

A Series of White Papers
From the Five Sections of the
Council of the Convention

September 23, 2009



FOCUS ON: FUTURE DIRECTIONS FOR USP

At its core, the United States Pharmacopeial Convention (USP) is a standards-setting organization with an important national history and gathering recognition around the world. The USP leadership has transformed the organization in remarkable ways in the last decade and will depend on the wisdom and will of its member organizations to help guide it into the future—a future that promises to be equally amazing and challenging.

The Council of the Convention (CoC) is pleased to offer a series of white papers for member consideration. The white papers are an excellent source of information about USP for delegates and member organizations interested in understanding the nature of the USP Convention and its many activities. The papers describe:

- The current role and value of USP public standards
- Environments in which USP standards are used, or could be used
- Key challenges and opportunities facing the USP Convention as it attempts to realize its vision of a world where all citizens have access to high quality, safe and beneficial medicines and foods.

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ADVANCING HEALTH THROUGH PUBLIC STANDARDS



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WHITE PAPER

USP'S ROLE IN SETTING ENFORCEABLE QUALITY STANDARDS FOR MEDICINES

SEPTEMBER 23, 2009

COUNCIL OF THE CONVENTION SECTION ON
THE QUALITY OF MANUFACTURED MEDICINES

INTRODUCTION

For nearly two hundred years, the United States Pharmacopeial Convention (Convention or USP) has worked to set quality standards for drugs (medicines and their ingredients). Much has changed during that period, including the globalization of the pharmaceutical industry, ongoing availability of better drugs to promote health and treat disease, demands for access to good quality medicines, systems that deliver interchangeable multi-source products after periods of patent and market protection, advances in measurement and manufacturing science, and calls for regulatory and compendial harmonization. In these contexts, USP's public standards continue to play an important role in assuring both practitioners and patients that the medicines they use are of good quality relative to their safety and efficacy. If anything, recent events such as the rise in counterfeit and substandard medicines and adulteration crises (diethylene glycol, melamine, heparin) have heightened concerns about the quality of drugs, and reinforced the importance of USP's public standards as part of the safety net that protects practitioners and patients in the U.S. and elsewhere.

USP's standard-setting activities have a long and distinguished history. At the first meeting of the Convention in 1820, the convening practitioners established recipes for the first Pharmacopeia of the United States of America (*United States Pharmacopeia* or *USP*). These recipes were used in the preparation of medicines to assure their consistency—process standards for articles of medicinal commerce. In the latter part of the 19th century, Charles Rice, Chair of the Committee of Revision (predecessor of the Council of Experts), transformed the *United States Pharmacopeia* from a book of recipes to a book of tests with procedures and acceptance criteria for medicines and their ingredients—product standards for articles of medicinal commerce. The *National Formulary* (*NF*), originally a repository for preparations deleted from the *USP* when such preparations were deemed less effective, later became a compendium of excipient product standards. *NF* was acquired by the Convention in the 1970s, and *USP-NF* is published now as a combined text of documentary standards. In the early part of the 20th century, the Convention began offering reference



materials to assist analysts in the conduct of monograph procedures. Today the procedures for all monographs in *USP-NF* are likely to (or should) have an allied reference material.

USP's drug standards are given special force by their long-standing recognition in U.S. law. In the 1906 Pure Food and Drug Act, Congress created a role for the Federal government to enforce (assess conformity to) Convention standards by naming *USP* as an official compendium of the United States. Congress strengthened this role in the 1938 Federal Food, Drug, and Cosmetic Act (FDCA) and made USP's standards enforceable by the newly-created Food and Drug Administration (FDA) under the adulteration and misbranding provisions of the FDCA. *NF* was subsequently added as well as an official compendium of the United States. Today, the FDCA continues to mandate compliance with *USP-NF* standards, giving them broad impact across both the innovator and generic pharmaceutical industry. This legal status and the public-private partnership between the United States Federal government and USP created through these laws reflects a societal agreement recognizing the importance of public standards for both manufactured and compounded medicines. Many state laws also recognize USP's standards, reaffirming this societal agreement.

With this history in mind and looking towards the future, the Council of the Convention Section on Quality of Manufactured Medicines describes in this white paper ways that USP might be further transformed to better fulfill its historic and legal role of establishing quality standards for drugs and helping to address current challenges in assuring a safe global drug supply. A general thesis of this white paper is that the original societal agreement reflected in Federal and state laws tying the Convention and FDA together in the early part of the 20th century must evolve in today's environment to allow continued availability of public standards to help assure the quality of drugs. At the same time, modern measurement science allows opportunity for change that can transform USP and pave the way both for global harmonization and rapid detection of adulterated medicines.

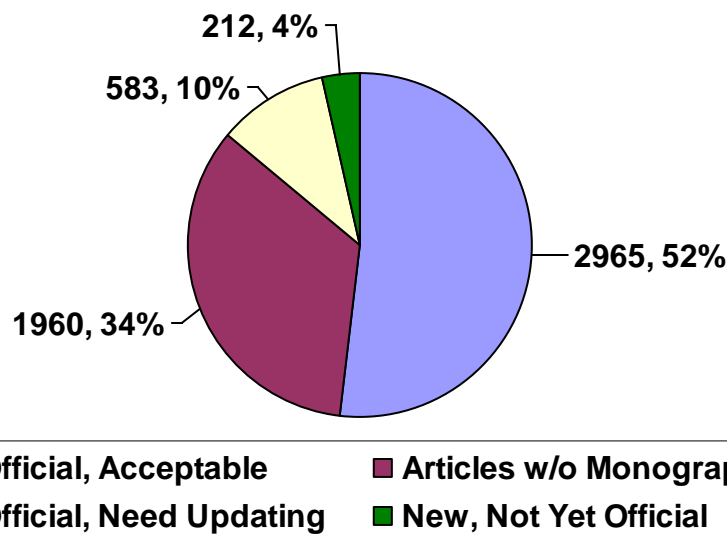
The *Overview* section below discusses the current status of USP standards, and the deficiencies that exist today in the *USP* and *NF*. The next section explains the challenges USP faces in acquiring and maintaining sound public standards. It also describes the innovative approaches USP has taken to address these challenges, and how USP is working to facilitate movement towards more harmonized standards while advancing the measurement science behind its standards. The last two sections explore the current societal problems of adulteration and contamination and ways that USP identity standards can play a role.

OVERVIEW AND CURRENT STATUS OF USP STANDARDS

Although the complexity of the discovery, development, registration, and utilization processes for a medicine can be staggering, the concepts behind these processes are straightforward. A medicine and its ingredients must have specified quality and be produced under good manufacturing practices. Based on consistency in quality attributes over time (sometimes termed "equivalence") relative to clinical study materials, practitioners and patients can expect predictable safety and efficacy outcomes when a medicine is administered. For new drugs, quality attributes are developed and maintained privately as part of the new drug application process and eventually, if a manufacturer is willing to provide this information to USP, can become public standards in *USP*. The private and public standards contain tests, procedures, and acceptance criteria that form the specification for the article, for both the medicine itself and its ingredients. Those in Congress and at USP framing the societal agreement embodied in the legislation of 1906 and 1938 may have expected a public standard for all medicines legally marketed in the U.S. While that expectation is currently expressed in USP's Board of Trustees strategic plan for the 2005-2010 cycle, it has not been realized. The table below indicates the current status of *USP* in terms of monographs in four stages: 1) approved drug

articles where no monograph exists, 2) articles with newly acquired monographs that are not official, 3) articles with official monographs that need updating, and 4) articles with official monographs reflecting the state of the industry.

