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Commentary

The Value of USP Public Standards for Therapeutic Products

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INTRODUCTION

The word *pharmacopeia* means to make a drug. Before the Food and Drug Administration (FDA) and modern pharmaceutical manufacturing, virtually all medicines in the United States were prepared by physicians or pharmacists. Medicines were prepared in the early years of the Republic according to a number of publications—pharmacopeias and dispensatories—from this country and abroad. These differing approaches, coupled with the absence of laws regulating either the practice of medicine and pharmacy or the medicinal preparations used, led to irregularities in how medicines were prescribed, prepared, dispensed, and administered. This lack of consistency was widely recognized then, as it is now, as a barrier to quality medical care. It prompted agreement by a group of physicians to create a national pharmacopeia. These physicians held the first United States Pharmacopeial (USP) Convention in 1820 in the Capitol Building of the United States (1).

Delegates representing regional medical societies and schools arrived in Washington, D.C., to determine the contents of the first *Pharmacopoeia of the United States of America (USP),* which presented the best medicines, named and provided recipes for their preparation, and gave instructions for their use. Over time, with the rise in modern pharmaceutical manufacturing, the task of making a drug has shifted from practitioners to pharmaceutical manufacturers. A residuum of the original approach remains with practitioners who compound a medicine, using at times a *USP* preparation monograph pursuant to a physician's prescription. But only a relatively small fraction of prescriptions in the United States are compounded.

USP was incorporated under the laws of the District of Columbia in 1900. It is a 501(c)(3) corporation working in the public interest. The USP Convention meets at 5-year intervals, when it elects its governing body, the Board of Trustees, and its standards-setting body, the Council of Experts. With staff support, the Council of Experts creates the content for the *United States Pharmacopeia–National Formulary (USP–NF)*. With the exception of staff, all participants in USP, the convention members, members of the Board of Trustees, and the Council of Experts work as volunteers. USP has strict conflict-of-interest rules and also confidentiality rules that protect sensitive commercial and trade secret information that is provided by sponsors of monograph and General Chapter proposals.

Although several public health laws controlling biologicals and drugs were created in the early part of the twentieth century in the United States, modern regulatory control really began with passage of the Federal Food, Drug, and Cosmetic Act (FFDCA) in 1938. This act incorporated prior legislation and created the FDA. FDA regulates pharmaceutical manufacturing closely. *USP–NF* has evolved in concert with these changes to become a book of public standards. The modern pharmacopeia is presented as two compendia, the original *USP* and, more recently, the *NF*. In 1975, USP purchased the *NF,* a compendium of public standards primarily for excipients. These are now published annually as a combined text, *USP–NF,* with two annual *Supplements*. The current edition, *USP 27–NF 22,* became official in January 2004 and contains monographs for prescription and over-the-counter (OTC) drugs, biologicals, dietary supplements, and allied therapeutic products (including some devices). Excipient monographs continue to appear in *NF*.

The two compendia are named in the FFDCA as official compendia of the United States (2). The FFDCA integrates USP standards in the adulteration and misbranding provisions for drug products. Section 501(b) of the act provides that a drug is adulterated if it is recognized in *USP–NF* and does not adhere to *USP–NF* standards or does not state on the label how the drug strength or purity differs from these standards. Section 502(g) of the act states that a drug is misbranded if it is recognized in *USP–NF* and does not meet *USP–NF* packaging and labeling requirements set forth. Section 502(e) requires that the established name of the drug must appear on the label and states that the established name of a drug or ingredient is the one appearing in *USP–NF*.

The modern *USP–NF* now comprises more than 4000 monographs for named ingredients and products, which are termed *articles*, as in articles of commerce. This is also how

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they are termed in the FFDCA. Although *USP–NF* is extensive, it is not exhaustive; that is, the two compendia are missing many hundreds of ingredient and product monographs. This arises because a manufacturer's submission of information (Requests for Revision) to support new ingredient and product monographs is voluntary. The modern pharmacopeia represents a collaborative enterprise between pharmaceutical manufacturers and USP that results in public standards that are available to other manufacturers, practitioners, patients, governments, policy makers, and the community at large.

