in Spain

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## INTRODUCTION

"Hospital pharmacy service" refers to the pharmacy that is inside a hospital to serve inpatients and outpatients who receive care in the hospital or require drugs that are only delivered in hospitals. "Hospital pharmacy practice" makes reference to all activities carried out by hospital pharmacy service personnel to serve those patients.

In Spain, by law, there must be a hospital pharmacy service in every hospital with 100 beds or more.[1] This service must be under the supervision of a hospital pharmacist. The total number of pharmacists depends on different factors such as number of beds, services provided to patients, and type of hospital. All hospital pharmacists working in the service must be hospital pharmacy specialists.

Activities common to all hospital pharmacy services in Spain are pharmacy management, dispensing of drugs, drug information, and drug manufacture. Many other activities are also conducted in many hospital pharmacies such as centralized parenteral admixture preparation, design and preparation of parenteral and enteral nutrition as well as follow-up of patients under this kind of nutrition, therapeutic drug monitoring, pharmacoeconomics, drug surveillance, research, activities related to medical devices, radiopharmaceutical activities, clinical pharmacy activities, pharmaceutical care, participation in committees, and so on.

In what follows, hospital pharmacy practice in Spain will be described. As an introduction, a brief history and description of the evolution of this discipline and the Spanish hospital pharmacists training program will be presented. Then, activities currently conducted by hospital pharmacy service personnel will be described and clinical pharmacy opportunities will be indicated. And finally, future trends will be outlined. Useful references will be given throughout the report.

## BRIEF HISTORY OF HOSPITAL PHARMACY IN SPAIN

Pharmacists have always worked with doctors and nurses, in and outside hospitals, but it was not until 1955 that a National Association of Pharmacists from Civil Hospitals was created in Spain. In 1967, the Spanish Public Health Service created its own hospital pharmacy services in state hospitals. In 1977, hospital pharmacy services were regulated as was the training of hospital pharmacists. In 1988 the name of the association changed to the Spanish Society of Hospital Pharmacists, as it is known today.[31] In 1990, the Spanish Parliament approved the "Medicine Law",[1] which consolidated hospital pharmacy services as the basic structure for the rational use of drugs and specified the residency program as the training needed to work in those services.

## EVOLUTION/TRANSITION

Hospital pharmacy is a discipline in permanent transition. In Fig. 1, activities conducted by hospital pharmacists as well as the number of hospital pharmacists in Spain from 1955 are presented. Originally, hospital pharmacists were responsible for management and delivery of stocks of drugs to the wards. Since then the role of the pharmacist has evolved to include a more rational dispensing system (unit-dose delivery) and clinical activities and pharmaceutical care.

Hospital pharmacists in Spain, as in other countries, are increasing their direct communication with patients, nurses, and doctors and at the same time are transferring some activities to others, such as drug manufacture to the pharmaceutical industry. The therapeutic role of drugs is increasing; furthermore, the responsibility of pharmacists

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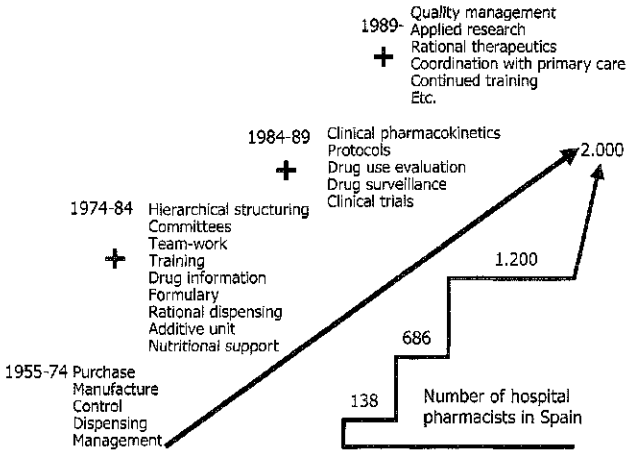


**Fig. 1** Activities conducted by hospital pharmacists and the number of hospital pharmacists in Spain since 1955.

goes beyond simple delivery of prescriptions. Clinical pharmacy is appearing as a new culture for professional practice. Clinical pharmacy can be defined as a compound of beliefs, rules, and values that constitute the foundation of the pharmacy practice, cooperation in the health care team, and direct pharmacist interventions.[2] The objective is better patient care. Spanish health care organizations are incorporating this new role of the pharmacist in different ways. An example is the addition of activities involving direct contact with patients (clinical pharmacy and pharmaceutical care) to the hospital pharmacist training program.

Clinical pharmacy is founded on three basic activities: drug selection, drug information, and rational distribution (unit-dose). If these activities are not present, other clinical activities cannot be developed. Drug information, the unit-dose delivery system, parenteral and enteral nutrition programs, therapeutic drug monitoring, participation in clinical trials, and other activities developed by Spanish hospital pharmacists are modest examples of what is known as clinical pharmacy.[2] Clinical pharmacy is slowly changing society's idea of hospital pharmacy in Spain.

## THE HOSPITAL PHARMACIST TRAINING PROGRAM IN SPAIN (RESIDENCY)

In Spain, a hospital pharmacy training (residency) is mandatory in order to work as a hospital pharmacist. This specialization has been regulated by law since 1982.[3,29] Until 1999 the residency program lasted for three years; it is now four years. The reason for this extension is that activities conducted by hospital pharmacists have increased considerably and training had to adapt to these changes. Activities outside the pharmacy service and in proximity to the patient and health care team are necessary. In the fourth year, residents are supposed to take their knowledge to the bedside and be with the patient and health care team. They have to take responsibility for the pharmacotherapy given to each patient, work as part of a team, and develop a critical ability to solving all pharmacotherapeutic problems.[4] The residency program is regulated, practice-based, and can be done only in certain accredited hospitals, and students have to first pass a national exam.[3,5,6] Currently, approximately 100 pharmacists per year can be admitted to the residency program, which includes all activities conducted in hospital pharmacy services.

## ACTIVITIES CONDUCTED IN HOSPITAL PHARMACY SERVICES: CURRENT SITUATION

Activities developed in a hospital pharmacy service can be conducted either from inside the service or outside of it. In the latter case, activities are obviously connected to centralized activities.

In order to completely understand the situation in Spain, it is important to know first how the Spanish health system works. In Spain, there are public and private hospitals (around 795 hospitals; see Fig. 2).[30] Every Spanish person has the right to free public health care; however, if patients prefer, they can go to a private hospital and pay for the health care that they receive. In addition, some

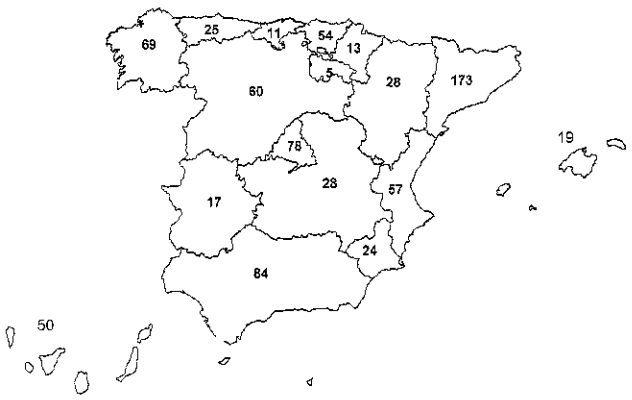


**Fig. 2** Number of hospitals per region in Spain (From Ref. [30]).

private hospitals have agreements with the public sector or with insurance companies.

In what follows, some activities conducted by Spanish hospital pharmacists will be briefly described. Three activities are considered the foundation of hospital pharmacy in Spain: adequate drug selection, drug information, and drug delivery. Some Spanish references include most of the activities developed at Spanish hospitals[7,8] as well as statistics on hospital activity.[9] Recommendations of the Spanish Society of Hospital Pharmacists (SEFH) for some of the activities can be found at www.sefh.es/normas/normasy.htm. In addition, there are now many possibilities for networking. The SEFH facilitates interhospital communication and interest groups have been created.[31] Some other international organizations provide the same opportunities for their specific topics (e.g., www.senpe.com/Gtrabaj/textos2.htm for parenteral and enteral nutrition). Statistical data will not be presented here but can be obtained from a survey conducted by the SEFH in 1995;[10] more up-to-date figures will become available from the year 2000 survey.

## Management

There are two important areas in management, clinical and purchasing management. In every hospital pharmacy service it is necessary to establish basic procedures for drug selection, acquisition, reception, storage, and distribution with the least cost and risk for patients.

Clinical management refers to an efficient and safe use of drugs according to pharmaceutical criteria. To achieve this goal there are many possible courses of action; however, the most basic one, which is conducted in all Spanish hospital pharmacy services, is the definition of a hospital-specific drug formulary that lists all the drugs approved by the hospital's Pharmacy and Therapeutics (P&T) committee. In Spain a hospital pharmacist is one of the members of P&T committee, frequently the president or the secretary. The P&T committee has the following tasks: to select drugs; to recommend a drug use policy; to educate about correct drug use; to set drug use protocols and establish the means of ensuring compliance; to introduce a program for the detection, follow-up, and evaluation of adverse drug reactions; and to cooperate in a quality control program. Criteria used by the P&T committee for drug selection are, in order of importance: efficacy, safety, cost-effectiveness, therapeutic contribution, and incidence.

Regarding purchasing management, the main responsibility of the purchasing unit of a hospital pharmacy service is to have available the necessary drugs to treat hospital patients. Almost all purchasing units in Spanish hospital pharmacies are computerized and all have the following tasks: to define requested drugs, to establish purchasing procedures according to Spanish law, to place orders, to inform hospital directors of acquisitions, and to develop a quality control program. Spanish references to management techniques are given in the bibliography.[7,8,11]

## Drug Dispensing/Distribution

Drug dispensing/distribution is one of the main clinical activities of Spanish hospital pharmacists. Many studies have shown that the unit-dose distribution system has reduced drug errors, and it is one of the main contributions of the hospital pharmacy[12] to patient care. Pharmacist participation in medical rounds and presence at the time of prescription can result in even better patient care and a prompter detection of treatment failures.[13,14] Such "clinical pharmacy" activity is being conducted with some groups of patients in some Spanish hospitals[15] and is becoming more frequent.

Most Spanish hospitals have a unit-dose drug distribution system (Fig. 3). The main objectives of such a system are the following: knowledge of patient pharmacotherapeutic profile, which encourages pharmacist intervention before drug dispensation and administration; decrease of drug errors, interactions, and adverse reactions; reduction in treatment costs; decrease of drug manipulation by nurses on the wards; and billing or economic assignment according to each patient's real expenses.

In a unit-dose system, the pharmacy service delivers drugs to be directly administered to the patient without need of further intervention by others. In hospitals, the distribution of some drugs (e.g., narcotics, compassionate-use drugs, research drugs, and drugs for emergencies) requires a special control and distribution procedure. Normally, these drugs are not sent with the rest of the medication; and the procedure for these drugs will be presented later on. The following is a description of the unit-dose system as it is applied in most Spanish hospital pharmacy services.

Medical orders are handwritten by doctors and a copy is sent to the hospital pharmacy service, where it is recorded in the computer system. However, in some hospitals, doctors enter the medical order directly into the computer; few proceed in this way at the moment but the number is increasing. In a few hospitals, with some types of patients, pharmacists are present at the time of prescription. Prescriptions may specify generic or brand names depending on the hospital's policy, and pharmacists can choose bioequivalent drugs depending on what is available.


**Fig. 3** Unit-dose area in a Spanish hospital pharmacy service.

Medical orders are checked by pharmacists, and doctors or nurses are consulted if necessary. At this point, pharmacists have a good opportunity for intervention. To prove the appropriateness of the prescription for a specific patient, patient data must be checked. The unit-dose system is computerized in all hospital pharmacies. Computer programs may be in-house or standard. Some information can be checked on the computer; in some cases programs even make suggestions.[16] Subsequently, lists are created for auxiliary personnel to prepare the delivery trolleys to take the medications to the wards. In a few hospitals, for some specific units, automated delivery (e.g., Pyxis®, Suremed®, Omnicell®) is used. In this case, pharmacists, or someone under their supervision, have to check the accuracy of the delivery content. Quality and security in delivering medication must be fully guaranteed. These systems require a medical order, and information regarding patient name, doctor, and quantity of drug dispensed must be recorded.

In most Spanish hospitals, there is just one delivery a day, in the afternoon, because in many hospitals doctors see patients between 8 A.M. and 3 P.M. However, the number of visiting hours is increasing and pharmacy working procedures may have to adapt to the new situation. Parenteral admixtures and nutritional preparations, if chemically stable, are generally prepared for each patient in a centralized unit (described later), labeled, and then delivered with the rest of the medication. Cytotoxic drugs require special control and handling and are not normally sent with the rest of the medication. Sometimes, in intensive care units and other acute care settings, drug delivery is not based on a unit-dose system but on stocks kept on the wards.

Some outpatient services are provided by the inpatient pharmacy, but discharged patients in Spain cannot receive drugs from the inpatient pharmacy. At discharge, patients may receive drug information and a copy of their medication administration record for reference. Computer software (InfoWin®) has been developed by a Spanish group (with a Spanish drug database) for this purpose.