Exhibit 1: USP Monograph Status



Note: Total USP Monograph Universe = 5720, as of June 23, 2009

The numbers indicate that about 44% of USP is deficient—either because of articles for which there are no monographs (34%) or because of monographs that need updating (10%).

MONOGRAPH ACQUISITION AND MODERNIZATION

1. CHALLENGES TO DEVELOPING AND MAINTAINING PUBLIC STANDARDS

A key reason for the lack of up-to-date monographs in USP lies in the fact that USP has no way to compel information and receipt of candidate materials to support a public monograph. Via the FDA Freedom of Information Act exemptions at 21 CFR Part 20, FDA is prohibited from giving USP the private regulatory specification—a prohibition generally termed trade secret or data protection. Manufacturers may resist voluntary donation of needed information and materials because of: 1) the need for some time after market access for controls in the private specifications to finalize, 2) the involved resource burden, and 3) a desire to protect trade secret information. Moreover, despite the fact that the societal agreement reflected in federal law does not distinguish between single-source and multi-source



drugs, the innovator industry sometimes questions the need and rationale for a public monograph prior to generic entry.

USP has been slow to develop a monograph in the absence of donated information and material because of the difficulty in developing suitable analytical procedures and certain science and technical constraints. For example, without knowledge of synthetic and degradation routes for a drug substance (active pharmaceutical ingredient or API), USP has little understanding of which impurities exist within a drug product or its ingredients. Similarly, understanding of degradant impurities requires special studies that are, for the most part, beyond USP's capability to conduct. Patent barriers may limit access to and availability of certain reference materials.

2. USP EFFORTS TO ADDRESS CHALLENGES

a. *Alternative Monograph Development Paths*

One way in which USP has attempted to respond to its monograph acquisition challenges is to develop alternative pathways for monograph development. These allow greater flexibility for manufacturers and may enhance the usefulness of monographs to manufacturers, regulators, and—ultimately—practitioners and patients/consumers.

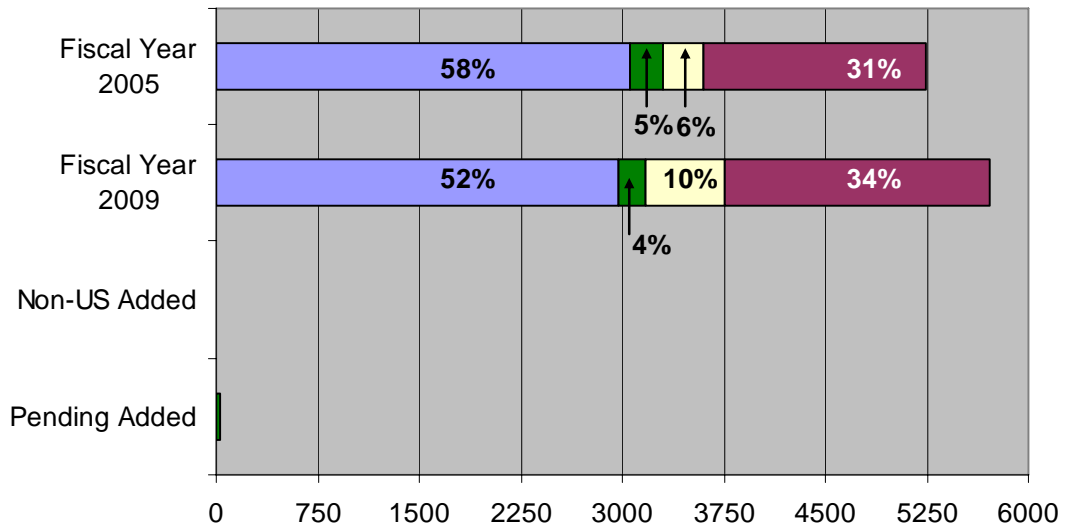
- The *flexible monograph* moves away from a “one size fits all” approach for the monograph's specification to an approach that allows differences in the tests, procedures and acceptance criteria of the monograph depending on routes of synthesis, differences in formulation, or other factors. This approach facilitates voluntary donation of information from multi-source manufacturers of pharmaceutical ingredients and products and reduces the likelihood of “lock-out” specifications from any single manufacturer.
- The *pending monograph* encourages voluntary submission of information and material to support a Web-based public monograph in advance of a regulatory decision, coupled with rapid advance to official status in *USP* at the time of regulatory approval. This approach is particularly applicable to multi-source manufacturers.
- A *non-U.S. monograph* allows USP to develop Web-based monographs for medicines and their ingredients that are marketed outside the United States. This approach is an effort to provide standards for manufacturers and the public interested in having a sound public monograph irrespective of (and at times in the absence of) strong regulatory systems. Thus, these monographs may be of special value to manufacturers, purchasers and regulatory authorities in developing countries who are seeking assurance of quality. The program is limited now to medicines and their ingredients intended to treat neglected infectious disease, and thus has a very targeted public health focus.
- The *performance based monograph* (PBM) is a new idea to USP, although the approach has been widely used by other industries. Conceptually, the model is straightforward. A PBM might consist of tests and acceptance criteria, as presented now, but the procedures of the monograph would not be specified. Instead criteria for an acceptable procedure would be provided, and over time a list of acceptable procedures would be made available. The approach is based on the availability of a qualified reference material, and this reference material preferably would be certified. The reference material would be the drug substance itself or an “equivalent” material, or one or more impurities.



Taken together, the general approach has many positive advantages, as well as features that merit special consideration. From a global standpoint, the approach might allow rapid advance towards compendial harmonization. Only the tests and acceptance criteria would need to be harmonized—the procedures themselves would be the responsibility of manufacturers and their corresponding regulatory agencies. Any acceptable procedure would be allowed for determining if a medicine or its ingredients were suitable for use. And these procedures could be public or private, depending on the interests of involved parties. The relationship between these repositories can be clearly understood based on modern metrological principles and careful collaborative studies. The PBM approach is still in the exploratory stage and there are many important questions to be answered, including those related to FDA's need for a default or referee procedure in a monograph to readily determine non-compliance with USP standards.

While all of these opportunities are of interest and have some value, those implemented to date have not had a substantial impact on the acquisition of new monographs or the updating of existing monographs. Comparisons of monograph backlogs at the beginning and close of the 2005-2010 cycle indicate a rise in the backlog (i.e. the number of articles for which there is no up-to-date monograph).