Representative examples of ingredient and product monographs USP–NF appear in Figs. 1 and 2. The standards of a monograph consist of introductory material (definition, description, packaging, and storage statements) followed by the article's specification, which includes tests, procedures for the tests, and acceptance criteria. A monograph is meant to stand alone; that is, an analyst should be able to perform all the procedures listed in a monograph to assess conformity of the named article to the compendial specification. If the article complies, its identity is established. For this reason, *USP–NF* is sometimes referred to as a dictionary that defines a named article via the standard in the monograph. A monograph thus helps mitigate both consumer and manufacturer risk—the article either passes or it fails, and the elements for conformity testing are clearly specified.

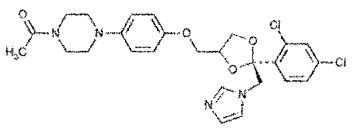
DEVELOPMENT OF PRIVATE STANDARDS IN THE UNITED STATES

Therapeutic products and foods include drugs and recombinant biologicals (proteins, vaccines, blood and blood products, and cell and gene therapy products), devices, dietary supplements, food additives, functional foods, foods with health claims, and foods. Regulatory control of these products in the United States proceeds according to risk-based approaches. In some but not all instances, these approaches require premarket review of information submitted by a manufacturer in a regulatory application and manufacture according to current Good Manufacturing Practices (cGMPs). Postapproval changes in method of manufacture and/or components and composition may require advance notification to and approval by FDA. Sometimes premarket review is not required, although manufacturing in most cases still should proceed according to cGMPs (see, e.g., Ref. 3). As part of a premarket review for a drug/biological product and its excipients, extensive characterization studies may be needed, out of which a private specification is developed. The applicant validates the procedures in the private specification, and FDA conducts confirmatory studies when needed.

DEVELOPMENT OF PUBLIC STANDARDS IN THE UNITED STATES

USP public monographs are developed by the USP Council of Experts and its Expert Committees, who are elected, together with USP's volunteer Board of Trustees, at the quinquennial meetings of the USP Convention. The next meeting will take place in Washington, D.C., in March 2005, and the recruitment process is under way (see www.usp.org for further details) (4). The Council of Experts and the Expert Committees comprise skilled experts from industry, academia, and government. Based on Requests for Revision, primarily from manufacturers and from others as well, these experts create the monographs and associated General Chap-

Ketoconazole



$C_{26}H_{28}Cl_2N_4O_4$ 531.43

Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, *cis*-.

(±)-*cis*-1-Acetyl-4-[*p*-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine [*65277-42-1*].

» Ketoconazole contains not less than 98.0 percent and not more than 102.0 percent of $C_{26}H_{28}Cl_2N_4O_4$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Ketoconazole RS.*

Identification, *Infrared Absorption* ⟨197K⟩.

Melting range ⟨741⟩: between 148° and 152°.

Specific rotation ⟨781S⟩: between 1° and +1° (t = 20°).

Test solution: 40 mg per mL, in methanol.

Loss on drying ⟨731⟩—Dry it in vacuum at 80° for 4 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1% from 2 g.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Chromatographic purity—Dissolve 30 mg in 3.0 mL of chloroform (*Test solution*). Dissolve a suitable quantity of USP Ketoconazole RS in chloroform to obtain a *Standard solution* having a known concentration of 10 mg per mL. Dilute a portion of this solution quantitatively with chloroform to obtain a *Diluted standard solution* having a concentration of 1.0 mg per mL. Apply separate 10-µL portions of the *Test solution* and the *Standard solution* and a 2-µL portion of the *Diluted standard solution* to the starting line of a suitable thin-layer chromatographic plate (see Chromatography ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in a suitable unsaturated chamber with a solvent system consisting of a mixture of *n*-hexane, ethyl acetate, methanol, water, and glacial acetic acid (42 : 40 : 15 : 2 : 1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, and air-dry. Expose the plate to iodine vapors in a closed chamber, and locate the spots: the principal spot obtained from the *Test solution* has about the same size and R_F value as that obtained from the *Standard solution*, and the sum of the intensities of any secondary spots obtained from the *Test solution* does not exceed the intensity of the principal spot obtained from the *Diluted standard solution.*

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Assay—Dissolve about 200 mg of Ketoconazole, accurately weighed, in 40 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 26.57 mg of $C_{26}H_{28}Cl_2N_4O_4$.

Fig. 1. Example of a USP drug substance monograph. Reproduced with permission from USP.

