A GUIDE TO DRUG COMPENDIA

In May of 1988, the Joint Senate/House Conference Committee recommended that the Secretary of the Department of Health and Human Services consult three specific drug compendia when establishing standards for drug coverage under the outpatient drug amendment of the Medicare Catastrophic Coverage Act of 1988. Oncology Issues *interviewed representatives of the Associations that developed these references: the U.S. Pharmacopeia, the American Medical Association, and the American Society of Hospital Pharmacists.*

Keith W. Johnson, Director, Research & Development, Drug Information Division, the United States Pharmacopeia.

Can you provide us with some of the history behind the U.S. Pharmacopeia?

The original goal of the USP, when it was founded in 1820, was to establish standards (or, at that time, recipes or formulas) for drug preparations in the United States. This standards-setting process continues today, with manufacturers having to meet the standards specified in the *United States Pharmacopeia (USP) and the National Formulary (NF)*—standards that are legally enforceable by the Food & Drug Administration by a Congressional mandate. The *USP* and *NF* are recognized not only by federal, but by state laws, as well as many foreign countries, as the primary sources of industry standards. In meeting the needs for public standards, *USP* continuously reviews and revises existing standards to account for new data and technology, and develops standards for new products, including genetic and biotechnology products, such as interferons.

How is the organization structured?

Eligible organizations that may appoint delegates to the quinquennial meeting of the USP Convention include the U.S. Colleges of Pharmacy and Medicine; State Pharmaceutical Associations and Medical Associations; National Professional and Scientific Organizations, such as the American Medical Association, the American Hospital Association, and the Pharmaceutical Manufacturers Association; and federal agencies, such as the FDA, the National Bureau of Standards, the Public Health Service, and the Department of Health and Human Services. In addition, there are positions for consumer and international representatives, as well as a small percentage of at-large members who are appointed because of their special knowledge and expertise.

However, the USP is a public interest group; it doesn't represent industry, medicine, pharmacy, or any other special interest group. It represents the public in its need for unbiased standards of drug quality and information. For instance, a national association like the AMA, or a governmental body like the FDA, is entitled to only one delegate out of more than 300 convention delegates.

When did the organization begin publishing the *USP drug information (USP DI)* guide?

The database was initiated in 1977 and, after three years of development, the first edition of *USP DI* was published in 1980. The information is under constant review with new print publications released annually (with bimonthly updates) and electronic versions updated on demand.

How does the review process work?

USP DI is developed and finalized by USP's Committee of Revision, which is comprised of 95 of the top scientists and physicians in the country, and its 26 specialized advisory panels. The process is public, however, and all interested parties have the opportunity to comment.

First, *USP DI* parameters are established by the Drug Information Division (DID) Executive Committee. Then DID staff drafts monographs based on those parameters, which initially are reviewed by ad hoc experts, who have a special knowledge about the drug being reviewed; drug manufacturers; and the USP's various advisory panels (comprised of approximately 350 experts) consisting of specialty panels in such areas as consumer interest, nursing practice, anesthesiology, geriatrics, and hematologic and neoplastic disease (see the table on page 20).

Once an initial consensus is reached by the advisory panels, the proposed changes are published in the *USP DI Review*—a bimonthly publication. This publication is then available for public review by all interested parties. Suggested changes are again reviewed by DID staff, the advisory panels, and ad hoc experts. When a final consensus is reached by the advisory panels and the Committee of Revision, the *USP DI* is updated to reflect those changes. Final decisions rest with the elected Committee of Revision and its advisory panels, not USP staff or any special interest group.

Can you give us an idea of the percentage of unlabeled indications that are included in the *USP DI*?

In the 1988 database, approximately 25 percent of the indications *USP DI* listed as accepted therapy fell outside of FDA labeling. However, the USP is conservative about adding new unlabeled indications to the *USP DI*. Before new unlabeled indications are deemed acceptable for addition to the *USP DI* database, the literature must clearly document these uses, and USP advisory panels must support the findings. The USP does not evaluate unproven methods of cancer treatment, such as the highly controversial immunoaugmentative therapy. However, the organization is working on a program that would develop unbiased information sheets that describe what is known about each method in question. These sheets could be used by both patients and providers.

Does the *USP DI* provide any information on combination drug therapy?

Combination cancer chemotherapy is routinely addressed in *USP DI* monographs. This is a recent addition and the accrual of such treatment regimens is difficult,

because of the rapidly changing knowledge base and the unique problems this presents in terms of consensus generation.

What other publications does USP produce?

A companion volume to the *USP DI Volume I (Drug Information for the Health Care Professional)* is *Advice for the Patient (USP DI Volume II)*. This patient information volume is written in easy-to-understand language that can be used by most patients. The information is set up so that providers can photocopy the monographs (permission granted with certain limitations) and use in patient education programs. This database in turn serves as the basis for many other patient-oriented programs, including AMA's Patient Medication Instruction sheets, NCI's bilingual chemotherapy leaflets, and the *Consumers Union's Drug Information for the Consumer*, which is available to the general public.