**Exhibit 2: Monograph Status Comparison
(Fiscal Year 2005 vs 2009 with Pending & Non-US Monographs)**



| | Pending Added | Non-US Added | Fiscal Year 2009 | Fiscal Year 2005 |
|-------------------------|---------------|--------------|------------------|------------------|
| Articles w/o Monographs | | | 1960 | 1646 |
| Official Need Updating | | | 583 | 301 |
| New, Not Yet Official | 27 | 5 | 212 | 235 |
| Official, Acceptable | | | 2965 | 3064 |



b. Sponsor Outreach and Prioritization Efforts

USP has increased its efforts in recent years to educate manufacturers as to USP's role and the value of public standards. In order to lessen the resources required from manufacturers to provide needed information, USP has assisted with monograph development—including providing easy-to-use templates for monograph submission and furnishing USP staff on-site at a manufacturer's facilities to work on monographs. Although these efforts seem to have been well-received, as the table above indicates they have not had an appreciable effect in increasing the development of USP standards.

Understanding that the effort needed to correct all of the deficiencies in *USP* is an immense challenge, USP has made efforts to prioritize its monograph acquisition and modernization activities so that it can conduct more targeted outreach to manufacturers. This includes working with industry to identify those monographs that are of greatest importance in terms of public health impact. Such prioritization activities help USP to more effectively utilize its acquisition resources, and make it easier for manufacturers to understand and allocate the resources requested of them for development of high-priority monographs. USP has also worked to expand the recognition it gives to sponsors of monographs and reference standards, so that it can more publicly acknowledge the contribution that monograph sponsors make to the public health. It is too early to tell whether these efforts will prove fruitful in increasing the quantity of monograph submissions.

3. INTERNATIONAL COMPENDIA AND COMPENDIAL HARMONIZATION

In today's global pharmaceutical market, the desire and need of industry for harmonized standards and requirements have become more pressing, and USP has recognized this. Harmonization of regulatory requirements has occurred in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) for countries and regions with advanced drug regulatory systems, and at the World Health Organization (WHO) for all countries. The primary mechanism for compendial harmonization has been the Pharmacopoeial Discussion Group (PDG), begun through Convention impetus in 1989, which continues to this date and operates in connection with ICH. PDG includes representation from organizations that elaborate the major compendia of the world—the *European Pharmacopoeia* (European Department for the Quality of Medicine and Health Care or EDQM), the *Japanese Pharmacopoeia* (Ministry of Health, Labor, and Welfare or MHLW), and USP, with WHO as an observer. WHO itself continues to elaborate *The International Pharmacopoeia*, which focuses on essential medicines. PDG does not work to harmonize monographs for medicines or their active ingredients; rather, PDG has concentrated on excipient monographs and allied general chapters (with 40 monographs and 26 general chapters concluded to date) and other non-excipient general chapters. PDG-harmonized documents may undergo a further evaluation in ICH to become guidances to assist in developing the private regulatory specification for the ICH regulatory agencies (FDA, Japan's MHLW, and the authorities of the European Union, including the European Medicines Agency). Recently, PDG participants agreed to continue and expand their work. However, the PDG process, which requires the pharmacopoeias to retroactively revise varying and conflicting standards to achieve harmonization, remains slow and laborious. Moreover, although a 2005 Convention resolution encouraged USP to broaden harmonization efforts outside of PDG, for the most part this has not occurred as a PDG activity, although all major pharmacopoeias hope for and at times realize opportunities to work together. USP has been particularly vigorous in these activities in this cycle, reflecting the intent of prior Convention resolutions.



Another harmonization opportunity has arisen through a pilot currently being conducted by USP and EDQM, known as “prospective harmonization,” in which a manufacturer works with USP and EDQM simultaneously on the development of a monograph and accompanying reference standard. The advantage of this approach is that a monograph would at least be harmonized between the *European Pharmacopoeia* and *USP* from the outset, avoiding the difficult process of attempting to harmonize such standards after the fact. In addition, because manufacturers benefit from obtaining a harmonized monograph through a single process, they may be willing to provide the necessary information and materials for such monograph and reference standards at an earlier stage in the life of the product. Although, again, it is far too soon to tell whether this new approach will be successful in significantly accelerating the development of harmonized monographs. Early phases of the pilot have proceeded well.

Harmonization with less-developed pharmacopoeias may also be advanced through USP’s “adopt/adapt” approach. Under this activity (started in the 1990s with plans to reinvigorate the general approach), USP permits pharmacopoeias in regions with limited resources to incorporate *USP* monographs and general chapters in their own pharmacopoeias as they see fit. While the primary purpose of this initiative is to help these countries develop better standards for use with their domestic manufacturers and raise the standard of quality in these regions, it may also result in de facto harmonization between *USP* and other pharmacopoeias.

4. MODERN MEASUREMENT SCIENCE

In recent years, USP’s standard development activities have been aided by its growing understanding and application of measurement science—termed “metrology.” Metrology is the science of measurement and embraces both legal and fundamental aspects. The societal agreement created by Congress between FDA and USP relies on metrology, which in this context helps assure that a material is fit for its intended use; i.e., that a medicine may be used suitably by practitioners and patients to maintain health and treat disease. Today, modern measurement science undergirds the tests, procedures, and acceptance criteria in USP’s standards.

Metrology originally was driven by needs of commerce, and commerce still is the major motivation for legal aspects of metrology. Fundamental metrology is of more academic interest and involves the establishment and realization of measurement units (such as the International System of Units or SI), research into new measurement methods, the development of measurement standards, and the transfer of metrological traceability throughout a measurement system. A country’s national metrology institute—in the United States, the National Institute of Standards and Technology—typically has statutory responsibility for a nation’s measurement system, including the advancement and maintenance of the nation’s primary standards. The interface of legal metrology and fundamental metrology is often called “applied metrology,” which concerns the application of measurement science to manufacturing, ensuring the suitability of measurement instruments, their calibration, and quality control of measurements. The Convention’s official compendia, *USP* and *NF*, represent the application of applied metrology, which includes both legal and fundamental metrology.

Through staff and Council of Experts’ activities, the Convention has worked to enhance metrological science in *USP*. In part, the way has been made easier by a general movement of national drug control laboratories (official medicines control laboratories) towards International Organization for Standardization (ISO) 17025 and other standards. These standards encourage traceability of results to enhance consistency and reliability of measurements. A specific example of the Convention’s use of applied metrology is release of a certified reference material as an official USP Reference Standard by the



Council of Experts Reference Standard Committee. Such certified reference materials may result in a better understanding of repositories of reference materials at the global (global primary), regional (regional primary), national (national primary), and manufacturer (secondary, house, or working standards) levels and their respective uses to assess the quality of drugs in global commerce. They also allow manufacturers, regulators, and others to compare results across different procedures—a critical task now with supplier-purchaser relationships in question—and also assess contributions of manufacturing and analytical variability to avoid “out of specification” results.