Ketoconazole Tablets

» Ketoconazole Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{26}H_{28}Cl_2N_4O_4$.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Ketoconazole RS. USP Terconazole RS.*

Identification—Transfer a quantity of finely powdered Tablets, equivalent to about 50 mg of ketoconazole, to a suitable flask, add 50 mL of chloroform, shake for about 2 minutes, and filter. Apply separate 10-µL portions of this solution and of a Standard solution of USP Ketoconazole RS in chloroform containing 1 mg per mL to the starting line of a thin-layer chromatographic plate (see Chromatography ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in an unsaturated chamber with a solvent system consisting of a mixture of *n*-hexane, ethyl acetate, methanol, water, and glacial acetic acid (42 : 40 : 15 : 2 : 1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, air-dry, and view under short-wavelength UV light: the R_F value of the principal spot obtained from the test solution corresponds to that obtained from the Standard solution.

Disintegration ⟨701⟩: 10 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Methanol methylene chloride—Mix equal volumes of methanol and methylene chloride.

Mobile phase—Prepare a suitable (7 : 3) mixture of a solution of diisopropylamine in methanol (1 in 500) and ammonium acetate solution (1 in 200).

Internal standard solution—Dissolve USP Terconazole RS in *Methanol methylene chloride* to obtain a solution containing about 5 mg per mL.

Standard preparation—Transfer about 20 mg of USP Ketoconazole RS, accurately weighed, to a 50-mL volumetric flask, add 5.0 mL of *Internal standard solution*, dilute with *Methanol methylene chloride* to volume, and mix.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg of ketoconazole, to a suitable screw-capped bottle, add 50.0 mL of *Methanol methylene chloride,* shake by mechanical means for 30 minutes, and centrifuge. Transfer 5.0 mL of the clear supernatant so obtained to a 50-mL volumetric flask, add 5.0 mL of *Internal standard solution,* dilute with *Methanol methylene chloride* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩) The liquid chromatograph is equipped with a 225-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation is not more than 2.0%, and the resolution, *R,* between ketoconazole and terconazole is not less than 2.0.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.6 for ketoconazole and 1.0 for terconazole. Calculate the quantity, in mg, of $C_{26}H_{28}Cl_2N_4O_4$ in the portion of Tablets taken by the formula:

$$10W_S(R_U/R_S),$$

in which W_S is the weight, in mg, of USP Ketoconazole RS taken, and R_U and R_S are the ratios of the peak responses of ketoconazole to those of terconazole from the *Assay preparation* and the *Standard preparation,* respectively.

Fig. 2. Example of a USP drug product monograph. Reproduced with permission from USP.

ters that represent the content of *USP–NF*. Manufacturers frequently submit information from the private standard that was concluded during the regulatory process to support the USP monograph development process. This information from the private standard is usually adjusted so that other manufacturers of the same article also can conform. A "give and take" process occurs to achieve a common public standard via comments in USP's *Pharmacopeial Forum* (*PF*). Increasingly, a monograph will be flexible to account for different routes of synthesis for ingredients and different performance and other characteristics for dosage forms. With this flexibility, the public and private standards may become more closely aligned. A staff of approximately 400 supports the three volunteer bodies of USP. These are: convention members, the USP Board of Trustees, and the USP Council of Experts and its Expert Committees, which form the standards-setting body of the organization.

THE VALUE OF A MONOGRAPH

Support for the Public Health Transaction

In the past, the value of a public monograph for a medicine was seen by purchasers as a requirement in order to complete the purchase. In this sense, the term *article of commerce* takes on special meaning for a public monograph in *USP–NF*. The public monograph sets the stage for the subsequent transaction, whether that transaction is between an ingredient supplier and dosage form manufacturer, wholesaler and pharmacy, or practitioner and patient. It is crucial for the provider and purchaser to be able to confirm that the goods sold meet requisite quality standards. This is a common practice in most industries, but it has become less so with regard to pharmaceutical manufacturing with the rise in regulatory control. Yet it remains important given that practitioners, patients, and purchasers, at times, lack the capability to discern that failure to respond or unanticipated toxicity may be the result of a failing product and not the natural course of disease. Indeed, product failure is rarely considered to be an issue in treating patients in the United States, given both the rigor of FDA review and enforcement, coupled with the availability of public standards in *USP–NF* and attentive manufacturers who will recall a product if it fails to meet its private or public standards. Given the possibility of bioterrorism, the rise in parallel imports, and the possibility of counterfeit and substandard drugs, the need for a public monograph may be expected to increase. Without a public mechanism to test the quality of an article, the purchaser must rely on FDA to release such information through the Freedom of Information Act or the good will of a manufacturer to provide the necessary private testing approaches.

