A contract manufacturer is about to begin manufacturing a new product, and the director of quality control needs to know what tests to conduct for batch release. Where does she go? To her trusty United States Pharmacopeia-National Formulary, of course.

But how do those pages get into that tome? And why is it that everyone seems to trust the methods described there? How are they written, updated, and verified?

In other words, we know the what of the United States Pharmacopeia. But USP is also a who. That’s the part that most of us don’t know.

We know USP is not a government agency, although its headquarters in Rockville, Maryland, are less than a mile from the Food and Drug Administration. So how did it get to be so official?

Asked to explain the essence of USP, its executive vice-president and chief executive officer, Roger Williams, MD, laughs. “It’s still a mystery to me,” he replies. He’s joking, of course. But it turns out that USP really is a bit complicated.

The Council of Experts: at the heart of USP

Sitting at the center of the USP are the Council of Experts (CoE) and its Expert Committees. The strange thing is, they don’t really sit at the center. They are all over the country, and even in other countries. And they never receive a USP paycheck— because they are volunteers, mainly from industry and academia (see sidebar, “Who are the experts at the US Pharmacopeia?”). And there are about 650 of them.

Compare that to the mere 350 people actually on staff back in Rockville. (Did we mention that an additional 400 volunteers serve as members of the USP convention?) “The heart of USP is the Council of Experts,” says Williams.

The Council of Experts performs the core USP activity: setting standards. Then revising them, and revising them, and revising them. The joke at USP is that they wrote the original book in 1820 and have been trying ever since to get it right.

Because the CoE and the Expert Committees make the final decisions about what new material to include and what changes to make, Williams stresses that having a top-notch CoE is critical. “You want to be sure that the CoE is the best they can be in terms of their science,” he says.

Judy Boehlert, PhD, is one of those experts. She is the former vice-president of quality control at Hoffman-LaRoche, Inc. and now owns a pharmaceutical consulting company. She has served...
USP’s core activity is setting standards. The most widely known product of that work is the publication and continuous updating of the United States Pharmacopeia and the National Formulary, two volumes that are published together as one book, the USP-NF. According to the 1938 Federal Food, Drug, and Cosmetic Act, USP standards are enforceable by the Food and Drug Administration for drugs manufactured or sold in the United States. The USP-NF is the only official pharmaceutical compendium in the world that is not published by a government agency.

The USP comprises two main sections: official monographs and General Chapters. A monograph is a detailed description of what USP calls a “medical article.” Most of the monographs describe prescription or over-the-counter products, but some define dietary supplements, medical devices, or other healthcare products. The monograph includes a description, definition, requirements (such as packaging, labeling, and storage), and a specification. The specification consists of the tests, procedures, and acceptance criteria for the ingredient or product. If a substance is tested and conforms to the standards in the monograph, it can be identified as that ingredient or product.

The monographs also contain references to standard tests and assays that appear in the General Chapters of the USP (rather than repeating this information in each monograph, which would make the book unwieldy). In addition to the General Tests and Assays, there is another type of General Chapter, numbered above 1000, called the “General Information” chapters. These provide additional information that is considered interpretative or optional.

The monographs in the National Formulary follow the same model as those in the USP. The difference is that, whereas most drug substances and dosage forms are included in USP, the National Formulary is limited to excipients. If an article is used as both a therapeutic agent and an excipient, it is included in the USP, with a cross-reference from the NF to the USP monograph for the convenience of the user.

**Reference standards**

In addition to establishing tests, procedures, and acceptance criteria for USP and NF monographs, USP maintains a collection of reference standards. The reference standards are highly characterized chemical substances used to test drugs and dietary supplements for compliance with USP standards for identity, strength, quality, and purity. These standards are specifically required in many pharmaceutical assays and tests. Modern chromatography and spectrophotometry, for example, require measurements relative to a reference standard to get accurate and reproducible results.

USP currently maintains more than 1300 pharmaceutical reference standards and has another 500 under development. These samples are donated by industry and then undergo extensive testing by various groups before being approved by the USP Reference Standards Committee. They also are carefully packaged and controlled for quality before being distributed.