DETERMINING “QUALITY” MEDICINES: CONCEPTS OF ADULTERATION AND IDENTITY

In some respects, issues of adulterated or substandard medicine—and the challenges USP faces in trying to address these through compendial standards—are far from new. Even in the earliest edition of the *USP*, the presence of a recipe to assure consistency in the quality of what we would now term a “compounded medicine” could not protect against the possibility of a medicine that might be deemed unacceptable or adulterated. Efforts to protect patients gained great force in Congressional decisions of the early 20th century as the Federal government sought ways to remove medicines from the market that were unsafe, ineffective, and/or of substandard quality. Congress relied on the terms “adulteration” and “misbranding” in the FDCA, and it is in these provisions that *USP* and *NF* are specifically recognized as official compendia of the United States as a means of assessing adulterated or misbranded products. In modern terms, USP’s standards speak to the identity of a medicine, as well as its strength, quality, and purity—terms now comprised, through harmonization, under the overarching term “quality.” Our understanding of identity insofar as it relates to a medicine, its ingredients, and its packaging is rapidly evolving based on the science of spectroscopy. The use of both identity testing and spectroscopy to help combat today’s problems of substandard and intentionally adulterated drugs is addressed below.

1. ADULTERATION

Over the years, many countries around the world, including the United States have been challenged by economically motivated adulteration. Examples include melamine in pet food and infant formula, oversulfated chondroitin sulfate in heparin, and diethylene glycol in glycerin. Such instances involve the deliberate substitution of a less costly substance for a more expensive one, resulting in patient harm and even death.

USP’s role in helping to address these challenges stems from its legal recognition and the requirement under the FDCA that medicines meet the identity, strength, quality, and purity standards in *USP* relative to an established name, as discussed more fully below. Even a well manufactured medicine may at times fail these standards and must be removed from the marketplace or risk a claim of adulteration. The approach is used daily by manufacturers (first parties), and information about it is often publicly available at <http://www.fda.gov/Safety/Recalls/default.htm>. The public-private partnership established by Congressional and Convention forebears a century ago thus works still today—quietly and without notice—when a manufacturer tests a batch to assure it meets requirements in *USP* or withdraws a drug from the marketplace when it does not.

The matter becomes more challenging when manufacturers themselves may unknowingly or, worse, intentionally adulterate a medicine or its ingredients. Work at FDA and in the Convention is advancing approaches that rely on identity standards to reduce the likelihood of economically motivated



adulteration. Placement of limits on known adulterants in the Identification test of a *USP* monograph requires manufacturers of a medicine to test to assure absence of the adulterant prior to use of a material in manufacturing. The approach relies on knowledge of the adulterant and thus is limited to known examples. Unfortunately, there are many other materials that might be used to adulterate a medicine, either for economic or other motivations, which at this time remain unknown.

2. IDENTITY PROVISIONS IN THE FDCA

Identity standards (and related tests and reference standards) play an important role in defining or characterizing what is meant by a “drug” as defined in *USP*. The identity component of a compendial standard is distinct from the array of specifications related to strength, quality, and purity. Identity may not legally vary from the *USP* specifications, although strength, quality, and purity can, if a medicine is appropriately labeled. The 1906 Pure Food and Drug Act first officially recognized the role of *USP* standards for strength, quality, or purity in terms of defining when a drug would be deemed to be adulterated. The 1938 FDCA built on the 1906 Act with Section 501(b), which contains the more extensive, two-part, modern, *USP*-related provisions related to adulteration:

501(b) - “If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium. Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium,” FDCA 501(b).

The first highlighted section (yellow) creates an implicit compendial role in establishing standards for identity (i.e., is it, or is it not, the drug addressed in the compendium?). The second highlighted section (green) includes the explicit compendial role for standards related to strength, quality and purity (i.e., whether the drug measures up in terms of various quality parameters). FDA regulations subsequently established an important and unambiguous role for compendial standards of identity, and reflect the interconnection between the naming and identity authority in FDCA [at 502(e)] and the compendial adulteration standards [at 501(b)].

Part 299 of the Code of Federal FDA regulations concerns official and established names. One subsection in particular addresses the role of compendial naming and identity requirements, as well as other compendial standards; it has remained unchanged in FDA regulations since Part 299 was first promulgated in 1975 (40 Fed. Reg. 14041, March 27, 1975). Under FDCA and in Part 299, a drug with a name recognized in *USP* must comply with compendial identity standards or be deemed adulterated, misbranded, or both. Such drugs may vary in terms of strength, quality, or purity, if truthfully labeled [per FDCA 501(b)], but they may not vary from the compendial identity specified for such a drug.

As noted above, *USP* has worked with FDA to leverage this distinctive role of identity standards to address recent cases of intentional adulteration. These recent efforts reaffirm the value of the public-private partnership created in law and reinforce the ongoing importance of public standards in today’s environment.



3. THE ROLE OF SPECTROSCOPY

Identity frequently relies on use of portions of the electromagnetic spectrum to “see” an article — just as humans recognize each other (relative to their established names) by sight — which relies on the visible portion of the electromagnetic spectrum. For well-manufactured medicines, USP has long allowed the use of infrared (IR) spectra as a means of establishing identity in the USP Identification test (General Chapter <197> *Spectrophotometric Identification Tests*). And spectral images (photographs) have long been used by practitioners to identify medicines, e.g., *Physician Desk Reference (PDR)* photographs. Modern analytical instrumentation offers the opportunity to use far larger portions of the electromagnetic spectrum and with modern informatics and hand-held devices can now bring identity tests to any site on the globe for screening purposes. Using near-IR instrumentation, China’s government has led the way in the use of mobile vans and personnel to utilize this technology to check for counterfeit and substandard medicines.

USP has considered using Raman spectroscopy to assess identity in the field, and pharmaceutical manufacturers have built non-public spectral libraries to allow rapid identification of incoming materials. Results typically require confirmation via more in-depth laboratory studies—as with the eye, instrumentation recognizes what it has seen before. Consequently, identification of materials used to adulterate for economic or other purposes require additional study. But even here, understanding of likely adulterants would pave the way for spectral libraries using repositories of likely and potentially dangerous adulterants. For episodes of intentional adulteration, such as the production of fake medicines (counterfeits), rapid reporting systems might allow the detection of outbreaks of poor quality manufacturing, just as we now identify outbreaks of infectious disease. Thus, scientific advances in instrumentation and informatics, linked with repositories of spectral images of legally marketed medicines (and their ingredients and packaging), coupled with spectral images of undesirable materials and medicines, allow understanding of identity in ways that would have amazed Convention forbears 100 years ago. At the same time, the use of “sight” to establish the identity of a medicine and its ingredients would have been entirely comprehensible to them. USP intends to continue the exploration of spectral libraries as a potentially important weapon in the ongoing global battle against adulterated and substandard medications.

CONCLUSION

This white paper suggests several avenues that might be pursued to help resolve current deficiencies in the availability of public monographs and reference materials, promote compendial harmonization, advance the availability of good quality medicines, and detect and deter adulterated (counterfeit/substandard) medicines. The basic approach remains the concept of a public monograph containing product standards for all legally marketed medicines and their ingredients, allied with publicly available reference materials. The procedures of the monograph would be clearly linked to and supported by global, regional, national, and manufacturer reference materials for both the medicine (drug product) and its ingredients and their packaging. Availability of this material would allow comparisons across procedures and yield results, where feasible, traceable to SI units. Public reference materials would be a public repository of chemicals and mixtures of chemicals reflective of legally marketed medicines and their ingredients. The repository would also include likely adulterants. The materials of the repository would be associated with spectral images drawn from the electromagnetic spectrum to allow screening to assure identity and to detect and deter adulterants.