Updating Older Procedures

Updating public monographs is an additional public health value of a pharmacopeia. Of the thousands of ingredients and products in the U.S. marketplace, only a relatively small number have been approved in the past several years. *USP–NF* has become a mechanism to advance analytical capability in a way that affects all manufacturers equitably. A procedure referenced in a modern *USP–NF* General Chapter can be referred to in many monographs. Thus updating a General Chapter, or the availability of a new General Chapter, becomes a way to advance analytical capability in a way that affects multiple ingredients and products. USP also provides a *General Notices* section that speaks to all manufacturers, wholesalers, distributors, repackagers, and dispensers in ways that have broad impact. Regulatory agencies work well

with sponsors prospectively via their application processes and requirements for supplements and annual reports when a manufacturer-initiated postapproval change occurs. Regulators face a challenge, however, when a product is on the market and the manufacturer has little or no incentive to change. To affect products in the marketplace, then, a regulatory agency may propose a rule, which is resource intensive and time consuming. In contrast, USP can effect change to all products in the marketplace by modifying a procedure for a given monograph test or altering either a statement in the *General Notices* or one or more General Chapters. This is occurring now, for example, with respect to organic volatile impurities. Agreements reached via the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (5) are being extended to all marketed articles in the United States, both ingredients and products, via proposed changes in General Chapter <467> *Organic Volatile Impurities*.

Public Naming of Articles

A further public health rationale for public monographs relates to nomenclature. As noted in the first pharmacopeia of 1820, clear, appropriate names for ingredients and dosage forms is an important means of helping practitioners and patients/consumers use medications sensibly and safely. In this regard, USP is a key member, together with the American Medical Association (AMA), the American Pharmacists Association (APhA), and FDA, in AMA's United States Adopted Names Council, which provides nonproprietary names for active ingredients. For dosage forms, USP's Nomenclature and Labeling Expert Committee works closely with FDA counterparts to develop clear and useful names for dosage forms. These terms are crucial to the availability of a rational set of therapeutic products in the marketplace and help practitioners avoid medication errors.

Over-the-Counter Products Subject to an FDA Monograph

For over-the-counter (OTC) medicines marketed under an FDA OTC monograph, market access is achieved without a regulatory review, providing that the product conforms to the requirements of the appropriate FDA OTC monograph. The approach also relies on conformance to *USP–NF* monograph(s). The combined FDA and *USP–NF* monographs allow regulatory control without a regulatory approval process. The public health is served by the FDA monograph, which speaks to safety and efficacy relative to a specified dose, and the USP monograph, which speaks to the strength, quality, and purity of the OTC ingredient and product. Both can be used by FDA inspectors in ensuring conformance not only to the monographs themselves but also to cGMPs. Taken together, the combined approach makes OTC drugs readily available in the United States for practitioners and patients and also reduces review resource burdens both on FDA and on pharmaceutical manufacturers. It is a time-honored approach that has worked well.

Dietary Supplements

The Dietary Supplement Health and Education Act (DSHEA) allows dietary supplements in the U.S. market as of October 1994 to remain in the market. They are considered safe pending new information, with the burden falling on FDA to document lack of safety. DSHEA names *USP–NF* as official compendia for dietary supplement ingredients and products. This part of DSHEA was incorporated into Section 402(s)(2)(D) of the FFDCA, which states that a dietary supplement is considered misbranded if it states conformance to a *USP–NF* monograph and fails to do so. As noted in the language, conformance is voluntary (i.e., a dietary supplement manufacturer may state conformance to other standards). Because conformance is optional, most manufacturers of dietary supplements do not conform or conform only partially to the public standards in *USP–NF*. For example, a manufacturer may use one ingredient in a complex dietary supplement mixture that conforms to a monograph in *USP–NF* or may follow only one procedure (e.g., dissolution) in that monograph. USP is working to provide a complete set of dietary supplement ingredient and product monographs with official USP reference standards, where needed. In this regard, USP works in several ways to promote, under the stipulations of DSHEA and at no cost to government, the strength, quality, and purity of dietary supplements. Consistency is achieved in part through standard recipes and directions that define how some botanical dietary supplements should be grown and processed, as well as the more usual testing mechanisms. USP also has the capability to require administration and other information in product labeling and labels that can enhance the safety of dietary supplements.