Drugs that require a special delivery procedure are:

1. *Drugs for compassionate use.* Hospital pharmacists have to control the ordering, dispensing, and use of compassionate-use drugs. These are drugs for nonauthorized indications and/or research drugs not included in a clinical trial. In Spain, activities in relation to these drugs are regulated.[1,17] In order to use a drug for compassionate care, the pharmacy service of the hospital applies to the Dirección General de Farmacia y Productos Sanitarios with the following documents: a clinical report in which the doctor justifies the application for the drug, a consent form signed by the patient,

and a form signed by the hospital medical director who is responsible for drug use. It is common practice for the pharmacy service to prepare a technical report with relevant references to support the application and to inform hospital directors of the process.

2. *Research drugs.* Regarding drugs for clinical trials conducted at the hospital, the pharmacy service is responsible for their reception, storage, dispensing, distribution, and return of unused drugs. Spanish requirements are that clinical trials be regulated.[17] A copy of the clinical trials committee approval must be kept at the pharmacy service, and dispensing is done only after a written and signed prescription is received.

3. *Foreign drugs.* Drugs marketed in a foreign country but not available in Spain may, according to Spanish law, be obtained but only for the specific indications for which the drug is approved in that foreign country.[1] The hospital pharmacy service applies to the Dirección General de Farmacia y Productos Sanitarios with the necessary documentation for use with an individual patient or according to a protocol.

4. *Stocks in wards.* There are some drugs (e.g., urgent medications, PRN, drugs dispensed as needed) and medical devices that have to be in stock on the ward. These are normally sent to the floor on a regular basis, according to a fixed schedule. These stocks are periodically checked by pharmacists (with regard to composition, expiry date, correct identification), and the results of the control are filed. The nurse supervisor of each ward is responsible for the safekeeping of the stock; the pharmacist is responsible for control and supervision.

## Manufacture

Manufacture implies the manipulation of active substances and drugs in order to make them suitable for direct administration to patients. Separate areas are needed for the manufacture of intravenous admixtures and parenteral nutrition, cytotoxic drugs, and sterile preparations. No separate areas or biological security are needed for other, nonsterile preparations or drug repackaging. Following Spanish regulation,[18] written protocols and procedures for manufacturing processes must exist in every pharmacy service. A sterile area is normally achieved with a vertical or horizontal airflow hood.

## Central Intravenous Additive Service

Centralized units of intravenous therapy (or CIVAS, for "central intravenous additive service") were created in Spanish hospital pharmacy services as both a consequence of the growing importance in the hospital of intravenous drugs, and parenteral nutrition and fluids and as a consequence of the clinical and technical progress in this area of the pharmacy. In recent years, Spanish hospital pharmacy services are almost obligated to have a CIVAS,[19] and it is now considered, along with the unit-dose distribution system, one of the main units in the pharmacy service.[19] The main objectives of the CIVAS are preparation of products therapeutically and pharmaceutically appropriate for the patient (right dose, administration route, chemically compatible, stable); preparation of admixtures free of particles, microorganisms, or toxins; preparation of admixtures with the correct drug in the exact amount; labeling, identification, storage, and distribution of admixtures according to good drug control principles; cost control of intravenous fluids; monitoring and clinical follow-up of patients; drug use evaluation studies; and participation in the

**Fig. 4** Nurse preparing an anticancer drug in a central unit in a Spanish hospital pharmacy service.

intravenous therapy policy of the hospital (indications, selection, preparation, administration, etc.).

Most hospitals have a computerized CIVAS that is integrated into the unit-dose distribution system. Preparations handled in these units include cytotoxic drugs, antibiotics, parenteral nutrition, other drugs, and therapy with fluids (Fig. 4). References to Spanish articles dealing with recommendations for managing these units can be found in the bibliography.[7,8,19,20] Protocols must include every procedure carried out in the unit, from preparation to identification, hazard handling, waste treatment, and so on. In Spain, admixtures and nutritional preparations are normally prepared by pharmacy nurses supervised by pharmacists.

Centralized units have some advantages, such as less investment in equipment, better use of multidose vials, recycling of unused preparations, better working conditions, a good opportunity for clinical intervention by pharmacists, and improvement in the quality of patient care when the CIVAS is well coordinated with the unit-dose system.

## Enteral and Parenteral Nutrition

In Spain, preparation of enteral and parenteral nutrition is carried out in the centralized units of the pharmacy services. Hardly any hospitals obtain their parenteral nutrition preparations from an external company. In most hospitals there are some standard nutritional preparations as well as others designed for specific patients. Nutrition design and patient follow-up is done by hospital pharmacists or by a team of various professionals (doctors, dieticians, nutritionists, pharmacists), depending on the hospital. Normally, laboratory data, clinical results, and patient progression are observed by pharmacists and nutrition support is changed accordingly, which gives pharmacists another opportunity for clinical intervention. References on how to manage such a service are given in the bibliography.[7,8,19] Computer software is used to make this task easier, permitting data entry (general patient data, lab results, prognosis, nutritional status, diet) and preparation of working sheets, reports, and labels for nutrition identification. Complications or incidents can also be registered; some software programs include Spanish products for nutrition support (e.g., NutriData®, Nutri2000®).

## Drug Information

Drug information is one of the main responsibilities of pharmacists in hospitals and one of their most important contributions to a rational use of drugs and better patient care. In 1973, the first drug information center was established in Spain, and today activities related to drug information are part of every hospital pharmacy service. Drug information is another area where clinical intervention by pharmacists could be increased.

Information provided by pharmacists can be classified as passive or active. The former includes answering questions and preparing the requests/controls for foreign, compassionate-use, and research drugs. Active information includes providing support to the P&T committee (drug formulary preparation, diffusion of main decisions), establishment of protocols, writing of the drug information bulletin, sessions, adverse drug reactions programs, advising in- and outpatients, health education activities, information management, and so on. Some hospitals make their drug formulary and other information available on the Internet (e.g., www.hsanmillan.es/farma/index.htm) and some participate in the dissemination of drug information, in the Spanish language, to patients.[32] Additional sources of information and recommendations for the management of drug information centers that have been proposed by the SEFH and others are given in the bibliography.[7,8,11,21,22]

## Clinical Pharmacokinetics and Therapeutic Drug Monitoring

Clinical pharmacokinetics is a multidisciplinary field that has been growing in importance over the last 20 years. Its main objective is therapy optimization by achieving drug concentrations in the therapeutic range and thereby obtaining maximum efficacy with minimum adverse effect. The concentration–effect relationship of many drugs is better than the dose–effect relationship. This is due to high interindividual variability. In these drugs, therapeutic drug monitoring is justified.

To assure the best efficacy, the pharmacist designs a pharmacotherapy that is specific to each individual patient. This is achieved by obtaining blood samples, gathering patient data (clinical situation, laboratory results, physiopathology, progression, therapy), applying pharmacokinetic principles, and applying knowledge of drug behavior in the population in which the patient is included. Even though drug concentration is an important piece of information, it is not enough on its own and patient follow-up is required. Times of sample collections must be carefully established in order to obtain maximum information from the minimum number of samples.

The usefulness of therapeutic drug monitoring has been demonstrated for some drugs (e.g., some antibiotics, cardiovascular agents and antiepileptics, theophylline, inmunosupressants, litium, methotrexate),[8,23] and these are the drugs that are included in clinical pharmacokinetic programs in Spanish hospital pharmacy units. The be-

nefits of therapeutic drug monitoring of other drugs, such as some anticancer drugs, are now being studied in some centers.[24]

Sample analysis requires specific techniques, such as fluorescence polarization immunoassay (FPIA) and high-performance liquid chromatography (HPLC). These techniques are not always available in the pharmacy and so sample analysis is not always done in Spanish hospital pharmacy services but in laboratories. However, it is a pharmacist who interprets results, makes recommendations, and follows up on patients, all as part of clinical activities to pursue better patient care. In all hospitals with such a pharmaceutical service, doctors and other members of the health team welcome the contribution of pharmacists, with their pharmacokinetic knowledge, to the rational use of drugs.

### Drug Surveillance

Drug surveillance includes drug follow-up with the purpose of observing, evaluating, and communicating any adverse reactions that a drug can produce when used in clinical practice. A drug surveillance program must be established in every hospital in order to detect these reactions, and the drug information center must support this activity technically. Observed events are communicated to the regional center for drug surveillance, either directly or through the SEFH. The Spanish Drug Agency[33] facilitates drug surveillance activities and the diffusion of information among professionals. Spain has an organized drug surveillance system—a national committee reporting to the Ministry of Health was constituted for this purpose in 1987. Spontaneous communication of adverse drug reactions is voluntary in Spain and is conducted through an official form known as the "yellow card."[8]

### Radiopharmacy

In Spain, pharmacy practice is also applied to the study, manufacture, control, and distribution of radiopharmaceuticals. Radiopharmaceuticals must be isolated from other drugs and personnel, and devices must follow Spanish regulations.[25] Radiopharmacy is part of the hospital pharmacy service; however, it is recommended that the unit be located close to the nuclear medicine department and supervised by a pharmacist specialist in radiopharmacy.[7]

### Pharmacoeconomics

Pharmacoeconomic evaluations consist of comparing different alternatives in terms of costs and benefits. In Spain, pharmacoeconomics is becoming more important due to increased pressure to make the best use of limited resources. Furthermore, advances in the methodology[26] have increased the scientific rigor of pharmacoeconomics. Pharmacoeconomics is used by Spanish hospital pharmacists as a tool for decision making regarding drugs, medical devices, or related activities. Studies are conducted and pharmacists adapt published studies to each unique hospital setting.

### Activities Related to Medical Devices

Many Spanish hospital pharmacies participate in the selection, ordering, storage, distribution, and provision of information relating to medical devices. Such hospital pharmacies are also involved in rational use programs. A guide to medical devices used in Spanish hospitals has been published, which gives a classification to each device.[27]

## FUTURE TRENDS

The number of activities conducted by hospital pharmacy services is continually increasing as the needs of doctors, personnel, and patients evolve. This gives the pharmacist the opportunity to develop a range of activities (clinical roles, management, administrative duties) that are of interest to and positive for the hospital. Pharmacists must continue to focus on the impact that technological and professional changes may exert on the efficacy and safety of medications as well as on patient care.

The role to be played by hospital pharmacists should be determined by all health care professionals, not just by pharmacists themselves. The 1999 meeting of the Spanish Society of Hospital Pharmacists took this into account and a roundtable was held incorporating representatives of all health team members as well as a representative of patient opinion based on a survey of patients. Better information for patients, more integration of pharmacists in the health team, and more direct contact with patients seem to be the activities to be developed in the future.[28]

Any activity that contributes to patient care must be nurtured, no matter who suggests it. Pharmacists as well as other professionals know that teamwork is the key to improving results for the patient.

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PROFESSIONAL DEVELOPMENT

# Hyperlipidemia Pharmacy Practice

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## INTRODUCTION

Hyperlipidemia is a disorder that is widely prevalent in the U.S. population. Elevations of total and low-density lipoprotein (LDL) cholesterol have been documented to increase the risk of coronary heart disease (CHD). The Third National Health and Nutrition Evaluation Survey (NHANES III) estimated that 52 million Americans have cholesterol elevations that require intervention, of which 12.7 million may require drug therapy.[1] A number of studies have shown a reduction in cardiovascular mortality or morbidity with lipid-lowering therapy in subjects with CHD (secondary prevention)[2–5] and in some patients without known CHD (primary prevention).[6,7] Despite this, the use of lipid-lowering agents in patients who have had a prior coronary event is disturbingly low.[8] When drug therapy is initiated, compliance may be poor and adherence to therapy may be as low as 35% in some series.[9,10] Other data indicate that even where cholesterol-lowering drugs are prescribed, many patients do not reach the goals of therapy recommended by the National Cholesterol Education Program (NCEP).[11]

Hyperlipidemia is a disease particularly suitable for pharmacist management for a number of reasons. It is a disorder that can be diagnosed and monitored primarily by laboratory testing. There are accepted guidelines for LDL goals. The drugs that are used vary in their effectiveness for altering the different lipoproteins and require someone skilled in this knowledge to select them for use. The rate of adherence to drug therapy is low, possibly in part because patients do not feel elevated cholesterol and therefore do not understand the need to take medication. These drugs are in some cases unpalatable or difficult to tolerate and require much patient education to initiate therapy and maintain compliance. Drug interactions with cholesterol-lowering agents can be clinically significant. These include inhibition of absorption of drugs such as levothyroxin or warfarin given concurrently with bile acid binding resins, or inhibition of the metabolism of statin drugs resulting in myopathy or even rhabdomyolysis.

## JUSTIFICATION OF PHARMACIST INTERVENTION

Pharmacist intervention was effective in maintaining compliance and achieving LDL goals in patients treated with colestipol.[12] In a small study at a Veterans Administration (VA) Medical Center, patients received 1 hr of education and assessment by pharmacists before initiating colestipol therapy. They also were telephoned at 2-week inervals until an 8-week follow-up appointment. They were contacted by telephone again at 26 and 52 weeks. When compared at 52 weeks with patients receiving usual care, the pharmaceutical care group had greater persistence with colestipol therapy, were taking higher doses, had lower mean LDLs, and had a higher rate of reaching goal.

The effect of weekly contacts with patients initiated on combination lipid-lowering therapy of lovastatin and colestipol was investigated.[13] Patients from a university-affiliated tertiary care center were enrolled if they had undergone coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty (PTCA). In addition to instructions on appropriate drug use prior to hospital discharge, patients were telephoned at home weekly for 12 weeks at which time "emphasis was placed on the importance of therapy in reducing the risk of cardiac events." Interestingly, when these patients were compared with a control group at the end of the 12 weeks compliance with therapy was high in both groups and not significantly different. However, when refill history was obtained from the patients' pharmacies at 1- and 2-year intervals, the patients in the intervention group had significantly higher rates of compliance.