Many aspects of the approach are transformational. Yet none are beyond current scientific capability, nor would the general approach require major changes in policy, with possibly the exception of adjustment in barriers to the availability of reference materials. While full expression of the concept might await stronger global institutions, the approach could be implemented now nationally or regionally. The USP Convention might be a major advocate for advancing the general approach, working on the assumption that the Convention itself supports public standards for medicines and their ingredients—in the 21st century as it did in the 19th and 20th centuries—and recognizes the value of such standards in assuring patients and practitioners of good quality medicines.



WHITE PAPER

A MODEL SYSTEM TO PROMOTE ACCESS TO GOOD QUALITY COMPOUNDED MEDICINES

SEPTEMBER 23, 2009

COUNCIL OF THE CONVENTION SECTION ON
THE QUALITY OF COMPOUNDED MEDICINES

INTRODUCTION

Extemporaneous compounding of preparations is a worldwide practice dating back centuries. Today, compounding is commonly defined as the preparation of a medicine in accordance with a licensed practitioner's prescription or medication order. This definition evolves from a triad—the prescribing practitioner, the compounding professional, and the patient/consumer. Historically, what was once viewed as an art is now deeply rooted in the scientific study of how to prepare and assess compounded preparations, together with provision of stability data to allow assignment of a beyond-use date (BUD).

In the following white paper, USP's Council of the Convention Section on the Quality of Compounded Medicines provides a general description of non-governmental and governmental approaches to provide compounding standards and conformity assessment to these standards. Conformity assessments may be conducted by various parties—first (compounding group/individual), second (purchasing group/individual), or third (group/individual independent of first or second party). While data are limited, all types of conformity assessments are likely to be conducted in the United States. The white paper then articulates a proposal for a model system of standards and conformity assessments to standards that assure access to good quality compounded preparations.¹

¹This paper is intended to address both compounding for human use and compounding for veterinary use. However, there are some significant differences between the two, including differences in the relevant laws. The federal laws regulating veterinary compounding are found in the Animal Drug Amendment of 1968 and the Animal Medicinal Drug Use Clarification Act of 1996 (and related regulations and guidances) which are intended to protect consumers of foods of or from animals, as well as the animals themselves that might be treated with drugs, including compounded preparations. As with compounding for human use, there is controversy surrounding the distinction between legitimate compounding and manufacturing; the scope of the FDA's role in regulating veterinary compounding; and the efficacy, safety, and appropriate labeling of these products, as well as other issues. A detailed discussion of the particular considerations that apply in the veterinary context is beyond the scope of this paper, but USP is committed to providing standards for compounding of preparations for both human and animal use, and the information and model system proposed herein is generally applicable to both human and veterinary compounding.



UNITED STATES NON-GOVERNMENTAL APPROACHES

1. USP: PREPARATION AND PROCESS STANDARDS

The compounding of the most “fully established and best understood” preparations for patient use was a founding principle for USP’s volunteer practitioners in 1820. USP still takes an active role in supporting the public’s access to the type of customized therapy offered by compounding and works to ensure the quality of such therapy by creating national standards and guidelines for compounding both sterile and nonsterile medications. These standards are process standards in that they provide appropriate techniques and procedures to guide practitioners in compounding. They also are product standards (commonly referred to as *preparation* standards to distinguish compounded formulations from manufactured products) to allow testing, both of the materials used in a compounded preparation and also the compounded preparations themselves, to assess quality and establish a BUD. Taken together, these preparation and process standards appear in official compendia of the United States—the *United States Pharmacopeia (USP)* and *National Formulary (NF)*. Just like manufactured medicines, compounded preparations must comply with the product standards in the *USP* and *NF*, which are recognized as official compendia in federal food and drug law. In addition, a number of States recognize USP’s process standards for compounding and require compliance with these standards. These legal requirements are discussed further below.

In the 2005-2010 cycle, USP supported two Expert Committees that provided these compounding standards. The Compounding Pharmacy Expert Committee of USP’s Council of Experts is composed of 10 experts, with proven extemporaneous compounding expertise representing varied pharmacy environments such as hospital, ambulatory, academia, veterinary practice, and private practice. The Sterile Compounding Expert Committee of USP’s Council of Experts is composed of 12 experts, also representing a wide range of pharmacy disciplines and infection control. These two Expert Committees: 1) develop compounded preparation monographs that can be used every day by pharmacists to prepare medications for patients requiring customized drug therapy, and 2) develop and revise General Chapters that describe good compounding practices.

As an emanation of the standards from USP’s two Expert Committees in the Council of Experts, USP supports several compounding constituencies through publication of the *Pharmacists’ Pharmacopeia (P2)*, now in its second edition. *P2* contains more than 115 compounding monographs, for use in both humans and animal patients, and 75 supporting General Chapters, all of which were excerpted from the *USP* and *NF*. In USP’s ongoing effort to develop more preparation monographs, academic and other laboratories are performing method development and stability studies for both sterile and nonsterile preparations. When these studies are completed, they provide information to support decisions of the compounding Expert Committees relative to a BUD designation. Currently, 17 compounded preparations are under study. USP also is reaching out to professional organizations and others to obtain candidate formulations, materials, tests, procedures, and acceptance criteria for the two compounding Expert Committees. The total universe of formulations needed for compounded preparations is unknown, but is well over 1,000. USP is attempting to focus on those that are most commonly compounded or that present the most significant risk.



2. PROCESS STANDARDS/CONFORMITY ASSESSMENTS FOR SITE ACCREDITATION

The Pharmacy Compounding Accreditation Board (PCAB) was launched in 2004 by eight pharmacy-related organizations (including USP) as a voluntary accrediting body to assess compounding pharmacies against high quality standards for compounding. The founders of PCAB, and the pharmacists they represent, believed that standards against which compounding pharmacies can be tested are not only good for patients, but also good for the practice of pharmacy.² To date, PCAB has accredited 65 compounding pharmacies. Each PCAB-accredited pharmacy undergoes a rigorous review of its policies and procedures and an onsite inspection against PCAB standards, which incorporate USP standards.

The pharmacies that have achieved the milestone of PCAB accreditation have demonstrated their commitment to quality standards and procedures. However, participation levels in PCAB are less than hoped for among U.S. pharmacies, which include approximately 3000 to 4000 pharmacies that emphasize compounding capability. This may be attributed to the rigor of the accreditation process and the absence of “drivers” that would compel pharmacies to seek accreditation, e.g., reimbursement and insurance. Nevertheless, PCAB in recent months has seen an upswing in applications with over 140 pharmacies awaiting survey. Emerging “drivers” include professional organizational endorsements of PCAB (beyond PCAB’s governing board institutions), including the American Medical Association, American Veterinary Medical Association, American Animal Hospital Association, American Association of Equine Practitioners, and others, as well as incentives offered by liability insurers.