Compounded Preparations

According to the FFDCA, any drug recognized in *USP–NF* must meet the standards of the corresponding monograph or be deemed misbranded or adulterated. Compounding practitioners filling a prescription that names an article in *USP–NF* may risk enforcement actions if the compounded article does not meet the requirements of the article's monograph. These standards have provided consistency among compounded preparations in the United States—something that was recognized more than 180 years ago when the pharmacopeia was initiated.

Pre-1938 and Other Medicines not Covered by a New Drug Application

In the United States, USP provides monographs for pre-1938 ingredients and products for which a New Drug Application (NDA) has not been submitted to and/or approved by FDA. Furthermore, it provides a mechanism for FDA to ensure the quality of re-imported drugs when an application has not been filed with FDA. In worst-case scenarios, counterfeit, substandard, and even harmful medicines may enter the United States as a result of economic fraud and bioterrorist activities. Federal, state, and local officials may ensure quality by requiring adherence to the public monographs in *USP–NF* and, if the products fail to conform, can take swift action via the adulteration and misbranding provisions of the FFDCA.

Packaging

Section 502(g) of the FFDCA requires drugs to be packaged and labeled in accordance with compendial requirements. This packaging requirement also applies to drugs that are dispensed under a prescription to a patient. Packaging

requirements expressed in the packaging and labeling statements in a monograph provide useful instructions to practitioners and patients. Although the availability of many manufactured medicines is subject to strict regulatory control by FDA, at some point this strong federal system gives way to more variable control at state and local levels. For a manufactured medicine, the end of this control is approximately the point at which cGMPs are no longer applicable. Pharmaceutical manufacturers expend substantial resources to ensure that a regulated article maintains its quality characteristics according to its private or public specification during its shelf life in its original marketing package. However, many medicines are repackaged and are otherwise dispensed by pharmacists to patients in containers that differ from the original packaging material. Via specific statements in individual monographs, the *General Notices*, and General Chapters, USP can offer guidance to help ensure that a medicine has the requisite strength, quality, and purity from the point of manufacture to the point of use (6). But in the absence of a public monograph, no specific instructions are available to practitioners and patients/consumers other than those provided by the manufacturer in the original package.

Initiatives Pending Regulatory Activities

At times, USP can advance public health initiatives prior to finalization of FDA's activities with the understanding that the USP approach will diminish as the FDA's evolves. For example, USP required expiration dating on pharmaceuticals in 1976, 3 years before FDA did so. As discussed above, USP has developed nutritional supplement manufacturing practices before FDA has finalized its cGMP regulations for these products. Further, *USP–NF* includes General Chapter <1078> *Good Manufacturing Practices for Bulk Pharmaceutical Excipients*, which are not now part of FDA GMPs. USP also can aid in developing emerging science and technology approaches, pending final federal adoption. In addition, *USP–NF* General Chapter <1046> *Cell and Gene Therapy Products* establishes a common nomenclature and other standard approaches for this evolving technology. Recently, USP's Council of Experts Executive Committee concluded a decision to amplify the availability of ingredients and products that have not achieved specific regulatory approval in the United States, provided they can be deemed sufficiently safe for inclusion in *USP–NF*. Although details of the approach remain to be developed, these monographs are expected to assist regulatory officials, manufacturers, and many other groups throughout the world in understanding the regulatory status and quality standards of various therapeutic articles. USP's products and services, including *USP–NF,* are widely recognized throughout the world as a means of raising the level of quality for therapeutic products globally.

Reimbursement and Cost

The U.S. Social Security Act recognizes *USP–NF* in both its Medicare and Medicaid provisions. Medicare provides reimbursement for drugs that cannot be self-administered, such as those drugs administered in a physician's office. This act defines drugs as those that are included or approved for inclusion in the *USP, NF, United States Homeopathic Pharmacopeia,* or in *New Drugs* (7) or *Accepted Dental Remedies* (8) or approved by the Pharmacy and Drug Therapeutics Committee of a hospital.