“We’re after a pure ingredient or a pure impurity,” if that makes sense,” says Ron Manning, PhD, vice-president of Monograph and Reference Standards Development. “Impurities are more precious, in a way, because they are more rare,” he says. In some cases, Manning explains, the only way to get a certain impurity is by harvesting it from the active ingredient by a purification process.

Boehlert originally got involved because she wanted to help set the standards that industry follows. “I wanted to be on the inside,” she says. She also felt that it was important to provide an industry perspective, which was a bit lacking at the time. “There are three main groups that contribute to USP—industry, academia, and the regulators. I think you need that mix,” Williams agrees. The organization has made an effort to increase industry representation, which is now at 50%. “Industry has the dominant expertise about how products are made,” he says. “They are also the most impacted by the standards.”

**Missing monographs.** Before USP can send a new monograph to the appropriate Expert Committee for review, however, they must surmount another obstacle: getting the monograph in the first place. “We are missing about one-third of all possible monographs,” says Williams. The problem is twofold. First, industry has to supply the information, which involves a fair amount of work. To help make the submission process easier for companies, last year USP launched a new guideline for submissions (http://www.usp.org/standards/revision/guideline/index.html), which clarifies what information is needed. USP also is piloting a program to send staff to companies to help them prepare monograph submissions. “We look forward to judging the success of that program,” says Williams.

Second, some companies are reluctant to reveal proprietary information about a product before patent expiry. Eric Sheinin, PhD, vice-president of Standards Development at USP, dismisses that concern. “Most of the time, the generic company already knows what’s in the product and how to make it,” he says. The value of the monograph, then, is that it sets the standard. “And if the innovator company shares the information for the monograph, they establish the standard that every other company has to meet,” he says. Boehlert agrees. “If I am the innovator company, I wouldn’t want to have to evaluate, and possibly meet, someone else’s standard.”

USP has launched a monograph acquisition campaign, focusing on products that will come off patent through 2008. Most innovator companies start working with USP three years before patent expiry, though the organization would prefer to start the process much earlier. “Because of the long lead time to get a monograph approved and published, three years is actually a short time,” explains Sheinin.

**Evolving science, evolving USP**

In its ongoing work to add monographs and revise General Chapters of the USP-NF, the organization constantly evaluates the evolution of pharmaceutical science. One of the challenges, Williams says, is weighing the value of older analytical procedures against the sophisticated methods available today. “You don’t want to use a method that’s too primitive; on the other hand, you don’t want to use a method that is unnecessarily precise and wastes money,” he explains. “That balance makes the book good.”

**PAT methods.** As part of that process of keeping up with changes, USP has begun incorporating process analytical technology (PAT) methods into the USP-NF. “The USP standards
reflect the standards of the industry,” says Williams. “If the industrial standard shifts to PAT, the USP standards must change to reflect that.”

So far, the book includes a General Chapter on near-infrared methods, which has already been revised and updated. Gary Ritchie, who led the USP working group to update that chapter, was hired last year by USP as the scientific fellow for PAT.

Ritchie and a new project team are developing additional chapters on PAT methods, beginning with thermal effusivity, Raman spectroscopy, and acoustical procedures, as well as a chapter on chemometric techniques. “Chemometric techniques will be critical for how you handle the reams of data that are going to be generated through PAT methods,” says Sheinin. The new PAT chapters will be numbered above 1000, which indicates that they are advisory in nature and not intended to be enforced.

USP’s first annual scientific meeting, to be held 26–30 September in Iselin, New Jersey, will also include a track on PAT.

Alternative tests. Readers of the USP–NF will also see another change in some monographs: multiple, alternative tests for impurities. “There are different routes of synthesis for many drugs, and each route usually has a different impurity profile,” Sheinin explains. Similar flexibility has been introduced for drug release tests for extended-release products. “Some monographs may include as many as eight different performance tests, depending on the formulation,” says Sheinin.

Generic biologics

Generic biologics are a hot topic in Washington these days, and USP has thrown itself into the fire. USP formed an expert panel in 2000 to study the question of generic biologics, and will publish its findings soon. “I’m very pleased with the panel’s deliberations,” says Williams. “We hope USP can contribute to the public debate with a good scientific framework.”