Provision of patient education in combination with bimonthly cholesterol testing in a community pharmacy resulted in a significant reduction in cholesterol values over a 6-mo study.[14] Changes in patient-reported behaviors such as dietary habits and exercise were also noted. Although the lack of control group made this study less than definitive, it indicated that a combination of cholesterol monitoring and education could result in lower cholesterol concentrations. A second study demonstrated that screen-


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ing in combination with education and referral to a primary care physician when appropriate resulted in a significant number of patients receiving follow-up for cholesterol concentrations that were higher than the NCEP goals.[15]

## DEVELOPING A HYPERLIPIDEMIA PHARMACY PRACTICE

Hyperlipidemia management can exist wherever pharmacists practice, including community pharmacies, institution-based or free-standing ambulatory clinics, or inpatient services. Despite these different settings, some universal requirements need to be addressed.

The nature of the practice may be influenced by the availability of space in which to provide patient care. For example, the lack of facilities in which to meet privately with the patient may result in a telephone-based practice. Offering lipid management in the community pharmacy may require an investment in infrastructure. Some remodeling of the pharmacy may be needed to provide an area where confidential communications can occur. A lipid analyzer, as well as a dedicated clean area, must be supplied if blood lipid monitoring is to be offered.

Staffing must be adequate. A redistribution of duties among pharmacists and technicians, possibly in addition to hiring additional pharmacists, may be necessary to allow pharmacists time to provide the service.[16]

Most pharmacists will need to justify their provision of this service, whether it be in the form of a business plan for an independent pharmacist or a proposal demonstrating benefit to an institutional employer. If the pharmacist will be relying on referrals to the service or will be collaborating with physicians to implement therapy, the pharmacist must first determine whether physicians will use the service and be accepting of input. An evaluation of a cholesterol screening program found that a significant number of physicians in the geographic area were resistant to their patients directly receiving the results of their cholesterol tests from the pharmacy. These physicians were less likely to contact patients with the results of elevated cholesterol values obtained at the screening.[17] Patients may also be surveyed as to acceptance of pharmacist management, particularly if they are going to be expected to pay part or all the costs of the service.

In all models, a scope of practice agreement or protocol is recommended, if not required. This should outline the following:

1. The hours of operation.
2. The pharmacists who are responsible for providing the service.
3. The supervising physician, if applicable. This may be especially needed if the pharmacist has prescriptive authority.
4. The population to be managed. For example, in the case of limited resources, the service may be restricted to secondary prevention patients, patients requiring combinations of drugs, or those with mixed lipid disorders versus those with only elevated LDL, or other parameters as determined by the needs of the facility.
5. The means of identification of patients. This could vary from seeing potentially low-risk patients, such as any patient followed in a general medicine clinic or referred by a primary care provider, to identifying high-risk patients, such as anyone discharged from the hospital with a diagnosis of myocardial infarction or after a revascularization procedure or with other evidence of CHD risk.
6. The goals of the clinic and methods for achieving them. Explain how patients will be evaluated and how the need and type of therapy will be determined. Describe any protocols for deciding on drug therapy or the rationale for allowing clinical decision making instead of following an algorithm. Will patients be seen once for evaluation and recommendations, as often as necessary to achieve control, or indefinitely? How frequently will they be seen? Will all contacts be by visit, or will telephone calls be routinely used?

## PRACTICE MODELS

### Community Pharmacy Practice

The functions of a pharmacist in lipid management in a community setting may include screening for elevated cholesterol and/or low HDL cholesterol, providing patient education and counseling to enhance adherence with drug and nondrug therapy, monitoring of lipid profiles for assessment of efficacy, and making recommendations to providers for drug therapy management.

#### Screening programs

The accessibility of community pharmacists to both patients and physicians makes them an ideal resource for identifying the presence of lipid abnormalities. Screening may consist of offering to measure cholesterol levels to the general population, or may involve targeted screening of patients at high-risk for CHD, also called case finding. In either case, screening should involve more than pro-

vision of a laboratory value. The total and HDL cholesterol values should be evaluated and interpreted in the light of the patient's risk factors for CHD. Education about cholesterol and cholesterol-lowering strategies should be provided, and the pharmacist should be prepared to refer the patient to their primary care provider if warranted. Failure to interpret these values may result in unnecessary concern on the part of the patient or, potentially more damaging, result in a patient not seeking care when needed.

Gardner and colleagues[18] demonstrated that a community pharmacy prescription database can be used to identify patients at risk for CHD. This is important because it targets those individuals most likely to benefit from lipid-lowering interventions. They identified four clinical indicators that were believed to be likely to identify patients at risk for CHD: prescription for sublingual nitroglycerin, prescription for beta-adrenergic blocking agents or thiazide diuretics, males with a prescription for nicotine gum or patch, or those receiving oral hypoglycemic agents or insulin therapy and who were greater than 50 yr of age. A search of the pharmacy database was performed to identify individuals prescribed at least one of these agents, and the pharmacy profiles were screened to ensure the age and sex met the criteria. These subjects, who were invited to a free cholesterol screening, were compared with an unselected population who self-referred to the screening. Twenty-one percent of those identified as high risk responded to the invitation. A significantly greater percentage of the screened patients had cholesterol values that were higher than desired. In addition, two-thirds to three-fourths of the patients with a clinical indicator had cholesterol values over 200 mg/dl, indicating that these indicators may be predictive of the need for cholesterol-lowering intervention.

Einarson et al.[19] reported the financial feasibility of a pharmacy-based cholesterol screening program. Subjects were asked how much they would be willing to pay for a cholesterol measuring service in a pharmacy. Patients who completed a pharmacy service questionnaire indicated they would be willing to pay a mean of $11.54. Patients who received the service were surveyed afterward, and indicated a willingness to pay $14.47 (1987 dollars). Of note, it does not appear that these patients received pharmacist education as part of their testing but were reacting to the value of obtaining cholesterol results at a pharmacy.

## Lipid management practices

Shibley and Pugh[20] described the provision of pharmaceutical care in independent community pharmacies. Patients were recruited by the investigator and included in the study if their primary physicians agreed to allow them to do so. The physicians were recruited by letter and by meetings with the pharmacists. Pharmacists provided basic education about lipid disorders, the relationship to coronary artery disease, and diet and exercise. Lipoproteins were measured at the pharmacy using the Cholestech® analyzer. If warranted, drug therapy recommendations were provided to the physician via telephone or letter; if accepted, the patient was seen at 2 months to assess efficacy and adverse effects. All patients were also seen by a certified dietician. Significant reductions in LDL cholesterol were observed, although it is not clear how many patients reached their therapeutic goal. Given choices ranging from $15 to $55, patients indicated they would be willing to pay $23.75 ± $11.42 for each encounter with the pharmacist.

Project ImPACT: Hyperlipidemia was a multicenter community pharmacy-based demonstration project that aimed to demonstrate the benefits of a pharmacist on patient adherence and compliance with lipid-lowering therapy.[16] The pharmacists used cholesterol analyzers at their sites to enhance their interactions with patients and their physicians. Emphasis was placed on patient education and communication with the physicians to bring patients to their NCEP cholesterol goals. Of interest, 62.5% of the patients, who were predominantly primary prevention, did reach and maintain their goals by the end of the study. Persistence with therapy was excellent, with 93.6% remaining on the prescribed cholesterol-lowering agent throughout the study. Compliance with therapy, defined as fewer than five missed doses or refills obtained within 5 days of when due, was 90.1%. Physician acceptance of pharmacist interventions was high, with 76.65% of recommendations resulting in a change. These interventions involved coordination of care, adverse drug reactions, drug interactions, drug dosing, drug selection, and side effects.

The participating pharmacies were primarily independents, with some chains, clinic pharmacies, health maintenance organizations, and home health/home infusion pharmacies. All pharmacies scheduled patients for appointments with the pharmacist. Most used time before the regular pharmacy hours or on weekends, as well as during usual business hours. Seventy-two percent of sites changed the pharmacist's duties to accommodate this new role, and 59% changed technician duties. Increasing pharmacist overlap was also a commonly used strategy. Fewer than one-third added pharmacist staff to implement the program. The average amount of time spent on patient encounters was about 45 min for a new patient and 22 min for a follow-up appointment.

### Clinic Models

Development of lipid management practices in the institutional or free-standing clinic settings may take many forms. The types of practice can range from provision of consultative services by pharmacists in conjunction with patients' appointments with their primary care provider, to free-standing pharmacist-managed clinics in which the pharmacist has prescriptive authority to initiate, discontinue, and change drug therapy.

Pharmacists in a consultative role improved management of lipid disorders in an ambulatory internal medicine clinic.[21] In this study, the pharmacist met with patients prior to their physician appointment. Medication histories were taken, compliance encouraged, drug costs were tracked, and the least costly recommendation made to the physician. The pharmacist reviewed laboratory data and recommendations with the physician and attached a copy of these to the front of the chart. Decisions to accept or decline the recommendations were made by the physician. The majority of recommendations were accepted. When compared with usual care where pharmacists were not involved, significantly more patients reached LDL goals.

Furmaga[22] described the structure of a pharmacist-managed lipid clinic at a VA Medical Center outpatient clinic. Initially patients were identified using the hospital computer database to identify those with a total cholesterol of greater than 260 mg/dl. These patients were invited to a general educational seminar and subsequently scheduled into the lipid clinic, if needed. As this resulted in more patients identified than could be reasonably accepted into the clinic, the system was changed so that patients were referred from outpatient clinics. Patients were scheduled for 30-min appointments. The activities of the pharmacist included patient education, identification of secondary causes of hyperlipidemia with subsequent referral to other clinics as indicated, compliance assessment, and intervention and recommendation of addition of drug therapy to diet therapy. Clinical judgment was used in lieu of a protocol for drug selection. The pharmacist did not have prescriptive authority but was responsible for monitoring of drug therapy for efficacy and adverse events, and determining when changes were needed. Activities were documented in the medical record.

Shectman and colleagues[23] demonstrated that use of physician extenders resulted in improved LDL cholesterol concentrations when compared with usual care. In this model, also at a VA hospital clinic, the pharmacist or nurse used an algorithmic stepwise approach to assist in drug selection and optimization in reaching NCEP LDL goals. More patients reached their LDL goals in the physician extender group. The total costs of the physician extender care was higher, primarily due to higher drug costs. The cost per unit of LDL lowering, however, was significantly less.

### Institutional Pharmacy Model

Inpatient pharmacists can also provide care by helping to initiate lipid-lowering therapy. In addition to the data that support treatment to lower cholesterol in patients who have had a coronary event, the National Committee for Quality Assurance is instituting a new Health Plan Employer Data and Information Set (HEDIS) indicator for cholesterol management in patients who have experienced an acute cardiovascular event. This will provide a challenge to identify and treat patients with coronary artery disease. A program by which pharmacists identified patients through acute myocardial infarction/percutaneous transluminal coronary angioplasty orders has been detailed.[24] Pharmacists placed a standardized note on the outside of the patient chart that included the goals of therapy and recommended that a lipid panel be obtained. The proportion of patients receiving lipid-lowering therapy at discharge was significantly increased after initiation of the program.

## USEFUL TOOLS FOR PROVISION OF SERVICES

### Pharmacist Education and Training

Regardless of the practice setting, a pharmacist needs certain tools to provide lipid management services. The first tool is an in-depth understanding about the disease and antihyperlipidemic drugs. Understanding of the disease includes knowledge about lipid metabolism, the influence of lipids on atherogenesis and vascular function, the risk of dyslipidemia and CHD mortality and morbidity, and the benefits of lipid-lowering as demonstrated in clinical outcome trials. Knowledge of the drugs includes pharmacology, pharmacokinetics (especially as pertains to the potential for drug interactions), adverse effects that are most often experienced or most severe, and how to manage these effects. The influence of each drug on the various lipoproteins, the effects of dose on lipoprotein lowering, the risks and benefits of combination therapy, and the goals to be targeted should be known. This type of education can be obtained through self study or by attending certificate programs, conferences, or other training programs.

The American Pharmaceutical Association's "Pharmaceutical Care for Patients with Dyslipidemias" is a

2-day training session that includes material on evidence of cholesterol-lowering and use of antihyperlipidemic agents, training on the Cholestech® analyzer, discussions on preparing the pharmacy practice site to provide the service, marketing to patients and physicians, communication with physicians, and reimbursement and billing. The National Pharmacy Cardiovascular Council offers a comprehensive three-tiered educational program. The Lipid Managers Training Program begins with the basics of lipid disorders and progresses to on-site training in a lipid clinic.[32] Many state organizations offer certificate programs in lipid management.

The NCEP was initiated by The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) in 1985. The goal of this program is to promote cholesterol awareness in the U.S. population as a risk factor for CHD and provide guidelines for cholesterol-lowering to physicians, patients, and the community, thus reducing CHD mortality and morbidity. The program consisted of five panels that are responsible for evaluation of the evidence and establishing guidelines in their specific areas: the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel or ATP) develops guidelines for the detection, evaluation, and treatment of high blood cholesterol in adults; and the Expert Panel on Blood Cholesterol Levels in Children and Adolescents developed recommendations for healthy diets for children and adolescents, and for detection and treatment of high blood cholesterol in children and adolescents from high-risk families.