In 2008, PCAB established a separate Accreditation Committee that now oversees the accreditation process, and more recently began the first formal review of PCAB standards since their adoption in 2004. The revised standards are expected to be available before the end of 2009.

3. CONFORMITY ASSESSMENTS FOR PRACTITIONERS

There are several organizations and accreditation activities that speak to conformity assessments for practitioners. The Accreditation Council for Pharmacy Education (ACPE) is the national agency responsible for the accreditation of professional degree programs in pharmacy. ACPE sets accreditation standards and guidelines for pharmacy education and conducts conformity assessment of institutions. Standardized assessment of practitioner competence also occurs through the North American Pharmacists Licensure Examination (NAPLEX) developed by the National Association of Boards of Pharmacy (NABP). NAPLEX is used by boards of pharmacy as part of their assessment of pharmacy practitioners’ competence prior to licensure. Certification through the Board of Pharmaceutical Specialties (BPS) is one additional conformity assessment for practitioners. BPS certification is a voluntary process by which a pharmacist’s education, experience, knowledge, and skills in a particular practice area are confirmed as well beyond what is required for licensure; however, there is currently no BPS specialty in compounding.

² Pharmacy Compounding Accreditation Board, www.pcab.info 2009.



UNITED STATES GOVERNMENT APPROACHES

1. FEDERAL

The role of federal law and regulatory oversight of compounding has proven to be one of the most problematic for FDA, particularly in recent years. As a general rule, FDA has tended to avoid involvement with activities that relate to the practice of medicine and pharmacy, both of which traditionally are regulated at the level of the states in the U.S. However, FDA pays close attention to the quality of products regardless of whether they are manufactured products or compounded preparations. Sorting out the scope of state versus federal authority, and the demarcation between compounding and drug manufacturing, has proven elusive. Congressional efforts to resolve the issue have so far failed. For now, there is a legal and regulatory stalemate, leaving compounding practitioners and regulatory authorities in a state of uncertainty.

The federal legal history leading up to this point helps illuminate the current situation. In FDA's view, compounded drugs in interstate commerce are "drugs" under the Federal Food, Drug, and Cosmetic Act (FDCA), and are potentially subject to the full panoply of requirements (including pre-approval prior to marketing, such as a New Drug Application (NDA), good manufacturing practices (GMPs) required for manufacturing, and compliant labeling). In recognition of the role of compounding, FDA has generally, in the exercise of its enforcement discretion, excused such compounded drugs from most requirements otherwise applicable to "drugs." In particular, under FDA Compliance Policy Guidance (CPG) 460.200, eligible compounding has been exempted from: the adulteration provisions of the FDCA with respect to GMPs; the misbranding provisions regarding labeling with adequate directions for use; and the new drug requirements, that is, approval of an NDA or Abbreviated New Drug Application (ANDA).

In 1997, Congress sought to codify many aspects of FDA's compounding policy and generally provide a limited regulatory exemption from certain requirements of the FDCA for compounding. Section 127 of the FDA Modernization Act (FDAMA), which added §503A to the FDCA, in large part reflected CPG 460.200, and, among other things, provided that bulk drug substances used for compounding must comply with *USP* or *NF* requirements. To identify the compounding eligible for the less stringent regulatory requirements of 503A, Congress stipulated that such eligible compounders could not "advertise or promote the compounding of any particular drug, class of drug, or type of drug," although the "compounding service" itself could be advertised and promoted. These limits on advertising were found by the 9th Circuit U.S. Court of Appeals in the *Western States* decision to be unconstitutional; moreover, the 9th Circuit held that the advertising restriction was not severable from the rest of FDCA 503A, thereby leaving at least the 9th Circuit in a pre-FDAMA condition (in terms of the application of the overall FDCA). The Supreme Court later affirmed *Western States*, but declined to consider the severability issue. More recently, the 5th Circuit declined the request of pharmacists to find that compounded drugs are exempt from the "new drug" provisions of the FDCA, but also found that the unconstitutional advertising restrictions of FDCA 503A are severable (leaving what some now call a "503A safe harbor").



Thus, in the 5th Circuit, 503A, absent the advertising provision, applies to eligible compounders. Elsewhere in the country, FDA’s current compounding policy continues to be reflected in the CPG it issued in the wake of the *Western States* decision.³

While these federal uncertainties are sorted out, USP continues to play an important role: 1) state law may incorporate USP process standards (e.g. General Chapters <797> *Pharmaceutical Compounding – Sterile Preparations* and <795> *Pharmaceutical Compounding – Nonsterile Preparations*) in regulating the practice of compounding, and 2) compounded preparations remain “drugs” under the FDCA and must comply with any applicable USP monographs if they use the name recognized in *USP-NF*.

2. STATE

In the U.S., pharmacy practice, including compounding, is regulated at the state level by state boards of pharmacy. Each state establishes and enforces its own laws and regulations governing the practice of pharmacy and performs routine inspections of pharmacies to ensure compliance. State boards also issue licenses to pharmacists—evaluating their competence to practice—and to pharmacies. When needed, state boards also investigate complaints. There are times when states recognize standards from non-governmental third parties; for example, several states recognize *USP* for sterile and nonsterile compounding and, to a more or lesser degree, other *USP* standards related to compounding, drug product labeling and packaging.

In an effort to maintain a certain level of consistency among the states, NABP offers to boards of pharmacy model language that may be used when developing state laws or board rules. The current set of model regulations also contains the NABP Model Rules for Pharmacy Interns, Institutional Pharmacy, Pharmacist Care, Nuclear/Radiologic Pharmacy, and Sterile Pharmaceuticals.

NON-U.S. APPROACHES

1. ARGENTINA

In Argentina, the Health Department regulates the practice of pharmacy compounding. Legal difficulties abound for compounding practitioners because there are few established regulations to guide compounding practices and the guidelines that do exist are based on outdated legislation. Technical and scientific advances in drug therapy are not considered in the guidelines. Even though the regulatory framework may be lacking in certain respects, some restrictions do exist that ultimately limit patient access to medicines. For example, several dosage forms and therapeutic categories—such as troches, nasal preparations, and ophthalmics—are excluded and hormone replacement therapies, as well as medicines the U.S. would term over-the-counter, are not permitted to be compounded. In addition, Olanzapine (*Zyprexa* for schizophrenia/acute manic episodes) is the only drug that cannot be used in compounding.

³ <http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm>.



2. BRAZIL

The Brazilian National Health Surveillance Agency (ANVISA) regulates compounded pharmaceuticals. In 2005, ANVISA proposed new rules for compounding pharmacies, including:

- Disallowing compounded drugs of the same formulation as manufactured products;
- Setting limits on the marketing of products to the general public; and
- Requiring the pharmacist to provide the patient with more product information, including the drug formulation, adverse effects, and duration of treatment.

Veterinary pharmaceuticals are regulated by a number of different agencies, including the Ministry of Agriculture and the Ministry of Agriculture, Cattle and Supplying. Brazil appears to be one of the most advanced countries in regards to compounding. Brazil has 306 Schools of Pharmacy and graduates 14,000 pharmacists per year. In contrast the U.S. has slightly over 100 Schools of Pharmacy. There are 7,211 pharmacies in Brazil that are solely engaged in compounding and 16,000 compounding pharmacists. Brazil offers Continuing Education (CE) on compounding over standard TV channels throughout the country. ANFARMAG is Brazil's National Association of Compounding Pharmacies and has a membership of over 4,000 pharmacists.