“In a nutshell, the panel has determined that yes, you can consider generic biologics, which requires a scientific framework with three aspects,” Williams explains. “The first is, what is the basic question? I argue the basic question is, how do you show that two biological drugs are bioequivalent?” He continues: “Once you decide that it’s an equivalence question, the second question is, how do you determine bioequivalence? And the third question is, what are the statistical requirements, and how confident do you have to be in your answer?”

“Essentially we’re saying that anybody can try to show equivalence,” Williams concludes. “There should be a set of data for any product that could be generated by an interested manufacturer and submitted to FDA.”

The other question, says Williams, is the relationship between a USP monograph and a generic biologic. “Essentially the monograph is the start to the generic process,” he says, because a monograph standardizes the analytical procedures used to test a product’s identity and quality. “A monograph is not an unimportant part of the whole process,” he says. The USP–NF already includes 144 monographs for biological pharmaceuticals. Twenty-eight more monograph proposals have appeared in Pharmacopeial Forum and another 41 are under development.

In addition to the monograph, Williams says, it’s also critical that public reference standard material be available. “USP’s role as a repository of public reference standard material is another way that we can support an interchangeable system of generic biologics.”

International harmonization

As if setting and revising standards weren’t complicated enough, USP is also harmonizing its standards with the two other main pharmacopeias: The European Pharmacopeia (EP) and the Japanese Pharmacopeia (JP).

The big question industry always has about harmonization, Sheinin says, is whether or not a harmonized document in the three pharmacopeias means that the procedures will be considered interchangeable by regulators in the three regions. “Industry wants to know if they can reference just one of the pharmacopeias rather than do development work using three different procedures to demonstrate that they’re equivalent,” he explains.

He says that the pharmacopeias finally realized that this wasn’t a question they could answer. All they could do, he said, was pharmacopeial harmonization. That means if you examine a substance by a procedure in a harmonized monograph or General Chapter, you’ll obtain the same results and reach the same decision (e.g., whether or not to accept a batch). “But that doesn’t mean the procedures are interchangeable,” he adds.

As a result, the pharmacopeial discussion group (PDG) of the three main pharmacopeias asked the International Conference on Harmonization (ICH) to address the issue. The ICH is a project of the pharmaceutical regulatory authorities of Europe, Japan, and the United States, and its goal is to harmonize the interpretation and application of technical guidelines and procedures.

USP achieves ISO Registration

When it comes to standards, USP doesn’t just talk the talk. The organization has gone to great lengths to follow standards set by other standard-setting bodies. Not satisfied with having achieved 9001–2000 ISO registration of all of the organization’s business practices, USP contracted, on its own initiative, for a GMP audit to test its conformance to all applicable good manufacturing practices. And it is now on its way to obtaining ISO 17025 registration of its laboratories.

“Our desire was to improve our business practices by having external auditors look at what we’re doing,” explains Steve Lane, vice-president of Reference Standards Operations at USP. Although some organizations limit ISO registration to one part of their organization, USP did it across the board, from monograph development to IT and public relations.

Lane is proud of that, and believes it was worth the trouble. “For example, one result is our new document management program,” he says. “It gives us change control over processes and procedures that are used company wide.” Manning agrees that the organization has gained a lot from the process, citing improvements in productivity and efficiency. “The key has been to have external auditors come in and look at us closely,” he says. “There’s nothing like putting yourself up to external examination.”
requirements for pharmaceutical product registration. Following the PDG request, ICH created the Q4B Expert Working Group, "Regulatory Acceptance of Pharmacopeial Interchangeability," The working group will start by examining three of the eleven chapters included in ICH guidance Q6A on test and acceptance criteria: extractable volume for parenterals; residue on ignition (called sulfated ash in Europe); and sterility. By the spring of 2005, the working group hopes to have a document ready for step two of the five-step harmonization process. (More information about ICH and the harmonization process is available at www.ich.org).