The guidelines for treatment recommended by the ATP are considered the standard for dietary and drug therapy in adults. The most recent guidelines were released in May 2001;[25] the panel is currently revising these and updated guidelines are anticipated after Spring 2001. The pediatric guidelines were released in 1992.[26] The American Diabetes Association clinical practice guidelines make recommendations for managing hyperlipidemia in persons with diabetes that are more aggressive than the current NCEP guidelines, as well as more specific to this population.[27]

**PATIENT NAME** **ID#** **DOB** **HT:**
**REFERRING CLINIC/ PROVIDER** **PRIOR DIETARY CONSULT / INTERVENTION?**
**DX:**
**SMOKER?** **ETOH? (QUANTITY):**
**RISK FACTORS:**

| | | | |
|---|---|---|---|
| MALE > 45 YR | FEMALE > 55 YR | CHD | HDL > 60? |
| DIABETES | SMOKING | FAMILY HX | |
| HTN | CVD | PVD | |

**LDL GOAL** **TG GOAL**

| DATE | LIPID DRUG / DOSE | WT | TC | TG | HDL | LDL | HBA1C | LFTS | OTHER LABS | COMMENTS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |

**Fig. 1** Sample lipid monitoring form.

## Patient Education

The second set of tools involves imparting some of this information to the patient. This can be done verbally, with written educational materials, with videotapes, or a combination thereof. The level of the material should be adjusted for the educational level of the patient population. The information should include definitions of cholesterol, triglycerides, and lipoproteins; factors that increase or decrease these values; and the goals for the patient. A risk calculator that can be used to illustrate to patients how their individual factors increase or decrease their risk of a coronary event should also be included.[28] In patients without physical limitations, handouts and counseling about beginning an exercise program may be provided, although patients with known vascular disease should be referred to their primary care provider for guidance on appropriate activity. Providing a diary in which patients can document their activity, heart rate, notes on dietary changes, and weights can be helpful, especially in the initial stages of making lifestyle changes. Information sheets about the individual drugs should also be distributed. The American Heart Association (AHA) web site provides a variety of tools for the health care provider to order for a fee or to download at no charge.[29]

Pharmacists who practice lipid management should be familiar with dietary factors that influence lipids. If referrals to a dietician are allowed by law, the pharmacist should have a referral base from which to guide the patient. Handouts that describe the goals of fat content, specific foods to choose and avoid, and how to read and interpret food labels should be available for distribution. These are available from a variety of sources. Patients may be referred to the AHA web site, which offers information about recommended diets as well as recipes. Drug companies that market cholesterol-lowering medications often provide free patient information materials that may not be product specific but will contain a company logo and product brand names.

## Documentation

The third set of tools involves the pharmacist's documentation of interventions and results. If lipids are to be measured and followed, the use of a monitoring flow sheet is extremely useful (Fig. 1). Flow sheets may be on paper files, created on computer spreadsheets, or use special software programs.

Initial demographic data including height should be collected. The information obtained at each visit should include weight, exercise, lipid values, drug therapy (if any), and compliance. If available, other pertinent labs such as glucose or hemoglobin A1C, liver transaminases, or measures of renal function should be noted. A comments section is useful to document items such as adverse drug effects, noncompliance, or other issues that can affect lipid control.

## Communication

The fourth set of tools regards communication with physicians or other primary care providers. Interventions made by the pharmacist or recommendations to the physician may be made by telephone, letter, fax, or personal contact, depending on the practice setting. These communications are important in both obtaining and maintaining provider buy-in as well as demonstrating the active role the pharmacist is playing in the care of the patient. In addition, there is less likelihood for misunderstanding than if all information is provided by the patient.

## Lipid Measurement Devices

Lipid analyzers are not necessarily a needed tool for providing lipid management services but can be very

**Table 1** Cholesterol monitoring tests granted CLIA waived status

| System | Manufacturer | Lipoprotein measured |
|---|---|---|
| Advanced Care | Johnson & Johnson | Cholesterol |
| Cholestech LDX | Cholestech | Total cholesterol, HDL, triglycerides, glucose |
| Accu-Chek InstantPlus | Boehringer Mannheim | Cholesterol |
| ENA.C.T Total Cholesterol Test | ActiMed Laboratories | Cholesterol |
| Lifestream Technologies Cholesterol Monitor | Lifestream Technologies | Cholesterol |
| Polymer Technology Systems (PTS) MTM Bioscanner 1000 (for OTC use) | Polymer Technology Systems, Inc. | Cholesterol, HDL |

(Adapted from Ref. [31].)

helpful. They allow the pharmacist to provide information and make recommendations for dietary and drug therapy at the time of the interaction, instead of having to schedule another time or attempt to reach patients by phone. It allows reenforcement of the information provided at the last visit as the patient can see the results of the intervention, and the implications of adherence or nonadherence to therapy can be demonstrated and discussed, and strategies for improvement can be presented.

Measuring cholesterol in the practice setting requires both the equipment and the legal authority to perform testing. The 1988 Clinical Laboratory Improvement Amendments (CLIA) established quality standards for accuracy, reliability, and timeliness in all laboratory testing. Certain devices are considered to be of low complexity and are therefore regarded as CLIA waived, which means that the site where they are used must be enrolled in the CLIA program but that routine on-site visits and monitoring are not required.

The cholesterol measuring devices that are in the CLIA waived category are listed in Table 1. At this time, the only waived analyzer that measures total and HDL cholesterol and triglycerides is the Cholestech LDX®. State law will also need to be followed because some states, for example, do not permit pharmacists to act as laboratory directors or to obtain blood via finger stick. Information about obtaining CLIA certification, a list of waived devices, and contact information for state survey agencies may be found on the CLIA web site.[30]

### Reimbursement Strategy

Although obtaining reimbursement is beyond the scope of this chapter, a number of studies have tried to assess what patients will pay or perceive to be the value of provision of cholesterol monitoring and lipid management. The data range from assessing the value of a cholesterol level without attendant counseling to how much patients believe insurance companies should pay for each visit to the pharmacist where education and medication review and management are provided.

Project ImPACT is one of few studies that reports actual billing and reimbursement results. Both patients and insurers were billed for services. On average, pharmacists billed $28 for counseling services and $27 for lipid profiles. Seventy-five percent of patients billed paid an average of $35 per visit, and 53% of third-party payers paid an average of $30. Reimbursement by third-party payers was more frequent, however, for lipid profiles than for counseling.

## CONCLUSION

Pharmacist practices in hyperlipidemia management have been shown to be effective in improving compliance, adherence to therapy, and LDL lowering. Studies that establish cost effectiveness are limited and are needed to support efforts to expand pharmacist involvement and justify reimbursement.

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# Infectious Diseases Specialty Pharmacy Practice

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## INTRODUCTION

Since the 1980s, the specialty area of infectious diseases within pharmacy practice has evolved into a distinct discipline that is directed at providing optimum antimicrobial therapy to patients. The pharmacist is uniquely qualified to apply therapeutic, pharmacokinetic, and pharmacodynamic principles to antimicrobial therapy. These skills serve to complement rather than compete with the roles of infectious diseases physicians. Infectious diseases pharmacists are employed in private and teaching hospitals, clinics, academia, and industry. Literature that document the positive impact of the infectious diseases pharmacist on patient outcomes is now being published.

## EDUCATION/TRAINING

### Education and Postgraduate Training

Infectious diseases pharmacists have typically been awarded either a postbaccalaureate or entry-level Doctor of Pharmacy degree. In addition, most have completed 2 to 3 years of postdoctoral training that consists of a 1-year residency in pharmacy practice, followed by either 1 year in an infectious diseases specialty residency or a 2-year infectious diseases fellowship. It should be noted, however, that a select number of motivated practitioners have not completed these postgraduate training programs, but instead have become proficient in infectious diseases through "on-the-job training."

### Board Certification

Pharmacists who have been practicing for more than 3 years and/or have completed postgraduate training may become certified in pharmacotherapy (BCPS) through the Board of Pharmaceutical Specialties (BPS). This certification is achieved via examination. In addition, as of the year 2000, BCPS awardees could be granted Added Qualifications in Infectious Diseases Pharmacotherapy by submitting an application to BPS. The application consists of a portfolio that describes the applicant's practice in infectious diseases pharmacotherapy. The portfolio includes[1]

1. A letter from applicant requesting review of portfolio for purpose of granting Added Qualifications in Infectious Diseases Pharmacotherapy.
2. Current curriculum vitae (CV).
3. A detailed summary of each of the following elements (if not included in CV):
   a. Any special training or professional development programs in the area of infectious diseases pharmacotherapy.
   b. Work experience in the area of infectious diseases pharmacotherapy.
   c. Specific professional responsibilities for care of patients with infectious diseases in outpatient and inpatient settings.
   d. Any professional awards, honors, or special achievements relative to infectious diseases pharmacotherapy.
   e. Bibliography of applicant's relevant professional publications.
   f. List of applicant's past and present research or other scholarly activities in the area of infectious diseases pharmacotherapy.
   g. Summary of past and current educational/in-service activities for health care professionals in infectious diseases pharmacotherapy.
   h. List of memberships in professional organizations relative to infectious diseases, with specific notation of any service or leadership activities to the organization.

At this time, Board Certification in Pharmacotherapy with Added Qualifications in Infectious Diseases is a means for recognizing outstanding practitioners. It is not a means of licensure or a prerequisite for practicing in the area of infectious diseases pharmacotherapy.

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## VOCATIONS FOR INFECTIOUS DISEASES PHARMACISTS

### Hospital Practice

Pharmaceutical care of the hospitalized patient with infection is the most traditional role for infectious diseases pharmacists. Numerous opportunities for proactive interventions in antimicrobial selection, dosing, route of administration, and monitoring of patients with changing clinical status make this a popular practice setting for many individuals.

#### Practice solely in infectious diseases

Infectious diseases pharmacists typically practice in a hospital setting that allows them to devote all their time to managing antimicrobial therapy. All aspects of infectious diseases pharmacotherapy, including interventions on antimicrobial selection, antimicrobial dosing, and intravenous-to-oral conversion are the responsibility of the infectious diseases pharmacist. In addition, the pharmacist is usually responsible for analyzing new antimicrobials for formulary inclusion, medication use evaluations, and antimicrobial restriction or therapeutic interchange policies.

Some infectious diseases pharmacists may collaborate with infection control practitioners to reduce nosocomial infections and control antimicrobial resistance. Others may work closely with clinical microbiologists to design institution-specific susceptibility testing and reporting methods, and to generate periodic antibiotic susceptibility reports.

In hospitals with a significant pharmacy influence on antimicrobial therapy, it may be impossible for the infectious diseases pharmacist to perform all the functions described here. Instead, the pharmacist may need to delegate the responsibility for conducting standardized antimicrobial "protocols" (therapeutic interchange, intravenous to oral, aminoglycoside pharmacokinetics) to other pharmacists, while maintaining accountability for the quality of these programs.

Although the salary for many hospital pharmacists who practice exclusively in the area of infectious diseases comes from the hospital in which they practice, a substantial number are cofunded by hospitals and schools of pharmacy or medicine.

#### Combined with other responsibilities

In hospital pharmacy departments with limited resources or incomplete antimicrobial management programs, pharmacists trained in infectious diseases may practice in a clinical setting that requires not only expertise in antimicrobial therapy, but also other therapeutic areas. For example, an infectious diseases pharmacist may practice as a clinical coordinator who is charged with developing practice areas such as cardiology, nutrition support, etc., in addition to antimicrobial management programs. Other practice sites that require a working knowledge of infectious diseases include clinical pharmacokineticists, critical care pharmacists, and transplant pharmacists. These practice positions are typically funded 100% by the hospital in which they are located.

### Outpatient Practice

An increasing number of infectious diseases pharmacists practice in outpatient settings. These individuals usually practice in one of two areas. One area is in outpatient clinics, where they are directly involved in patient care. This is particularly true for pharmacists who specialize in treatment of patients infected with human immunodeficiency virus (HIV) or other chronic infectious diseases (e.g., leprosy). Pharmacists take medication histories, counsel patients about their medications, assess response to antimicrobial therapy, and make adjustments in therapy, as necessary.

Infectious diseases pharmacists also make valuable contributions to patient care in the managed care setting. By evaluating antimicrobial prescribing patterns, creating drug treatment protocols, directing formulary decisions, and "counterdetailing" prescribers, infectious diseases pharmacists help to curtail inappropriate antibiotic prescribing that may lead to increased antibiotic resistance.

### Pharmaceutical Industry

An increasing number of infectious diseases pharmacists have found a career in the pharmaceutical industry. Some initially take positions in pharmaceutical sales. Others may be hired as research associates, where they assist in the collection and analysis of data for clinical studies. More often, they are hired as "medical science liaisons." These individuals interact with physician and pharmacist practitioners, where they provide drug information, grant support for research and educational efforts, assist in medication use evaluations, and give in-services to medical and pharmacy staff.

Promotions within industry have lead many of these pharmacists into advanced positions such as Director of Medical Affairs, Associate Director for Research, or Associate Director for Education.

### Contract Research Organization

Some infectious diseases pharmacists join contract research organizations. These organizations work primarily with pharmaceutical companies to test the in vitro activity of new antimicrobials, assess their efficacy in intro and animal infection models, and conduct clinical trials. Pharmacists may be hired into positions ranging from researcher to director.