3. GERMANY

Federal Law, primarily the *Arzneimittelgesetz*, and subordinate federal directives, primarily the *Apothekenbetriebsordnung*, regulates the practice of pharmacy compounding in Germany. Extemporaneous preparation is mandatory when a prescription requiring compounding is presented to a community pharmacy. All dosage forms can be compounded; however, preparations that are difficult to compound (e.g. cytotoxic preps, injectables) can be compounded only after a pharmacist has completed special training. Over-the-counter (OTC) compounding is allowed and occurs frequently. There is a list of preparations that both community pharmacies and hospitals are not allowed to prepare, such as allergens used to trigger an allergic response in a patient. Beyond-use dating for 243 standardized formulas is provided in the *Neues Rezeptur-Formularium (NRF)*. There are 21,570 pharmacies in Germany.

4. SPAIN

In Spain, regional governments regulate the practice of pharmacy compounding. Four levels of compounding exist: 1) Dispensing; 2) Topical; 3) Oral, rectal and vaginal; 4) Sterile. Beyond-use dates for compounded preparations are based on literature and references, such as *USP-NF*. Health authorities in Spain have a very restrictive attitude toward pharmaceutical compounding. Compounded medicines are generally regarded as the last resource and authorized almost exclusively when all other therapeutic alternatives have failed. Pharmacies that only engage in compounding are not allowed. If a pharmacy only performs Level 1 compounding; i.e., dispensing, it must subcontract with a pharmacy that does other levels of compounding because it is against the law to refuse to serve any patient that enters a pharmacy. "Elaboracion a terceros" (third-party compounding) is the term used when a pharmacy contracts with another pharmacy specializing in higher-level compounding. Spanish patients receive most of their prescription medicines free or at little cost. However, compounded preparations are reimbursed according to a drug list that, according to Spanish practitioners, is currently out of date. Pharmacists are allowed to compound OTCs for sale in their own pharmacies, with the only limitation



being that the medicine must be described in the Formulario Nacional (National Formulary). Additional specialized training is not required to be a compounding pharmacist. AEFF is the Spanish Association of Compounding Pharmacists.

A MODEL SYSTEM

The goal of any model system is to assure access to good quality compounded medicines, assist compounding practitioners—pharmacists and physicians—in delivering such preparations to patients, and ensure patient safety, above all. While a number of standards, including USP's, exist to help ensure that compounded medicines are of good quality, the lack of strong conformity assessments to such standards leaves both practitioners attempting to provide access to good quality compounded medicines as well as patients/consumers who receive them at risk. In this setting, the Council of the Convention Section on Quality of Compounded Medicines offers the following model system of standards and conformity assessments, in which USP would play a primary role in developing monographs and process standards and could play a role in other areas as well.

1. PEOPLE, PROCESS AND PREPARATION STANDARDS

- Ingredient and Preparation Standards (Product)

Optimally, a preparation monograph in *USP* exists for all compounded preparations in the U.S. Compounding monographs are prioritized so that standards for the most frequently compounded articles are developed first. The Compounding Expert Committee, working with compounding practitioners, associations and others, develops a preparation monograph. The Committee takes into account safety and other considerations, such as intended use in target species. This input is obtained through a variety of sources, including FDA (whose views are represented by FDA liaisons to the Committee), NABP, and other practitioner and board associations. As noted above, conformance to such monographs is required under the FDCA.

- Compounding Sites Standards (Practice and Process)

Optimally, practitioner associations and others, including associations representing state practitioner boards such as NABP, develop standards for all compounding sites (both in community and hospital locales where compounding is practiced, as well as practitioner office practices). Practice standards (<795>, <797>, and others) developed by USP for compounding are recognized in state regulations and accreditation standards (similar to the treatment of compounding provided by NABP in its Model Pharmacy Act and Pharmacy Rules).

- Practitioner Training and Accreditation (People)

Adequate professional education and training curricula are adapted in schools of pharmacy to ensure that competencies in compounding are acquired and are supported by assessment through NAPLEX and licensure requirements through the state boards. An independent certifying body, such as BPS, builds an accreditation to define specialty certification of compounding practitioners. Optimally, all practitioners who compound complex or sterile preparations beyond a certain frequency are certified.



2. CONFORMITY ASSESSMENTS

- Site Accreditation

Through Congressional and/or judicial and regulatory determinations, the line between compounding and manufacturing is clarified, with the states retaining responsibility for regulation of compounding and FDA retaining responsibility for regulation of manufacturing. State boards of pharmacy (and other disciplines' boards), working with PCAB or equivalent national practitioner associations, are responsible for conformity assessments of all compounding sites. When appropriate, a state board may deem non-governmental bodies, such as PCAB or equivalent associations, suitable to accredit traditional compounding sites. Optimally, all sites engaging in significant compounding activity require accreditation.

- Adverse Event Reporting

An adverse event reporting system that offers strong Federal confidentiality and privilege protections, as provided by the Patient Safety Act of 2005, is provided and maintained to ensure the capture of adverse events associated with compounded preparations, for deliberation and analysis regarding quality and safety.

SUMMARY

As a general matter, compounding remains both a responsibility for practitioners (those who prescribe compounded medicines as well as those who compound them) and an opportunity for their patients. At the same time, assurance that manufacturing does not occur under the guise of compounding is critically important. This white paper argues for a model system, building on good systems in the U.S. and other countries, that recognizes the interests of all parties in assuring access to good quality compounded preparations.



WHITE PAPER

IMPORTANCE OF STANDARDS IN ASSURING GOOD QUALITY FOOD INGREDIENTS AND FOODS

SEPTEMBER 23, 2009

COUNCIL OF THE CONVENTION SECTION ON THE
QUALITY OF FOOD INGREDIENTS AND DIETARY SUPPLEMENTS

INTRODUCTION

Most recent public concern and policy discussions about issues for food safety focus on surface (microbial) contamination, where substantial morbidity and mortality occurs in the United States (U.S.) each year. However, recent incidents of intentional adulteration of food with melamine have shown that harm arises not only from microbes, but from deliberately-added inappropriate substances as well. Within the U.S., the ability of regulatory bodies and food manufacturers to provide safe, high quality food to consumers is challenged by: 1) the increase in global trade, which places enormous competitive pressure on companies that, in turn, may put good quality and safe foods at risk; 2) supply chains that are longer, more complex, and international; and 3) fragmentation of the U.S. food regulatory framework, which is split among multiple agencies and levels with each frequently lacking sufficient resources. Further, if one looks at the value of all processed food sold globally—\$3.2 trillion—the significance to global economies becomes obvious. This huge market is supported by a complex web of domestic and foreign food and food ingredient suppliers. Could the United States Pharmacopeial Convention (USP) help in some way? Does USP have an obligation to do what it can within its standards-setting role to protect U.S. citizens and people around the world from tainted foods and food ingredients?