One of the other tricky issues about harmonization is how far-reaching a change can be. "In the past, the ICH has always developed guidelines that were prospective, looking forward to new products not yet registered," notes Sheinin. "But if you change something in a pharmacopeia General Chapter through harmonization, it applies to every monograph in every pharmacopeia that references that General Chapter. So it's not only prospective, it's retrospective."

To illustrate the point, Sheinin explains what happened when they harmonized the standards for testing the uniformity of dosage units. Before the harmonization, the US standard allowed content uniformity to be tested by checking weight variation (instead of using an analytical test) if the active ingredient was present in at least 50 mg and made up at least half the dosage form. But data from FDA laboratories showed that uniformity-of-mass of testing was sufficient to prove content uniformity even at lower drug levels and concentrations, so USP was willing to agree to a harmonized standard of 25 mg/25% (25 mg of active ingredient, making up at least 25% of the dosage form). This harmonized standard tightened the requirements in Europe, however, where regulations allowed the uniformity-of-mass method to be used for dosage forms containing 2 mg/2% active ingredient. Many European companies were worried that they could not meet the new standard for existing products. "The European regulators have said they will find a mechanism to implement this without causing products to be removed from the market," Sheinin acknowledges, but notes that it is a challenge.

Beyond setting standards
Although setting standards is USP's core activity, the organization is involved in a surprising number of other activities, ranging from a new verification program for the manufacture of dietary supplements to global outreach.

Verifying the quality of dietary supplements. With the launch of a dietary supplement verification program (DSVP) in 2001, USP is filling an important information gap for consumers, because dietary supplements are not regulated by FDA. It's also the first time that USP has moved beyond setting standards to assessing conformity to standards. Through this voluntary program, USP inspects supplements to ensure they contain the ingredients listed on the label in the stated amounts or strengths and meet appropriate impurity limits. USP also verifies that the company has followed FDA's standards for good manufacturing practices. If a product meets all the standards, USP awards its DSVP certification mark, which manufacturers can display on the label as evidence of the product's quality. To date, six manufacturers have joined the program.

Certification for pharmaceutical compounding. USP's involvement in the Pharmaceutical Compounding Accreditation Board (PCAB) brings USP back to its roots. Formed by a coalition of eight organizations, the board's primary purpose is to improve the quality of pharmaceutical compounding (the preparation of customized medications for individual patients).

In fact, the first US pharmacopeia was written for compounding pharmacists, and it was only with the growth of industrial pharmacy that the book's focus shifted to industrial manufacturing. But now compounding is growing in the United States, and the PCAB is a response to that.

Who are the experts at the US Pharmacopeia?
The USP Council of Experts (CoE) is a group of 62 nationally and internationally recognized scientists, academicians, and clinicians, each elected for a five-year term. Each member chairs an Expert Committee. In total, there are about approximately 650 members on the CoE and the Expert Committees. Thirty-one of the 62 Expert Committees are responsible for the ongoing revision and development of the United States Pharmacopeia and the National Formulary (USP–NF).

The other 31 CoE members and their committees form the Information Division that supports the USP Drug Information (USP DI) reference books and database covering drug prescribing, dosing, and use. Following this year's sale of two of the three volumes of the USP DI to Thomson Corporation, USP plans to scale back the Information Division committees and add seven standards committees. They may also create new committees to handle the work arising from USP's role in the 2003 Medicare bill.

How they are elected. The Council of Experts for the 2005–2010 term will be elected next March at the meeting of the USP Convention. Candidates for the CoE and the Expert Committees are nominated (by themselves or others) through an open process that ends 1 November 2004. The USP Nominating Committee then selects qualified candidates to run for election. Following the election of the CoE at the March meeting, voting is held for the members of the Expert Committees. The Nominating Committee consists of 10 members of the USP Convention and 20 members of the current CoE.