### Government

Some infectious diseases pharmacists have been hired into government positions. These individuals direct government-initiated studies, care for patients in clinics, and formulate policies regarding medication use. Infectious diseases pharmacists currently hold positions in the Food and Drug Administration, National Institutes of Health, and World Health Organization.

### Independent Consultant

Many infectious diseases pharmacists devote some time to work as consultants. In most cases, they serve as ad hoc consultants for pharmaceutical companies, where they assess the likely impact of a newer antimicrobial and/or providing advice on direction of future studies. They may also educate pharmaceutical sales staff or write review articles.

Other infectious diseases pharmacists work full time as consultants. Usually, they are employees of larger consulting firms that are hired by hospitals or other health care institutions to detect inefficiencies in process and to improve financial success.

## MODEL CLINICAL PRACTICE SETTINGS

### Hospital Setting

#### Rounding with an infectious diseases consult service

Most infectious diseases pharmacists who practice in a hospital setting round with an infectious diseases consult service. This service usually consists of an infectious diseases physician, an infectious diseases medical fellow, medical students, an infectious diseases pharmacist, and (possibly) pharmacy students, residents, or fellows. Patients are usually identified through infectious diseases "consults." The pharmacist usually acts to "optimize" the antimicrobial regimen by adjusting antibiotic doses and apprising the service members of any imminent drug interactions or adverse effects. The pharmacist also monitors patients followed by the service, to assess therapeutic response and/or adverse events. Finally, the pharmacist serves as a resource for drug information for service members.

The advantages of rounding with an infectious diseases consult service include a sense of "teamwork" and camaraderie; the backing of an infectious diseases physician, which means that most recommendations will be followed; direct interaction with only a limited number of (infectious diseases) physicians, which will quickly establish mutual trust and respect; and the potential for collaboration in research. Disadvantages include limited patient exposure (usually only patients involved in "consults" are followed) and, potentially, limited usefulness if the infectious diseases attending physician is knowledgeable in antimicrobial pharmacology.

#### Pharmacist–infectious diseases physician collaboration

Another common practice model for hospital-based pharmacists is a one-on-one collaboration between an infectious diseases pharmacist and an infectious diseases physician. Under this model, the infectious diseases physician is generally responsible for standard infectious diseases "consults." The pharmacist acts as an extension of the infectious diseases physician's clinical practice clinical practice, rather than competition or duplication. The pharmacist identifies patients in whom antimicrobial therapy is suboptimal (i.e., wrong drug, wrong dose, questionable indication, potential for IV-to-oral conversion). After conferral with the infectious diseases physician, an intervention is recommended or implemented. These interventions usually follow predefined criteria established by the Pharmacy and Therapeutics Committee.

Some advantages of this model are the establishment of a close relationship between infectious diseases physicians and pharmacists, the backing of the infectious diseases service and the Pharmacy and Therapeutics Committee on interventions, and the potential for pharmacists to bill for clinical pharmacy services through a physician provider. Potential disadvantages exist if the infectious diseases physician and pharmacist do not interact well.

#### Independent practice

Under a third practice model in the hospital setting, infectious diseases physicians and pharmacists conduct separate services: the physician handles infectious di-

seases consults, and the infectious diseases pharmacist identifies patients with inappropriate antimicrobial therapy and makes interventions. Under this system, the Pharmacy and Therapeutics Committee will ideally grant the pharmacist some authority to automatically order modifications in therapy. This model is used when infectious diseases physicians are either unwilling or unable to become involved in interventions concerning antimicrobial therapy. A potential disadvantage is the perceived "competition" between infectious diseases physicians and pharmacists for consults. Indeed, the Infectious Diseases Society of America (IDSA) has issued a statement condemning the independent practice of a pharmacist to advise physicians on selection of antimicrobial therapy.[2] In hospitals that have limited or no infectious diseases physician presence, this model may be the only viable option.

### Outpatient Setting

As mentioned previously, some infectious diseases pharmacists have established effective clinical practices in the outpatient setting. The most common example of this is the presence of a pharmacist in an HIV clinic. The myriad of antimicrobial drug interactions and adverse effects associated with antiretroviral therapy, the need to periodically assess antiretroviral efficacy, and the considerable potential for noncompliance literally necessitate the need for a pharmacist in any established HIV clinic. Infectious diseases pharmacists work with infectious diseases and/or immunology physicians. Pharmacists conduct medication histories and answer drug information questions. In some settings, they may act under protocol to assess patient response to antiretroviral therapy based on virologic and immunologic measures, and to make appropriate modifications in therapy.

## IMPACT OF INFECTIOUS DISEASES PHARMACISTS ON PATIENT CARE

The original published reports of the impact of infectious diseases pharmacists' interventions on patient outcomes were limited to therapeutic drug monitoring of aminoglycosides. Therapeutic drug monitoring of aminoglycosides by pharmacists resulted in more appropriate utilization of serum aminoglycoside concentrations, more serum concentrations within the therapeutic range, and reduced nephrotoxicity when compared with monitoring by physicians (Destache et al.).[3]

Subsequent reports of the impact of interventions by infectious diseases pharmacists have focused more on improving the antimicrobial therapy process. Specifically, reports of "antibiotic streamlining" (narrowing the spectrum of therapy based on culture and susceptibility reports)[4–6] and intravenous-to-oral conversion of antibiotics[7,8] have shown that interventions by pharmacists can reduce costs and lengths of stay without adversely effecting quality of patient care. However, more research and publications are necessary to fully document the beneficial impact of infectious diseases pharmacist interventions.

## TOOLS/MATERIALS USED BY INFECTIOUS DISEASES PHARMACISTS

### Journals

A number of published journals specifically directed toward infectious diseases and antimicrobial therapy are available as resources for infectious diseases pharmacists:

*Clinical Infectious Diseases*—This journal, formerly named *Reviews of Infectious Diseases*, is an official publication of the IDSA. Articles are primarily directed at the diagnosis and treatment of infectious diseases, including clinical trials. Frequently, "State of the Art" articles are published that summarize current therapy of a particular infection. In addition, IDSA guidelines for the treatment of infectious diseases are published in this journal.

*The Journal of Infectious Diseases*—This journal is also published by IDSA. The contents of this journal are generally directed at the cellular mechanisms of pathogenesis and immunity of infection. From a pharmacist practitioner standpoint, it is of less usefulness than *Clinical Infectious Diseases.*

*Antimicrobial Agents and Chemotherapy*—One of the official journals of the American Society for Microbiology, this journal focuses on characterizing and quantifying the activity of antimicrobial agents against various pathogens. Many papers are directed at mechanisms for antimicrobial resistance and activity of newer antimicrobials in vitro. Studies of the efficacy of antimicrobials, as measured via in vitro pharmacokinetic and animal infection models, are published frequently. Studies of drug treatment in humans are also published, but less frequently.

*Journal of Antimicrobial Chemotherapy*—This British publication addresses all aspects of infectious diseases pharmacotherapy and therapeutics. Both American and European authors contribute to this journal. A review article at the beginning of each issue addresses a pertinent clinical issue. Supplements are published regularly that

focus on new antimicrobial agents. More so than other journals, this journal regularly addresses pharmacokinetic/pharmacodynamic issues. Although it is very popular, it occasionally suffers from lack of relevance, in that position papers are usually European rather than American organizations.

*Infectious Diseases Clinics of North America*—This quarterly, hardbound journal focuses on a single infectious disease topic in each issue. Experts in the field of infectious diseases author state-of-the-art articles that are useful for review or for teaching purposes. Although the articles usually do not present breaking information, they are useful in defining current practice in infectious diseases.

*Infectious Diseases in Clinical Practice*—This is a very pragmatic journal with topics that clearly state that this journal is authored "by practitioners, for practitioners." Although it is not currently referenced in MEDLINE, this journal offers special insights into practice-related issues that are authored by eminent infectious diseases practitioners.

*Journal of Infectious Diseases Pharmacotherapy*—This journal, still in its infancy, is the first attempt by clinical pharmacy practitioners to author a journal devoted entirely to infectious diseases pharmacotherapy. It is also not referenced in MEDLINE. Although it has suffered from "identity crisis," the articles are excellent, well referenced, and pertinent to current practice. Hopefully, this journal will continue to grow in stature over the next few years.

In addition to those described here, a number of journals devoted to internal medicine and/or pharmacology topics will from time to time publish articles concerning infectious diseases. They are not discussed further in this article.

## Books/Texts

Although they are republished less frequently than journals and therefore may contain dated material, some books and texts have stood the test of time and remain valuable resources:

Mandell, Douglas, and Bennett, eds., *Principles and Practice of Infectious Diseases* (Churchill Livingstone, Philadelphia, 2000)—This "bible" of infectious diseases is a must for every infectious diseases practitioner's bookshelf. This book addresses virtually all infectious diseases topics from both a disease- and a pathogen-related perspective. Although the antimicrobial pharmacology component represents only a small portion of the text, it is well written and is a useful resource for those looking for information on antimicrobial pharmacokinetics, interactions, and adverse effects.

Kucers, Crowe, Grayson, and Hoy, eds., *The Use of Antibiotics* (Butterworth–Heinemann, Oxford, 1997)—"Kucers" remains the standard as a reference text for antimicrobial pharmacology. Arranged by drug classes, this text describes the clinical pharmacology of all known antimicrobials, and has the advantage of its long publication history to include "classic" references in antimicrobial pharmacokinetics, adverse effects, and interactions. Because of the evolving nature of antimicrobial resistance, the sections on in vitro activity are often dated and of limited usefulness when comparing antibiotics.

Yu, Merigan, and Barriere, eds., *Antimicrobial Therapy and Vaccines* (Williams and Wilkins, Baltimore, 1998)—This text, first published in 1998, is a laudable attempt to create a comprehensive reference of pathogenic organisms and antimicrobials. Unlike *Principles and Practice of Infectious Diseases*, the text does not specifically address infectious diseases syndromes. Approximately half of the chapter authors are infectious diseases pharmacists. Chapters are addressed by pathogen and by corresponding therapeutic agent(s). They are relatively short but extremely well referenced and clinically relevant. Each chapter devoted to a pathogen is divided into sections on general description, microbiology, susceptibility, and treatment of infections caused by that pathogen. Chapters on antimicrobial agents are divided into sections on chemistry, antimicrobial activity, pharmacodynamics, pharmacokinetics, and adverse effects. Overall, this is a very useful text. Hopefully, it will continue to a second (and subsequent) edition.

## Guidelines

Guidelines or consensus statements are important for infectious diseases pharmacists because they identify the "state of the art" on paper, which creates a template by which they may conduct their practice. For the most part, pharmacists are relatively content to follow and adhere to clinical guidelines, as long as they are logical and well written. Unfortunately, many guidelines written by physicians address diagnosis and patient assessment much more than the specifics of drug therapy, an area that is of outmost importance to infectious diseases pharmacists. Nevertheless, these guidelines are invaluable for pharmacists who seek "reinforcement" when developing treatment protocols for their own institutions.

*Infectious Diseases Society of America (IDSA)*—The IDSA is the single most common source of guidelines for treatment of infectious diseases in the United States. These guidelines are created largely on an ad hoc basis and are published in *Clinical Infectious Diseases*. Examples of such guidelines include treatment of community-acquired pneumonia, urinary tract infections, and febrile neutropenia. Unfortunately, no systematic process for generating and routinely updating these guidelines appears to be in place.

*Centers for Disease Control and Prevention (CDC)*—The CDC has begun to exert itself in the area of treatment guidelines for infectious diseases.[9] Well known for their reports and recommendations that are published in *Morbidity and Mortality Weekly Report*, the CDC has now also issued guidelines for treatment of community-acquired pneumonia. Although these guidelines are generally more conservative than those issued by other groups, they do carry the weight of the CDC and the U.S. government. Hopefully, the issuance of guidelines by the CDC will continue.

*American Thoracic Society (ATS)*—The ATS has issued guidelines for the treatment of community- and hospital-acquired pneumonia. These guidelines have also proven valuable as a reference point for clinicians want to establish treatment guidelines in their own institution. Although ATS guidelines carry considerable political influence, they are typically more consensus driven than evidence based in nature.

Other organizations—Other organizations may occasionally publish guidelines for the use of antimicrobials in selected clinical settings. For example, the American Society of Health-System Pharmacists published guidelines for surgical and nonsurgical prophylaxis in 1999. When such guidelines are published, most infectious diseases pharmacists will obtain them and use them as a resource. However, the sporadic publication of guidelines from these sources means that practitioners are often left without specific guidance in many therapeutic areas.

## PROFESSIONAL NETWORKING OPPORTUNITIES

### Professional Societies/Meetings

A number of professional societies exist that are either entirely devoted to infectious diseases or support subgroups directed toward infectious diseases. Infectious diseases pharmacists are active members of all the organizations.

*Society of Infectious Diseases Pharmacists (SIDP)*—SIDP, formed in 1990, is the only organization entirely devoted to practice and research by infectious diseases pharmacists. Currently, more than 400 infectious diseases pharmacists are members of SIDP. An elected Board of Directors and active standing committees conduct the majority of SIDP's business. SIDP provides grants to members to conduct research, and also awards funds to support three infectious diseases residencies annually. SIDP also cosponsors two to three educational symposia with other societies each year.

A 1-day annual meeting is held in conjunction with ICAAC (see below). In addition, members receive a quarterly newsletter and may visit SIDP's web site (www.sidp.org).