PUBLICLY AVAILABLE OFFICIAL USP REFERENCE STANDARDS

With the increased applications of modern chromatography and many other advanced analytical procedures in *USP–NF,* the need for comparator material has grown, which has led to the availability of a large number of official USP reference standards. For the most part, candidate reference standard materials are donated to USP by firms that manufacture the specified ingredient. USP characterizes this candidate material using monograph and other tests, then organizes collaborative testing in multiple laboratories (usually 2–3 or more depending on the candidate material) to assess the content of the active pharmaceutical ingredient in the reference standard (e.g., 99.7%). From a statistical perspective, the more laboratories correctly following a well-designed protocol, the better the estimation of content. Data from the characterization and collaborative studies are then submitted to the USP Reference Standards Committee, which is a special Expert Committee of the Council of Experts. Members of this committee review the data and make the final decision on the candidate material's suitability for use as an official USP reference standard. They also assign the content value that will be included on the reference standard container label.

Official USP reference standards and public *USP–NF* monographs are complementary tools to ensure the strength, quality, and purity of pharmaceutical substances and products. Consider a dosage form manufacturer who receives active pharmaceutical ingredients and excipients for which there are neither public monographs nor official USP reference standards. In this instance, the dosage form manufacturer will have to do substantially more work to verify supplier approaches. In some instances, the manufacturer may have to use a private house standard to verify that the received material is in fact what it is purported to be. The availability of a USP monograph and official USP reference standard can obviate much of this time-consuming activity. Consider also a regulatory inspector who wishes to evaluate the integrity of ingredients used to manufacture a dosage form. This official, too, must rely on the willingness of both the dosage form manufacturer as well as the supplier of the ingredient to provide the necessary tests, procedures, and acceptance criteria and house standards in the absence of a public monograph and official USP reference standard. Even in these circumstances, the house standard is unlikely to have undergone collaborative testing in multiple laboratories that allows a science-based estimation of content.

Consider further the situation when multiple manufacturers are making the same ingredients and/or products, a frequent occurrence in the modern world. Without a public monograph and official USP reference standard, each manufacturer works in isolation without a common set of analytical procedures and reference standards. For example, approximately 20 manufacturers produce finished ibuprofen dosage forms in the United States. In the absence of an official USP reference standard, manufacture to a common ibuprofen standard would not be possible—each manufacturer would have to rely on its own house standard. For this reason, USP prepares and provides in commerce only a single lot of an

official USP reference standard that is available to all manufacturers. Before this lot is exhausted, a new lot is prepared and becomes official.

The *USP–NF* monographs and official USP reference standards thus have wide public applications and implications. The absence of the public monograph and official USP reference standard creates a situation in which regulatory officials and the public must rely on a manufacturer for both the analytical procedures and the reference standard to demonstrate the strength, quality, and purity of an article. For the careless and/or fraudulent manufacturer or supplier, this reliance can be unwise. In cases where counterfeit, substandard ingredients and products are frequent, where unofficial import occurs, and in instances of bioterrorism, it can be dangerous.

PHARMACEUTICAL MANUFACTURERS' STAKE IN PUBLIC STANDARDS

Development

For any of several reasons, a pharmaceutical manufacturer may find value in public monographs and official USP reference standards during product development. Availability of public monographs can facilitate development of an investigational new drug substance and drug product. For example, an excipient used in the investigational drug product can be cited as *NF,* reducing or eliminating the need for further characterization and development of a private specification. Even for an unapproved new drug, standard procedures in *USP–NF* can be used for characterization studies and can be relied on in the final private specification for batch release. For example, the *USP–NF* Performance Test, which is satisfied either by procedures described in General Chapters <701> *Disintegration* or <711> *Dissolution*, is highly useful to all manufacturers as they attempt to optimize the *in vivo* performance of their products.

Without these standard approaches, a manufacturer would have to develop and validate complicated dissolution procedures, equipment, reagents, and procedural standards (e.g., dissolution calibrators). For combination products in which one of the ingredients is investigational but the other is marketed, a public monograph facilitates development because tests, validated procedures, and acceptance criteria for the marketed ingredient are publicly available. Perhaps most important for a manufacturer, a *USP–NF* monograph creates a fully expressed safe harbor where the specific elements needed to satisfy other parties are clearly stated, validated, and widely accepted. When legal challenges arise, availability of official *USP–NF* monographs and procedures that use official USP reference standards can assist a manufacturer in developing an appropriate response. In this way, a *USP–NF* monograph, which stands alone and is fully expressed in terms of its requirements, mitigates regulatory and legal risk and misunderstanding.