The USP Convention, which is a separate body from the CoE and the Expert Committees, includes an additional 400 volunteer members, who are drawn from medicine, pharmacy, nursing, professional health and scientific organizations, industry, government, and international and consumer organizations. Within each membership category, a number of organizations are invited to appoint individuals to represent them for the coming five-year cycle. A balance is maintained within the membership to ensure adequate representation from healthcare constituencies that are affected by USP's activities.
The recent revival of pharmaceutical compounding is tremendous,” says Loyd Allen, PhD, who chairs the expert committee on compounding pharmacy and is editor in chief of the International Journal of Pharmaceutical Compounding. He says this resurgence is a result of several factors, including:

- reductions in the variety of available dosage forms for many drugs
- industry discontinuation of many drugs
- temporary shortages in drug supplies
- physicians’ desire to prescribe drugs only available in other countries.

Allen says the relationship between industry and compounding pharmacy is symbiotic. “If a company drops a product for economic reasons, compounders will pick it up. If a drug is compounded a lot, industry will pick it up,” he explains. “It goes back and forth.”

The board hopes to accredit the first compounding pharmacy site by the end of this year. The next step will be establishing a certification program for the pharmacists themselves. USP already publishes standards for compounding in the USP–NF, including monographs for specific compounded formulations and several General Chapters on compounding procedures and requirements.

Medicare legislation. With the passage of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Congress has once again enshrined USP’s role in this country’s healthcare system. MMA calls for USP to develop a list of drug categories and classes to be used by Medicare prescription drug plans. Under the law, any formulation used by a drug plan provider must include drugs within each covered therapeutic category and drug class. It is up to USP to develop a list of those categories and classes.

“USP was very pleased to be named in the legislation,” says Williams. “It’s an exciting opportunity for us, and it amplifies our interest in drug information, which has been an ongoing effort for many years.”

Actually, USP recently scaled back its activity in that area. From 1990 to 1998, USP published the three-volume USP Drug Information (USP DI), a reference book for drug prescribing, dispensing, and use. In 1998, Micromedex, a division of Thomson Corporation, purchased the USP DI database, and in May of this year, Micromedex took over full responsibility for the first two volumes of USP DI (Drug Information for the Health Care Professional, and Advice for the Patient).

The intent of the transfer was to center USP’s activities on its standard-setting core, but it seems that effort wasn’t destined to last. Reducing the drug information effort, however, will free up resources for the Medicare work. USP has formed a new expert committee to create the model drug guidelines, and plans to announce detailed plans soon.

Supporting international public health. Through grants from the United States Agency for International Development, USP participates in numerous international public health projects. In Nepal, the Mekong Delta region, and Senegal, for example, USP is helping reduce antimicrobial drug resistance and supporting malaria-control efforts by ensuring the quality of antimalarial drugs. In Romania and Moldova, USP is collaborating on training programs for pharmacists and hospital drug committees to improve the selection and rational use of drugs.

An ongoing need
Regardless of whether or not USP continues to delve into public health projects like those in Nepal, its impact will continue to be felt worldwide. The USP–NF is sold in 131 countries, and regulators in countries that lack an official pharmacopeia often refer to USP. That reach will continue to grow as pharmaceutical manufacturing becomes increasingly globalized.

Allen thinks that is a big responsibility, and exciting at the same time. “Here I am in the middle of Oklahoma, and I’m working on setting standards that will impact not only the United States, but many countries around the world,” he reflects. “That’s pretty overwhelming.”

Williams has no doubt about the importance of USP’s role. “The world needs safe, effective, good quality medicines, and a pharmacopeia is in the vanguard of making that possible,” he says. “I’m very bullish on USP.” PR

How the USP–NF is revised

- Someone proposes a change. Changes may be proposed by anyone— a healthcare practitioner, a consumer, a scientist, or an organization.
- USP staffers review the proposal for completeness, then send it to the appropriate Council of Expert (CoE) committee.
- The CoE committee reviews the proposal, and publishes it in Pharmacopeial Forum, USP’s journal of standards development and compendium revision, for public review and comment.
- Comments are reviewed by the Expert Committee.
- The Expert Committee approves the proposal for official adoption.
- The USP Board of Trustees approves publication. The change can make its first appearance before the next annual update of the USP–NF by being published in a semiannual Supplement, an Interim Revision Announcement (issued as needed between supplements), or as a Revision Bulletin (issued as necessary).