*Interscience Conference for Antimicrobial Agents and Chemotherapy (ICAAC)*—The annual meeting, sponsored by the American Society for Microbiology (ASM), is the largest meeting devoted to infectious diseases in the world. Infectious diseases physicians and pharmacists, as well as microbiologists and infection control practitioners, comprise the majority of ICAAC attendees. More than 15,000 people gather at ICAAC to review the most recent research on antimicrobials and attend state-of-the-art symposia. The sheer volume of information presented at this meeting makes time management a priority. Numerous infectious diseases pharmacists attend this meeting every year and are able to network over the 4-day meeting.

*Infectious Diseases Society of America (IDSA)*—IDSA is an organization primarily composed of infectious diseases physicians. However, more than 50 infectious diseases pharmacists are members of IDSA. Topics at IDSA's annual meeting parallel the content of their two journals, *Journal of Infectious Diseases* and *Clinical Infectious Diseases*, and include cellular and biochemical mechanisms of infectious diseases, and the epidemiology, diagnosis, and management of infectious diseases. The limited presence of infectious diseases pharmacists at IDSA makes networking more difficult.

*International Society of Antiinfective Pharmacology (ISAP)*—ISAP is a small but influential organization of infectious diseases physicians and pharmacologists whose focus is infectious diseases pharmacokinetics/pharmacodynamics. The society is truly international in scope, with members from the United States, Canada, and Europe. ISAP's 1-day annual meeting is held immediately after ICAAC and consists of state-of-the-art lectures on current concepts in antimicrobial pharmacodynamics. The timing of the ISAP meeting and its relatively "low profile" limit the number of infectious diseases pharmacists that attend

this meeting, but those who do attend remain avid supporters of ISAP.

*American College of Clinical Pharmacy (ACCP)*—The ACCP is an organization devoted to the promotion of clinical pharmacy practice and research. ACCP holds two meetings annually. The content of material presented at these meetings spans the scope of clinical pharmacy practice. However, ACCP has created specialized practice and research networks (PRNs), one of which focuses on infectious diseases. For an additional $10, an ACCP member can join a PRN. PRN members hold business and scientific sessions at ACCP meetings, which allows for networking among members. ACCP also supports PRN listservs on its web site. Finally, ACCP supports a personnel placement service at its fall meeting, where members can recruit residents and fellows.

*International Conference of Chemotherapy (ICC)*—The ICC is a biannual conference that is similar in size and scope to ICAAC, but is usually held outside the United States. Although the content is excellent, the travel, registration, and housing expenses make this meeting cost prohibitive for most American infectious diseases pharmacists. Those who do attend enjoy the opportunity to interact with practitioners and researchers from around the globe.

*International Conference on Macrolides, Azalides, Streptogramins, and Ketolides (ICMASKO)*—ICMASKO is a biannual conference that is attended primarily by infectious diseases researchers who present their research on macrolides, azalides, streptogramins, and ketolides. This is a relatively small, intimate meeting that allows for networking for those in attendance.

*American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting*—ASHP's midyear clinical meeting is one of the largest annual meetings of pharmacists in the world. The scope of topics presented at the meeting is very diverse, ranging from clinical topics to reimbursement issues. No specific subgroup of pharmacists devoted to infectious diseases exists within the ASHP. However, numerous infectious diseases satellite symposia and research papers are presented during the meeting. Many infectious diseases pharmacists use this meeting to recruit residents and fellows.

*International Conference on Retroviruses*—The International Conference on Retroviruses focuses specifically on the treatment of patients with HIV infection. This conference attracts pharmacists who care for these patients. A variety of papers dealing with new antiretroviral agents and combinations are presented, in addition to presentations outlining the best means for caring for these patients. Unfortunately, infectious diseases pharmacists currently are not fully "recognized" at this meeting, and problems with registration have occurred. Many other pharmacist societies are lobbying to correct this problem.

## Industry Consultantships

From time to time, infectious diseases pharmacists are invited to serve as consultants at small meetings held by pharmaceutical manufacturers. Typically, 6 to 12 consultants are invited to give their opinions about the likelihood of success of a new antimicrobial, or to suggest new marketing or research strategies. These meetings serve an additional purpose in that they allow an additional opportunity for interaction and networking between the pharmacists in attendance.

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# Institute for Safe Medication Practices

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## INTRODUCTION

The Institute for Safe Medication Practices (ISMP) is a nonprofit organization devoted entirely to safe medication use and to the prevention of medication errors. A broad-based and interdisciplinary organization, ISMP aims to provide impartial, timely, and accurate medication safety information at all times. As an independent watchdog organization, ISMP receives no advertising revenues and depends entirely on volunteer efforts, educational project, grants, and donations to pursue its work. ISMP's work has been acknowledged and honored by a number of organizations worldwide. For example, in 2000 ISMP received the prestigious Award of Honor from the American Hospital Association (AHA). In addition, in 1998 the Institute received the highly regarded Pinnacle Award from the American Pharmaceutical Association (APhA) and the Healthcare Quality Alliance (HQA).

## MISSION

ISMP's mission is:

- To continually expand knowledge about medication errors and prevention methods through system analysis in an interdisciplinary and cooperative manner.
- To collaboratively develop and implement effective error-prevention strategies to reduce the risk of medication errors.
- To educate healthcare policymakers about legislative and regulatory steps that can help prevent medication errors.
- To communicate broadly and to educate healthcare professionals and the public about the nature of medication errors, how to prevent them, and how to manage errors that do occur.
- To provide professional support for healthcare practitioners in preventing and handling medication errors.

## OBJECTIVES

ISMP's work, which focuses primarily on improving the safety of medication distribution and use, naming, packaging, and labeling, falls into five key areas. These areas are knowledge, analysis, education, cooperation, and communication. All efforts are built on a non-punitive approach and systems-based solutions.

### Knowledge-Based ISMP Initiatives

- Independent review of all errors reported to the USP–ISMP Medication Errors Reporting Program (MERP) and acting partner in the FDA's MedWatch Program.
- Comprehensive collection/analysis of error information through the organization's global information-sharing network.
- Original and impartial research and practitioner surveys on medication errors and prevention.

### Analysis-Based ISMP Initiatives

- Comprehensive use of failure mode and effects analysis (FMEA) to learn where or when errors are most likely to occur and to help prevent them.
- A thorough review process, using an innovative computer software program, to study and prevent product name- and packaging-related errors.
- Site visits and confidential consultations in various healthcare delivery settings and throughout the healthcare industry.
- A wholly owned subsidiary called Medical Error Recognition and Revision Strategies (Med-E.R.R.S.™), which works confidentially with pharmaceutical companies to predict error potential and thereby avoid problems that might stem from proposed drug names, labels, and packaging.



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## Education-Based ISMP Initiatives

ISMP provides the following products and services that are targeted to healthcare professionals, pharmaceutical industry, insurance industry, and regulatory agencies:

- Slide programs, CD-ROMs, posters, books, and videotapes on medication safety including such topics as Failure Mode and Effects Analysis (FMEA); timely and accurate educational sessions and conferences, slide programs, and presentations.
- Knowledgeable and articulate speakers including nurses, pharmacists, and physicians.
- Free, Web-based access to archived issues of the biweekly *ISMP Medication Safety Alert!* newsletter.
- Safe Medication Management Fellowship that provides postgraduate training to healthcare practitioners in safe medication management.

## Cooperation-Based ISMP Initiatives

- Official partnership in the U.S. Food and Drug Administration's (FDA) MedWatch program.
- Collaborative work toward error prevention with the American Hospital Association (AHA), the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), the National Coordinating council on Medication Error Reporting and Prevention (NCCMERP), the National Patient Safety Foundation (NPSF), the United States Pharmacopeia (USP), and dozens of other consumer and professional organizations.
- Highly effective educational efforts with legislative and regulatory bodies to improve the safety of medication use.

## Communication-Based ISMP Initiatives

- *ISMP Medication Safety Alert!*—the nation's only biweekly publication that reaches nearly every U.S. hospital and tens of thousands of healthcare professional with warnings about medication errors and practical prevention strategies.
- Special electronic and direct mail hazard warnings targeted to healthcare professionals.
- Scholarly and practical articles and continuing education columns that reach practitioners in virtually every healthcare field.
- Web site with timely and accurate information on errors and prevention recommendations for healthcare professionals and consumers.
- Media relations campaigns that reach millions of healthcare professionals and the public every month by placing error-prevention information in healthcare publications and with the nation's most prestigious news organizations.

**Contact Information**: Martin S. Goldstein, Director of Program Development, Institute for Safe Medication Practices, 1800 Byberry Road, Huntingdon Valley, PA 19006, 215.947.7797, mgoldstein@ismp.org.

## FURTHER READING

Institute for Safe Medication Practices; www.Ismp.org.
*ISMP, Medication Safety Alert!* Huntington Valley, Pennsylvania.

# Institute for Safe Medication Practices—Spain

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## INTRODUCTION

The Institute for Safe Medication Practices—Spain (ISMP—Spain) is an independent, nonprofit Spanish organization committed to the prevention of medication-system errors and adverse drug events.

Called *Instituto para el Uso Seguro de los Medicamentos* in Spanish, the ISMP—Spain was established in Salamanca in October 1999, at the Clinic Hospital of the University of Salamanca. It is an interdisciplinary organization, currently under the direction of Alfonso Domínguez-Gil and María-José Otero.

As an independent organization, ISMP—Spain depends upon volunteer efforts, grants, and donations. It works in cooperation with healthcare practitioners, professional organizations, the pharmaceutical industry, and the government in an effort to enhance patient safety. The ISMP—Spain is also a partner of the ISMP—U.S.A., which has agreed to provide a full range of logistic and scientific support for ISMP—Spain, including consultative support and access to its resources and published recommendations for use in error prevention.

## MISSION

It is the mission of ISMP—Spain to enhance the safety of the medication-use system and to improve the quality of patient healthcare. The most important goal is to reduce the risk of medication errors and preventable adverse drug events.

## OBJECTIVES

Specific objectives of ISMP—Spain include:

- To maintain a national medication error reporting program to collect observations and experiences of healthcare practitioners and to analyze this information with a systems approach in order to draw valid conclusions. This program shares data with the ISMP—U.S.A. and is important for the exchange of information and the coordination of efforts in the prevention of medication-system errors worldwide.
- To increase awareness of the importance of medication errors among healthcare professionals, institutions, organizations, the pharmaceutical industry, the patients themselves, and throughout the entire healthcare system, and to build a safety culture of commitment to medication error reporting and prevention.
- To develop recommendations and effective strategies for preventing medication errors and reducing adverse drug events and to educate healthcare professionals and patients to ensure that these recommendations and practices are implemented appropriately.

## MEDICATION ERRORS REPORTING PROGRAM

The key to reducing medication errors lies in learning effectively from failures. Since its founding in October 1999, ISMP—Spain has maintained a national notification error reporting program. The principal objective of this program is to obtain information on medication errors and their causes in order to establish and transmit practical recommendations to prevent the recurrence of the errors.

This program has three main characteristics: it is voluntary, confidential, and independent. It collects observations and experiences concerning those potential or actual medication errors that healthcare professionals voluntarily report. The information is independently analyzed, with no conflicts of interests nor administrative pressure, and all information is treated confidentially.

Healthcare professionals can either complete a report form or contact the ISMP—Spain directly by e-mail, fax, or telephone to report medication errors with complete confidentiality. The types of medication errors submitted include confusion over look-alike or sound-alike drug names, ambiguity or similarity in packaging or labeling,



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misinterpretation of handwritten orders, errors in prescribing and monitoring, or errors in drug administration.

ISMP—Spain carefully reviews and analyzes all reported errors, and depending on the characteristics, sends a copy of the report to the Spanish Medicines Agency (AEM) and to the pharmaceutical companies whose products are mentioned in the reports. This information is also shared with the ISMP—U.S.A.

ISMP—Spain publishes information about submitted reports on their web site www.usal.es/ismp and includes safety recommendations designed to help reduce the probability of such errors recurring. The goal is to make this information readily available to healthcare professionals.

## OTHER ACTIVITIES AND PROJECTS

It is the belief of ISMP—Spain that the first step in the long road to reducing adverse drug events is getting everyone to recognize this problem and to become committed to combating it. To achieve this goal it will be necessary to effectively quantify the extent and cost of this problem on a national basis. The next step would then be to identify solutions appropriate for the Spanish healthcare system, solutions that will lead to the reduction of medication errors. For this reason, a key initiative of ISMP, Spain is to carry out and to promote research on the incidence, nature, and cause of adverse drug events in different settings, as well as their impact on patients and healthcare costs. This effort will compile important reference material to help improve safety in Spanish healthcare.

The education and dissemination of information is another primary objective of ISMP—Spain: If everyone understands the nature and causes of medication errors, there is a much greater possibility of improving patient safety. In this sense, ISMP—Spain makes educational presentations and holds conferences at healthcare professional meetings to provide information about adverse drug events. ISMP—Spain also publishes opinion articles and practical articles in Spanish healthcare journals in an effort to broadly disseminate a culture of safety and error prevention.

Another important goal of ISMP—Spain is to encourage the development of local medication error reporting and analysis systems in individual healthcare organizations. ISMP—Spain has coordinated a project with the Spanish Society of Hospital Pharmacy to create a standard terminology and classification system of medication errors so that healthcare organizations can design databases and analyze medication error reports using the same system.