Control

After approval, a public monograph in *USP–NF* becomes a means of supporting batch release and assuring practitioners and patients that a pharmaceutical product and its ingredients are scrutinized rigorously to ensure their strength, quality, purity, and performance. In this regard, the combined efforts of the FDA, manufacturers, and USP represent an impressive achievement of first-party (manufacturer) conformity testing. Manufacturers marketing in the United States pay close attention to a public monograph in *USP–NF*. Batches are tested to both private and public monograph procedures prior to batch release, and a batch is released only with assurance of conformity. As in the development process, a *USP–NF* monograph thus creates a safe harbor for a manufacturer and mitigates risk. If the article meets the compendial standard both at the time of release and throughout shelf-life, a manufacturer should be able to demonstrate to both an FDA inspector and the public at large that the article is of good quality and will achieve its expected safety and efficacy outcomes.

Many ingredients, including the active ingredient, used in the manufacture of a finished dosage form are purchased through suppliers. cGMPs require careful evaluation of these materials via quarantine and in-house testing and audit of the supplier. For suppliers that have been qualified, finished dosage form manufacturers and compounding professionals can at times rely on the integrity of the supplier and the latter's Certificate of Analysis. However, manufacturers may perform in-house testing, which sometimes can be extensive, to ensure the quality of purchased articles. This in-house testing is facilitated with the availability of a public monograph in *USP–NF* and an associated official USP reference standard. Failure to detect a counterfeit or substandard article can have serious consequences, as shown in the recurring deaths arising from diethylene glycol, a toxic chemical, mistakenly used as an excipient or at times contaminating an excipient.

REGULATORY OFFICIALS' STAKE IN PUBLIC STANDARDS

Regulatory reviewers may consider both compendial and noncompendial procedures in an application. The more firms rely on compendial standards, the less the need for private procedures. This, in turn, reduces the burden of analytical development for both characterization and batch release tests. The regulatory review burden can be reduced for *USP–NF* articles or when *USP–NF* procedures are cited. When determining whether a drug product is adulterated, inspectors can test according to *USP–NF* standards. In legal matters or cases of dispute in the United States, the *USP–NF* procedures are the official regulatory procedures, even though a manufacturer may be allowed to rely on other analytical procedures for release and shelf-life testing. Nonconformity to a public monograph in *USP–NF* can be a fast and efficient way to remove an adulterated or misbranded article from the marketplace as opposed to legal hearings. Indeed, many of the recalls that occur each week are manifestations of nonconformity to a public *USP–NF* standard. These recalls indicate that the regulatory system is working.

INTERNATIONAL VALUE OF PUBLIC STANDARDS

USP–NF standards are recognized worldwide, and several nations have adopted *USP–NF* standards for drug products marketed in their countries. Not all countries have regulatory processes as stringent as those of the United States. In those countries, public monographs in *USP–NF* can provide assurances of drug quality. Different countries may have dif-

ferent acceptance criteria, but even in these instances a *USP–NF* monograph can provide validated procedures for monograph tests. Without these standards, the uniformity, consistency, and quality of ingredients and products in global commerce could be deficient or absent.

CONCLUSIONS

A public monograph represents an opinion of the USP Council of Experts and its Expert Committees that the elements of the monograph are sufficient to identify the compendial article and to control its quality in the marketplace. The activity can bring a private consensus developed between a regulatory agency and applicant into the open and allows public scrutiny and endorsement. In some circumstances, the private and public standards may be similar or even identical, which is a desirable outcome. The public standard creates a level playing field for all manufacturers whereby individual approaches coalesce into a general public approach. From a public health perspective, it is highly valuable for all manufacturers to use the best, most relevant, and science-based analytical procedures that evolve with advances in science. Continuous updating of *USP–NF* facilitates this possibility. The public monographs of *USP–NF* thus can achieve, via testing to the standards of a monograph and with the use of official USP reference standards, the consistency sought by the founders of USP in 1820.

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