Another publication provided by USP is the *U.S. Adopted Names* and the *USP Dictionary of Drug Names*, an annual compilation of drug nomenclature.

How does the *USP DI* compare with the AMA *Drug Evaluations*?

I view the AMA *Drug Evaluations* and the *USP DI* as complementary rather than competitive. The *USP DI* provides indepth information about each specific medication, while the AMA focuses on the use of a drug for a particular patient. For instance, is drug A better than drug B for a particular condition?

Are there any major plans to expand the content of the *USP DI* or its companion consumer volume?

The 1989 *USP DI* has added an appendix on orphan drugs. This information will be expanded during the upcoming year. In addition, the new Volume III of *USP DI (Approved Drug Products and Legal Requirements)* presents FDA's therapeutic equivalence evaluations and other drug-product specific information. We also have a new appendix in the 1989 *Advice for the Patient* that provides monographs for commonly used combination chemotherapy regimens, thus allowing the patient to use one set of information rather than multiple monographs for each separate agent.

Carol Proudfit, Ph.D., Assistant Division Director, Division of Drugs and Toxicology, American Medical Association.

When did the AMA begin to publish *Drug Evaluations*?

The full effort began in 1971. Prior to that time, we published a small annual book entitled, *New Drugs. Drug Evaluations* has now had six editions. (It has been revised every three years.)

We will be introducing two new products to replace the old text version. In April 1990, we will introduce *Drug Evaluations Looseleaf*, a subscription service that will provide quarterly updates, and in November 1990, we will introduce an annual text. For the looseleaf product, each year one-half to two-thirds of the content will be updated. This will include new chapters and drug evaluations.

What type of information does the publication contain?

The AMA's *Drug Evaluations (DE)* is a unique product in that it contains discussions about indications for use, including unlabeled uses not found in the FDA insert; alternative therapies; and the drug(s) of choice for a particular condition. *DE* also discusses drug treatment in the context of other therapies, such as radiation therapy or surgery. Finally, it will also at least mention important investigational drugs that are nearing FDA approval. Most chapters in *DE* are therapeutically oriented, rather than based on pharmacologic classifications. *DE* also is fully referenced.

What portion of the publication is concerned with unlabeled indications?

I don't know the percentage. However, if an unlabeled use has any scientific basis for use, we are on top of it and it is discussed. There must be a significant body of scientific evidence to justify its use before it will be recommended by *DE* for an unlabeled indication.

How is the revision process structured?

We have a staff of pharmacologists who are responsible for updating the previous edition. We also use a select group of consultants who are experts in their fields—most of whom are practitioners—to review the revised draft. Approximately 6 to 10 outside reviewers will comment on a particular chapter of *DE*. We also send revised drafts to the major manufacturers of a particular drug for their input. Manufacturers primarily comment on the preparation information contained in the publications. However, on occasion, they provide important information on background pharmacology.

Each chapter of *DE* is then revised again by our inhouse staff and prepared for publication.

Does *DE* contain information on combination drug therapy?

Yes, *DE* covers combination regimens. Because of the therapeutic organization, *DE* lends itself to discussing combination drug therapy where appropriate to treat a disease.

In your view, how does *DE* compare with the other drug compendia?

It is definitely complementary rather than competitive. It has always been our position that *DE* is one of three compendia, and that no one of the three publications is preferable as a sole source of information. For instance, the other compendia do a good job of covering such concerns as adverse reactions and drug administration, but neither provides the evaluative aspect of drug therapy that is the focus of *DE*. This is particularly important in the case of the use of drugs for fringe situations. Basically, the *USPDI* is used by pharmacists, and *AHFS Drug Information* is identified with the pharmacy profession. *DE* is primarily directed to the physician.

Are there other, similar publications that we should know about?

A joint effort between the AMA and the USP that would be of interest is the Patient Medication Instruction (PMI) program. The program provides notepad leaflets for distribution by prescribing physicians. The PMIs provide patients with information on the use and adverse effects of a drug or a group of drugs. AMA is responsible for the scientific content of these notes, and USP handles the sales end of the program.

From time to time, the AMA's Counsel on Scientific Affairs will publish a monograph on a particular type of drug therapy.

Gerald K. McEvoy, Pharm.D., Assistant Director, Database Services Division, American Society of Hospital Pharmacists.