## FUTURE GOALS

ISMP—Spain believes in the importance of coordinating efforts to enhance patient safety in countries all over the world. It is open to the creation of a work platform in Europe and also to cooperating with Spanish-speaking countries with any initiatives they may undertake to improve their medication systems.

# Institute of Medicine

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## INTRODUCTION

The Institute of Medicine (IOM) was chartered by the National Academy of Sciences in 1970 "to improve the health of the American people and peoples of the world" by advancing the health sciences and by providing analysis of important issues in health and health policy for government, the professions, and the public and private sectors. The Institute is an independent, nongovernmental organization. It carries out its work largely through committees of pro bono experts who employ an evidence-based deliberative process to produce scientifically valid nonpartisan reports. Studies originate in several ways: by Congress mandating that an Executive Branch agency contract with the IOM; by direct request of Executive Branch agencies, foundations, or other private organizations; or as self-initiated projects when the Institute determines that an important or highly sensitive issue might not be the subject of a request from an outside organization. In addition to committee studies, IOM plays a unique convening role by sponsoring workshops, roundtables, symposiums, forums, and other activities that enable parties on all sides of an issue to come together and discuss problems and solutions in a neutral, unbiased setting.

The Institute also has an honorific function. Each year it elects 60 regular members, five senior members, and five foreign associates. Elected members include distinguished individuals whose expertise and leadership cover the broad range of biomedical sciences, public health, nutrition, environmental sciences, and social and community medicine, as well as pharmacy, the development of new drugs and biologics, and vaccine and drug safety. The Institute's charter stipulates that at least one-quarter of IOM members be from professions other than those primarily concerned with medicine and health. Thus, the membership includes leading ethicists, economists, and social and behavioral scientists, among others.

## ACTIVITIES

The Institute's portfolio of activities is extensive, ranging from issues of scientific integrity to the future of specific areas of health sciences research. The Institute has undertaken studies on the processes of innovation, including new drug, vaccine, and biologics development. Its Roundtable for the Development of Drugs and Vaccines Against AIDS was an important example of IOM's ability to convene disparate opinions around important issues. In this case, the roundtable included representatives of the National Institutes of Health, the Food and Drug Administration, the pharmaceutical industry, AIDS activists, and other interested parties. Other roundtables have considered such issues as the development of drugs for new and emerging infections, antibiotic resistance, and the development of biologics and devices.

The Institute's studies have had a profound effect on public health. The range of topics that have been the subject of IOM studies is wide and varied. Some examples follow:

- In addition to recommending priorities for new vaccine development, IOM committees have also provided analysis and advice regarding complications associated with vaccines, barriers to immunization, immunization finance, and appropriate uses of vaccines.
- An IOM committee examined the role of women in clinical trials—a complicated issue involving scientists, industry, and ethicists who evaluated the participation of women, particularly women of childbearing age, in drug trials.
- The 1999 report entitled *To Err is Human: Building a Safer Health Care System* emphasized that medication errors were an important contributor to morbidity and mortality. Yet this committee also noted that the elimination of such errors will require a comprehen-



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sive systematic approach involving physicians, nurses, hospitals, pharmacists, patients, and others in health care working together. Better information technology, computerized data entry, and nonpunitive reporting of near misses were a few of the elements recommended as an approach to accomplish this goal.

- Substance abuse has been the subject of several IOM studies, which have covered a whole host of issues related to the topic, including federal regulation of methadone treatment, the development of medications for the treatment of opiate and cocaine additions, and community-based research to find better ways to treat people who abuse drugs.
- Fluid replacement has been examined both in relation to conditions such as heat stress and when used to resuscitate and treat combat casualties and civilian injuries.
- The FDA Advisory Committee process and other FDA roles and functions have been the subject of IOM studies that have led to significant changes in the agency's function. In one important study, *Halcion: An Independent Assessment of Safety and Efficacy Data*, an IOM committee addressed the difficult problem of the criteria and procedures for withdrawing a previously approved drug from the market.
- In 1997, the report *Pharmacokinetics and Drug Interactions in the Elderly and Special Issues in Elderly African–American Populations* considered the special challenges confronted by proper use of agents in these groups.
- A landmark 1988 report, *The Future of Public Health* (soon to be updated), identified many of the critical challenges to education, practice, and applications of public health. In 1998, the Institute helped develop the prototype leading indicators for "Healthy People 2010," the nation's blueprint for prevention. The importance of community organization and partnerships in furthering the public health has been underscored by a number of other Institute reports.
- A series of studies on health and behavior and the role of the social and behavioral sciences in health have had important implications for public health, as well as for other aspects of medicine. The 1992 report *Emerging Infections: Microbial Threats to Health in the United States* was among the earliest warnings with regard to this issue and also focused on the development of antibiotic-resistant organisms. It has been followed by a number of efforts in both public and private sectors to respond to these threats.
- The Institute is also responsible for establishing "dietary reference intakes"—quantitative estimates of nutrient intakes to be used for planning and assessing diets for healthy people—which update and replace the recommended dietary allowances.
- The 1986 report *Confronting AIDS: Direction for Public Health, Health Care, and Research* was an IOM-initiated project that addressed seriously what had been to that time a largely ignored epidemic. Subsequent reports have addressed needle exchange, the behavioral and mental health aspects of HIV infection and AIDS, and the prevention of perinatal transmission of HIV. The most recent IOM report on the subject, *No Time to Lose: Getting More from HIV Prevention*, provides a comprehensive review of current HIV-prevention efforts in the United States, as well as a framework for future activities.
- Several studies have focused on environmental issues, including the concept of environmental justice, environmental and occupational education and training in medicine and nursing, and the role of environmental factors in illness (e.g., asthma).
- Among the reports issued by the Institute on tobacco and tobacco control, the 1994 report, *Growing Up Tobacco Free: Preventing Nicotine Addiction in Children and Youths*, was particularly influential in establishing national policy.
- The Institute also conducts a significant program in international health, including efforts to control hepatitis and diarrheal diseases in the Middle East, that are being conducted through collaborations involving American, Israeli, Egyptian, and Palestinian scientists. More recently, Jordan has joined the academies from these countries in addressing problems of water conservation and micronutrients in the region.

The full text of Institute of Medicine publications is available on-line at the National Academy Press' web site, www.nap.edu. Additional information about the Institute and its activities, as well as a list of all publications, can be found at www.iom.edu.

# Integrative Medicine

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## INTRODUCTION

Although the terminology "integrative medicine" has been used synonymously with such terms as complementary, alternative, and unconventional medicine, it in fact represents the emergence of a totally new model of healthcare delivery.[1–3] In the broadest sense, integrative medicine seeks to combine the best therapies of Western (conventional) medicine with the best alternative modalities to provide each individual patient with an optimal treatment plan for their specific situation.[4] In addition, this synergistic approach has as its foundation an assumption of the innate healing power of each human organism and a belief in the centrality of the healing relationship between doctor and patient.[1]

## BACKGROUND

Practitioners of conventional medicine are justifiably proud of the achievements of their profession, showcased by the pharmacological, radiological, and surgical advances of the 20th century. Fundamental reliance on such technologies, however, has led to the dismissal of numerous therapies developed outside the conventional medical model.[5] Exclusionary attitudes escalated when studies revealed that an estimated one-third of the U.S. population was using complementary and alternative modalities.[6–9] The result was increasing divisiveness between proponents and opponents of unconventional therapies, even though practitioners on both sides had received identical training during their medical education.[10,11]

Perhaps the greatest controversy of interest to the pharmacist has involved the increasing use of botanicals and nutritional supplements. Despite objections from conventional physicians and pharmacists, the U.S. Congress responded to pressure from the public and nutraceutical industry by passing the Dietary Supplement Health and Education Act of 1994 to ensure broad access to these products.[12] As further evidence of governmental intervention, the National Institutes of Health (NIH) created the National Center for Complementary and Alternative Medicine (NCCAM) and provided a current budget of $68.3 million.[13] More recently, the Office of Dietary Supplements (ODS) within the NIH has established four centers for phytomedicinal research, ensuring that selected botanicals will be evaluated by the same or similar processes expected for prescription medications.[14]

Why is the public turning toward complementary and alternative medicine (CAM)? Surveys showing that CAM use tends to be higher in patients with diseases often inadequately treated by conventional therapies (e.g., arthritis, cancer).[15,16] This may seem to suggest an inherent dissatisfaction with conventional medicine. However, studies specifically addressing this issue have demonstrated that patients are actually turning toward CAM in keeping with their individual philosophical values and belief systems.[17,18] Reasons for patient use not withstanding, it would be beneficial for conventional practitioners to investigate the attraction of CAM, and how it can be used to strengthen and enhance their individual practices. This perspective appears even more appealing in light of the fact that public interest and usage of CAM continues to increase.[7]

Although the breadth of CAM therapies range from traditional systems developed in other cultures (e.g., traditional Chinese medicine [TCM]) to recently developed practices loosely based on science (e.g., functional medicine), most tend to share certain underlying perspectives.[19,20] Such philosophies include belief in the interconnectedness of mind and body, preference for innate rather than artificial (e.g., pharmaceutical) sources of healing, and recognition of an ultimate meaning underlying each individual's illness.[20] Consequently, many



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CAM practitioners spend far more time with their patients than conventional practitioners, listening attentively and attempting to truly understand what the patient wants and who they are as an individual.[21] A patient can thus leave a session with a feeling of empowerment and a belief that they can be well again.

## DEFINITION OF INTEGRATIVE MEDICINE

The basic tenet of integrative medicine is that it neither rejects conventional medicine nor uncritically accepts CAM.[1] Just as various alternative practices are as yet unproven and some do carry significant risk, practitioners of integrative medicine recognize that it is also important to be just as analytical of conventional medicine. For example, the fact that adverse reactions to prescription medications represent between the fourth to sixth leading cause of inpatient deaths came as a shock to many in the healthcare field.[22] An Institute of Medicine survey found iatrogenic illnesses to be the eighth leading cause of death, exceeding the deaths attributable to motor vehicle accidents, breast cancer, and acquired immunodeficiency syndrome.[23,24] Consequently, in weighing the risks inherent to any therapy, conventional or CAM, the integrative practitioner seeks the least invasive, least toxic, and least costly interventions whenever possible.

Another cornerstone of the integrative model is the assertion that healing optimally occurs when all factors that influence health, as well as illness, are addressed. Beyond the patient's physical condition lie the mental, emotional, and spiritual influences on quality and duration of life.[2,20] Sir William Osler is quoted as saying, "It is more important to know what sort of patient has a disease than what sort of disease a patient has."[2] Whether searching for relief from illness or for promotion of health, patients choosing the integrative model are offered more tools than just drugs or surgery.[1] The most common recommendations made are modification in diet and increase in level of physical activity. Stress reduction techniques (e.g., biofeedback, yoga, tai chi) are encouraged to be used in place of negative coping activities (e.g., tobacco, alcohol, recreational drugs) during difficult times. Positive coping skills can also be based in spiritual practices such as prayer, church attendance, meditation, or even such common activities as nature walks. Community involvement including volunteer work can also help to increase an individual's positive outlook. These cornerstones of a healthy life (good nutrition, physical activity, and stress reduction) are considered the primary means by which illness can be both prevented and treated. Health, therefore, becomes more than just the absence of disease. Other tools that are available to the integrative medicine practitioner include hypnosis, guided imagery, TCM, Ayurvedic medicine, homeopathy, osteopathy, chiropractic treatments, and a host of others. Discussion of such complex systems is beyond the scope of this article.[25]

The actual foundation upon which the integrative model rests is the creation of a deeply respectful and understanding relationship between patient and practitioner.[21,26] The practitioner recognizes that they are merely the means by which patients can discover, or actually rediscover, their innate capacity to restore health. This process begins with asking open-ended questions and listening patiently to the answers with a nonjudgmental attitude.[21] Patients are allowed to make choices about therapies or lifestyle changes that are consistent with their values and philosophical beliefs, which reconfirms one of the primary reasons they are using CAM.[17,26] Medical decision making is shared rather than dictated by informing the patient of all possible alternatives, whether conventional or CAM. This requires that the practitioner becomes knowledgeable about a wide array of potential interventions that may be useful to their patient, as well as which interventions should be avoided.[26]

Essential to a partnership in medical decision making is the necessity that each patient realigns his or her own approach toward health and the healthcare system. Currently, our Western culture advertises and promotes poor choices in lifestyle that ultimately result in burgeoning healthcare expenditures. Fundamental to this new paradigm of healthcare is the requirement that individuals take responsibility for their own wellness, making healthy choices concerning nutrition, physical activity, and response to stressful situations.

Finally, it is recognized that to ensure patient trust and compliance, health professionals must develop and model a healthy lifestyle for themselves. To this end, integrative practitioners are encouraged to examine and remedy the indoctrination of the current system that rewards the overworked, driven, and harried healthcare professional.

As part of the analysis and critique of both CAM and conventional modalities, integrative medicine practitioners search for accurate information in texts, primary literature, and the Internet to counsel their patients on the relative efficacy, safety, and appropriate use of these therapies. To ensure validity of research findings, it is becoming increasingly evident that other methodologies, in addition to the randomized controlled trial, need to be conceived and completed to fully evaluate these unconventional therapies as well as the integrative medical model itself.