Can you give us some historical background on the *American Hospital Formulary Service (AHFS) Drug Information?*

AHFS Drug Information (originally known as the *American Hospital Formulary Service*) was first published in 1959 as an adaptation of the University of Michigan's *Hospital Formulary of Selected Drugs* by Don E. Francke. Originally, the Service was conducted through the Committee of Pharmacy and Pharmaceuticals of ASHP to assist the pharmacy and therapeutics committee of each hospital in preparing its hospital formulary. The purpose of *AHFS Drug Information* was to provide objective, evaluative drug information to assist clinicians in the safe and effective use of drugs. At the time of the publication's development, there was a dearth of evaluative information on drugs in a readily accessible form. From a historical perspective, drugs available for use in the United States were

required only to be safe; demonstration of effectiveness was not necessary. Thus, one of the principal goals of *AHFS Drug Information*, since its inception, has been to provide objective evaluations on a drug's use, including perspectives on the role of the agent compared with other therapies. Since then, the publication has grown beyond its original purpose to become a comprehensive, authoritative source that evaluates various aspects of drugs from their pharmacology and pharmacokinetics to uses and associated precautions.

What type of information does the publication provide?

As a general drug information source, *AHFS Drug Information* provides comprehensive information in a structured style on drug uses and dosage and administration, and includes discussions on chemistry and stability, pharmacology, pharmacokinetics, drug interactions, toxicity, and indepth descriptions of adverse effects, including associated precautions and contraindications. *AHFS Drug Information* includes information under the generic name of the drug, organizing the information on various drugs by pharmacologic and therapeutic classes. The publication provides information on virtually every single entity commercially available in the United States, and it is indexed by generic and trade names and by common synonyms.

Monographs are prepared by a professional editorial staff and incorporate the expert advice of leading medical scientists, clinicians, pharmacists, pharmacologists, and other qualified individuals. In addition to the multi-step information analysis and review by staff of ASHP's Database Services Division, the review process includes the contributions of many consultants in specific fields of therapy and the appropriate manufacturer(s). The monographs incorporate information from pertinent references in the literature, the labeling approved by the U.S. Food and Drug Administration (FDA), and from reviewers. Information on uses, dosages, and routes and/or methods of administration that may not be included in the FDA-approved labeling for a drug is also included. A typical monograph on a new drug incorporates information from more than 100 references, and some general statements incorporate information from well over 1,000 references. Currency of the publication is maintained through quarterly supplements, and a revised master volume is issued each year. The publication is supported solely through subscriptions.

What portion of the publication is concerned with unlabeled indications, and does it also cover combination drug therapy?

While a precise portion of uses included in *AHFS Drug Information* that are unlabeled cannot be given, the selective inclusion of unlabeled uses of drugs has long been a hallmark of the publication. Such descriptions represent uses that often are established in clinical practice long before being considered for inclusion in FDA-approved labeling, and some such uses may never be included in labeling. Just as advances in therapeutic knowledge and practice inevitably precede labeling revision by the sponsor and formal approval by the FDA, information in *AHFS Drug Information* on these advances frequently precedes such revision and approval. Some recent legislative actions (e.g., orphan drug provisions and revised treatment IND procedures) are aimed at stimulating and simplifying the approval of labeling for drug uses in cases of rare diseases or other diseases for which there is no reasonable expectation that the cost of investigating and marketing the drug for such a use in the United States would be recovered. Without incentives to sponsors, many of these uses would never find their way onto approved labeling, although they often represent the only effective treatment or one that is associated with substantially reduced toxicity compared with other available therapies. Such uses are included in *AHFS Drug Information*.

AHFS Drug Information includes descriptions of most combination preparations, both prescription and over-the-counter, that are commercially available in the United States. These descriptions are included in various monographs on the component single-entity drugs and can be accessed by the trade name through the index. In addition, depending on the complexity and nature of the drug regimen, discussions of combination drug regimens often are included in the "uses" discussion of the individual monographs or in the general statements on classes of drugs. For example, recommended combination regimens for the treatment of various infections, such as antituberculosis regimens, are described, as well as information on alternative regimens, such as those used for resistant disease. However, it is often beyond the scope of a general drug information publication to attempt to provide detailed discussions of the various dosages and sequencing of each drug in a regimen. Providing comprehensive information on combination regimens for antineoplastic agents is particularly difficult, because of the complexity and frequently evolving nature of such regimens for many cancers. In such cases, major regimens, such as cisplatin-containing regimens for the treatment of testicular cancers, may be discussed, but users of the publication are advised that clinicians actively engaged in the treatment and investigation of such a disease should be consulted for the latest and most advantageous forms of therapy.

In your view, how does the *AHFS Drug Information* compare with the other drug compendia?

Each of the publications has its strengths. One of the principal strengths of *AHFS Drug Information* is the variety and depth of information provided on each drug.

Are there any other related Society publications that we should be aware of?

ASHP publishes the *Handbook on Injectable Drugs*, a reference on the stability and compatibility of injectable drug products. This handbook covers injectable drugs used in admixtures, including investigational drugs, as well as information on formulation, concentration, pH, and dosages. The Society also publishes *International Pharmaceutical Abstracts (IPA)*, a semimonthly service that provides informative abstracts on drug therapy and pharmaceutical information to help simplify research on any drug-related subject. ■

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