## AN INTEGRATIVE CLINICAL MODEL

The past 10 years have witnessed the emergence of a large number and wide variety of integrative clinical models. Configurations have ranged from providing mostly conventional therapies with a smattering of complementary modalities to groups of alternative practitioners simply sharing both office space and patient populations. A feasible model that most accurately reflects the definition of integrative medicine incorporates practitioners who have been trained in both conventional and alternative therapeutic modalities. In support of this approach, a patient survey by the University of Arizona's Program in Integrative Medicine reports that their primary desire was to be treated by a physician who was knowledgeable in both conventional medicine and CAM.[27]

In the ideal integrative clinic, the initial visit entails an in-depth interview lasting from 60 to 90 minutes. During this visit, the practitioner concentrates on understanding the patient as an individual, as well as delineating the medical history and determining desired outcomes. After the initial interview and review of prior records, a comprehensive treatment plan is formulated and presented to the patient, not as a directive but as a series of options to be chosen under the guidance of the experienced practitioner. This approach provides the greatest potential of adherence and success due to the patient's sense of participation and empowerment. Often the treatment plan results in patient referral to other specialized practitioners. For example, a dietician might be suggested for nutritional counseling; a pharmacist for medication/dietary supplement counseling; a psychologist for hypnosis or guided imagery; or an osteopathic, homeopathic, or TCM practitioner to address specific issues. The patient is then followed either by return visits or by telephone to determine either success or need for treatment plan modification.

## CHALLENGES TO INTEGRATIVE MEDICINE

Because the integrative model incorporates practices that are often deemed "quackery" and unsafe by many conventional practitioners, there has been significant vocal and written opposition to the growth of CAM, in general, and integrative medicine, in particular.[11] One such avenue of opposition has been to block or strongly discourage incorporation of CAM teachings into medical school curricula.[10] Despite this resistance, 60% of medical schools and 72% of pharmacy schools have incorporated CAM into their curriculum.[28,29] One significant endeavor to close the gap between consumer demand and professional response has been the formation of the Consortium of Academic Health Centers for Integrative Medicine.[30] Their mission is to become a significant voice addressing the importance of reevaluating and restructuring medical education, and to have integrative medicine programs in one-fifth of the United States' medical schools within the next few years. Table 1 lists the current members of the consortium.

**Table 1** Current members of the Consortium of Academic Health Centers for Integrative Medicine

| |
|---|
| Albert Einstein/Yeshiva University College of Medicine, New York |
| Duke University School of Medicine, North Carolina |
| Georgetown University School of Medicine, Virginia |
| Harvard Medical School, Massachusetts |
| Jefferson Medical College, Pennsylvania |
| Stanford School of Medicine, California |
| University of Arizona College of Medicine, Arizona |
| University of California–San Francisco School of Medicine, California |
| University of Maryland School of Medicine, Maryland |
| University of Massachusetts School of Medicine, Massachusetts |
| University of Minnesota Medical School, Minnesota |

Another challenge to the growth of integrative medicine lies in the realm of reimbursement policies. Although third-party payers are increasing coverage of some CAM modalities, this tends to be a slow and erratic process.[31] Because CAM therapies tend to be less costly than conventional interventions, reimbursement should increase as research validates efficacy and cost effectiveness. If hypnosis decreases pain and eliminates the need for lifelong use of addicting medications or if techniques such as Feldenkrais prevent or postpone orthopedic surgery, the cost savings could be great for a healthcare system currently in economic crisis.

Difficulties have also arisen in relation to funding of CAM research. This has been partially addressed by the establishment within the NIH of the NCCAM and the ODS. However, NCCAM and ODS grants tend to be awarded to those following the conventional reductionistic research model when investigating a CAM modality (e.g., studying a single acupuncture point rather than acupuncture or TCM as a whole). Although this approach may add another tool to the conventional medicine arsenal, it does not address the fundamental questions of whether a different medical system (e.g., TCM) or a new medical model (integrative medicine) is appropriate and effective.

Research methodologies must be developed that allow for studying systems as a whole (e.g., using systems theory or multidimensional outcome measures) to determine whether component parts are truly synergistic.[32] A small step in the right direction has been the creation of four botanical centers by ODS.[14] These centers are charged with studying the effects of marketed dietary supplements currently purchased and used by the public, rather than the reductionistic search for a solitary active principle.

Another roadblock on the path to credibility is an apparent bias on the part of mainstream medical journals when reviewing research or position papers on CAM or integrative medicine. Journals may appear to be more willing to publish negative results for CAM modalities than those that indicate a positive outcome.[33] Although editors insist that the review process is objective, it may be that the bar is set higher for CAM, and such bias has been recognized by such authorities as the editors of the *New England Journal of Medicine*.[34] As research methodology in the CAM field improves and a biased editorial policy is corrected, the system of peer review may be more fairly applied to all scholarly submissions.

## INTEGRATIVE MEDICINE AND THE FUTURE OF HEALTHCARE

Given the current state of healthcare in the United States, most efforts by the political, academic, and corporate entities have been in the direction of repair of the system rather than creation of a new model. The results of these labors have been equivocal at best. A growing number of people planning the future of healthcare now envision the need for a totally new system, one that retains the beneficial technologies of conventional medicine while returning the focus of the profession toward health rather than illness.[35,36] The result would be a system of healthcare in which the public once again trusts and respects the healthcare practitioner as an ally, rather than as part of what often appears to be a mechanistic, profit-driven industry. Integrative medicine as a new medical model may fill the need for a totally new system, such that in the future the term "integrative" will no longer be needed, and we will all simply practice good medicine.[30]

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# International Pharmaceutical Abstracts (ASHP)

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## INTRODUCTION

*International Pharmaceutical Abstracts* (*IPA*) is the official abstracting and indexing service of the American Society of Health-System Pharmacists. *IPA* is unique in its international coverage of pharmacy and related health journals.

## AIMS AND SCOPE

An expert panel selects, abstracts, and indexes the most pertinent articles from over 600 journals published throughout the world. Translators with pharmacy expertise review the major pharmacy journals published in languages other than English and prepare abstracts in English. In addition, *IPA* publishes abstracts of meetings conducted by the American Society of Health-System Pharmacists and the American Association of Colleges of Pharmacy. Over 15,000 abstracts per year are added to the *IPA* database covering the clinical and scientific literature related to pharmacy, as well as legal aspects, professional practice issues, and trends in education and research. *IPA*'s unique structure supports searching by drug class, disease state, MeSH heading, generic or trade drug name, and chemical registry number.

Examples of topic areas targeted for coverage are drug evaluations, pharmacology, investigational drugs, toxicity, therapeutic advances, new technology, herbals, and adverse drug reactions. Although a printed version of *IPA* is available from ASHP, use is now primarily electronic. Online versions are available by subscription through several database vendors, including SilverPlatter, Ovid, Dialog, Cambridge Scientific Abstracts, STN International, DataStar, DIMDI, and EBSCO Publishing.

Individuals may also economically purchase online search blocks by selecting "IPA PharmSearch" at www.ashp.org.

## HISTORY

The inaugural issue of *IPA* was published in January 1964 under the leadership of *IPA*'s founding editor, Donald E. Francke. The seminal concept for *IPA* was created in 1957 when Dr. Francke established a section called "Selected Pharmaceutical Abstracts" in the *Bulletin*, the forerunner of the *American Journal of Health-System Pharmacy*. Dr. Francke's early objective for *IPA* was to "serve as an alerting service to keep the busy pharmacy practitioner, professor, researcher, and student keenly aware of a wide variety of information to permit him to do a better professional job."

In late 1966, Dwight R. Tousignaut succeeded Donald Francke as editor of *IPA*. *IPA*'s production process was computerized in 1970, and *IPA*'s first electronic licensing arrangement was formalized in 1971 in an agreement to supply magnetic tape to the National Library of Medicine for use in its ToxLine database.

*The International Pharmaceutical Abstracts* (Coden: IPMAAH; ISSN: 0020-8264) is published by the American Society of Health-System Pharmacists twice each month, on the 1st and 15th. Its circulation is primarily electronic. The print and electronic subscription rates are available upon request. Internet access to *IPA PharmSearch* is available at $90 per 100 searches. The editorial and subscription offices are located at 7272 Wisconsin Avenue, Bethesda, Maryland 20814, U.S.A. (Telephone: 301-657-3000, extension 1241; Fax: 301-664-8857; E-mail: ipa@ashp. org; Web site: http://www.ashp.org; Managing Editor: Victoria Ferretti-Aceto).

The first edition of the *IPA Thesaurus and Frequency List* was published in 1981. Now in its eighth edition, the *Thesaurus* provides a controlled vocabulary designed to support robust searching of pharmaceutical literature.

# International Society for Pharmacoeconomics and Outcomes Research

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## INTRODUCTION

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) is a nonprofit, 501(c)(3) member organization governed by an annually elected board of directors, with administrative headquarters located in the heart of central New Jersey's pharmaceutical corridor. (3100 Princeton Pike, Building 3, Suite D, Lawrenceville, New Jersey 08648; Tel: 609-219-0773; Fax: 609-219-0774. Its mission is to translate research and outcomes/results in pharmacoeconomics into practice to ensure fair and efficient distribution of healthcare resources.

## HISTORY

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR), formerly the Association for Pharmacoeconomics and Outcomes Research (APOR), was founded in 1995 by a group of 32 healthcare professionals and researchers with the goal of developing research practice standards for assessing the value of healthcare therapies to consumers, healthcare systems, and societies. In 1997, APOR merged with the International Society for Economic Evaluation of Medicines to form ISPOR, the first and largest international pharmacoeconomics society. In 1998, ISPOR launched *Value in Health*, the definitive, peer-reviewed journal for this scientific discipline. In that same year, two regional ISPOR chapters were established in Russia and Poland, and collegiate chapters were organized across the United States and Canada for students in the field. The student chapters include the University of Texas at Austin, University of Arizona, University of Toronto, University of Louisiana at Monroe, University of Michigan, University of Washington, University of Southern California, and the University of Maryland.

With a steadily growing membership of 2000 representing 29 countries, ISPOR remains steadfast in its mission to translate pharmacoeconomics and outcomes research into practice to ensure that society allocates scarce healthcare resources wisely, fairly, and efficiently.

The Society serves the public interest by:

- Providing a forum that fosters the interchange of scientific knowledge in pharmacoeconomics and patient health outcomes.
- Facilitating and encouraging communications among the research community, healthcare professionals, governmental, educational groups, the media, and the general public.
- Educating public and private agencies on the usefulness of research in pharmacoeconomics and patient outcomes assessment.
- Acting as a resource in the formation of public policy relevant to pharmacoeconomics, healthcare outcomes assessment, and related issues of public concern.
- Promoting this area of scientific research by providing services and educational activities that advance it.
- Representing the discipline before public and governmental bodies.

To implement these objectives, ISPOR has created several steering committees and task forces to lead the initiatives, formulate strategies, and promote good research practices. They are:

- Health Science Steering Committee.
- Prospective Studies.
- Modeling Studies.
- Retrospective Database Studies.
- Outcomes Assessment Using Quality of Life Indicators.
- Use of Pharmacoeconomic/Health Economic Information in Health Care Decision making.



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- Medical Information Access.
- Code of Ethics.
- Education Steering Committee.
- Fellowship.
- Short Course Development and Quality Assurance.
- Pharmacoeconomics and Outcomes Research Curriculum Development, North America.
- Pharmacoeconomics and Outcomes Research Curriculum Development, Europe.

Currently, ISPOR initiatives include developing standards of research practices to guide the activities of those conducting pharmacoeconomics and outcomes research, and developing educational programs to communicate those research results to healthcare decision makers who could greatly benefit from it.

ISPOR members are scientists, economists, and healthcare practitioners from 29 different countries and four different work environments: academia, the pharmaceutical and biotechnology industry, research and consulting organizations, and healthcare practice environments (hospitals, clinics, private practice, managed care, pharmacy benefit management, clinicians, and government). Their educational backgrounds reflect degrees in statistics, nursing, accounting, economics, business administration, public health, and other health sciences. A number possess doctoral degrees in medicine, philosophy, pharmacy, public health, and jurisprudence.

Through the ISPOR administrative staff, members are provided with a variety of services to support their research and professional growth, including:

- www.ispor.org—the Society's web site which provides key research, educational, and public information on the discipline, the organization, and its members.
- *LEXICON*—a unique dictionary of pharmacoeconomics and outcomes research terminology.
- *Value in Health*—the official peer-reviewed research journal of the Society published bimonthly.
- *ISPOR NEWS*—a bimonthly newsletter featuring the latest research activities and employment opportunities.
- PRAP (Professional Recruitment Assistance Program)—provides a specialized job placement service to members.
- The Annual International Meeting (generally held in May each year) and Annual European Conference (generally held in November or December each year)—promote the discipline of pharmacoeconomics and outcomes research through networking and education.
- Student chapters, special interest groups, steering committees, and task forces allow members to target and affect issues of particular interest to them and to the discipline.

The current ISPOR 2000–2001 Board of Directors is as follows: President: Jon C. Clouse, M.Ph., M.S., Ingenix Pharmaceutical Services; President-Elect: Eva Lydick Ph.D., SmithKline Beecham; Past President: Bryan R. Luce Ph.D., M.B.A, MEDTAP International; Directors: A. Mark Fendrick M.D., University of Michigan Medical Center; Karen Rascati R.Ph., Ph.D., University of Texas; Joan Rovira Ph.D., University of Barcelona and SOIKOS; Kent H. Summers Ph.D., Eli Lilly & Company; Adrian Towse M.S., Mphil, Office of Health Economics (United Kingdom); and Executive Director: Marilyn Dix Smith R.Ph., Ph.D.