In general, standards may be voluntary or mandatory and may originate from governmental and non-governmental sources. Conformity assessments to standards may be performed by first (manufacturer), second (purchaser), and third (individual independent of manufacturer and sellers) parties. As a standards-setting organization, USP has been recognized for publishing quality standards in the *United States Pharmacopeia (USP)*, (for drugs and biologics) and the *National Formulary (NF)* (for excipients). Over time, dietary supplements were added to the *USP* and now these standards have also been published in a separate compendium for the dietary supplements industry, the *USP Dietary Supplements Compendium*. USP further expanded its standards-setting activities to food ingredients, and these standards are published in the *Food Chemicals Codex (FCC)*. *USP* and *NF* are official U.S. compendia, recognized in the Federal Food, Drug, and Cosmetic Act (FDCA), and are thus mandatory in the U.S. for drugs (and for dietary supplements that are represented to be in compliance with official standards). As discussed further below, *FCC* is not named in



the FDCA and thus, except for certain isolated and specific regulatory references to specific *FCC* monographs, compliance with *FCC* standards is voluntary in the U.S. In certain other countries, as also discussed below, compliance with *FCC* standards may be required.

This white paper is offered by the Council of the Convention Section on the Quality of Food Ingredients and Dietary Supplements to stimulate discussion on the role of a volunteer-driven, standards-setting body in generating sound food and food ingredient standards and assessing conformity to these and other standards. Although overlap and similarities in use, production, and regulatory framework exist between food ingredients and dietary supplements, this document focuses on food ingredients.

BACKGROUND

The concept of a safe food supply for the world is of vital importance to the entire global community. However, many different approaches to regulating food and food ingredient safety, including the use of standards, exist throughout the world. Some individual countries have been developing their own regulations and standards for foods over the years, while others are more recently establishing their own systems to provide a safe food supply for their country. In addition, the United Nations established a food standards program several decades ago primarily to promote the coordination of various food standards activities around the world, but also to provide food safety standards for any country wishing to adopt World Health Organization (WHO) standards as a basis for their own food safety program.

This document, while not comprehensive, provides information regarding the approach to food safety and regulations both from an international perspective and within several specific countries. The white paper also provides information for consideration of the future role of the USP and its compendium, *FCC*, in food ingredient standards and regulations.

INTERNATIONAL APPROACHES

1. CODEX ALIMENTARIUS

The rules of global trade are set by the World Trade Organization (WTO)¹, which defers to the Codex Alimentarius Commission (CAC) for questions regarding food safety and standards. Created in 1963 by the United Nations' Food and Agriculture Organization (FAO) and the WHO, the CAC develops food standards, guidelines, and related texts, such as codes of practice under the Joint FAO/WHO Food Standards Program. The main purposes of the CAC are to protect consumer health, ensure fair food trade practices, and promote coordination of food standards activities undertaken by international governmental and non-governmental organizations. The general food standards adopted by the CAC are known as the *Codex Alimentarius* or food code. The CAC has established numerous committees to advance standards for consideration by the Commission. These include: 1) the Codex Committee on Food Additives (CCFA), 2) the Codex Committee on Contaminants in Foods (CCCF), 3)

¹ The World Trade Organization (WTO) is the only global international organization dealing with the rules of trade between nations. The U.S. is represented by the Office of the United States Trade Representative. For further information, see www.wto.org and www.ustr.gov.



the Codex Committee on Methods of Analysis and Sampling (CCMAS), 4) the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU), and 5) the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The importance of CAC standards has been strengthened through their incorporation into the Sanitary and Phytosanitary Measures (SPS) and the Technical Barriers to Trade (TBT) Agreements of the WTO. These agreements uphold *Codex Alimentarius* standards as one of the “international standards, guidelines or recommendations” necessary for protecting human health. CAC standards have been applied to settle disputes on global food trade. International Organization for Standardization (ISO) standards (see below) also are incorporated in the TBT agreement.

USP/FCC has applied for observer status in CAC, and is awaiting a decision on its application.

2. JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international scientific expert committee administered jointly by the FAO and the WHO. JECFA has evaluated more than 1500 food additives, approximately 40 contaminants and naturally-occurring toxicants, and the residues of approximately 90 veterinary drugs. The safety review of a food additive by JECFA is often time consuming, and the committee has a significant back-log of new ingredients to review. The following represents some of the work of JECFA and allied FAO and WHO groups.

- 1) *Combined Compendium of Food Additive Specifications*—four volumes based on JECFA decisions from the first to the 65th meetings (1956 to 2005); the fourth volume in the series provides procedures, similar to AOAC Official Methods of Analysis;
- 2) WHO Food Additive Series—monographs containing biological and toxicological data as well as exposure assessments with references;
- 3) WHO Technical Report Series—reports summarizing the conclusions of the Committee, with concise toxicological evaluations and exposure assessments;
- 4) A web site that provides general analytical procedures for colorants.

3. INTERNATIONAL ORGANIZATION FOR STANDARDIZATION

The International Organization for Standardization (ISO)² is the world's largest developer and publisher of international standards. ISO publishes numerous standards regarding food analysis and composition and the most broadly recognized third party quality systems, ISO 22000:2005, “Food safety management systems -- Requirements for any organization in the food chain.” ISO standards are voluntary by nature, however, recognized by WTO under the TBT agreement, and, while not referenced in U.S. law, are often incorporated into national legislation in many countries.

² The American National Standards Institute (ANSI) represents the U.S. in ISO. For more details, see www.iso.org and www.ansi.org



4. GLOBAL FOOD SAFETY INITIATIVE

The Global Food Safety Initiative (GFSI), an industry association, established a very comprehensive third-party audit system that within the U.S. is jointly operated by the American National Standards Institute (ANSI) and the Grocery Manufacturers Association (GMA) under the name Safe Quality Foods (SQF). SQF has gained significant momentum in the last few years, mostly due to the fact that the world's largest food retailer mandated SQF certification from most of its suppliers.

2. NATIONAL/REGIONAL APPROACHES

Selected national and regional approaches to food quality and safety standards and conformity assessment to these standards are briefly summarized below. In general, most countries distinguish between food additives that are the subject of premarket approval and food ingredients that are subject to other regulatory processes.

1. CANADA

In Canada, food additives must comply with relevant specifications in regulations issued by Health Canada. If no such regulations exist, food additives must meet the specifications of the *FCC* 4th Edition "as amended from time to time." The definition of "food additive" excludes spices, most vitamins, minerals, some amino acids, natural extracts, food packaging materials, and food ingredients. *FCC* occupies a supporting position in Canada as a source of information on the identity and specifications of food additives and related substances. Thus, when there is no official Canadian regulatory specification, a food additive manufacturer must comply with the specifications contained in the current edition of the *FCC*.

2. CHINA

The Ministry of Health publishes food additive standards in "Health Standards for the Use of Food Additives." China develops its food additive standards based on *Codex Alimentarius*, not *FCC*. Because of the recent devastating human and economic consequences resulting from the adulteration of toothpaste, pet food, and infant formula products made in China, the Chinese government is assigning increased importance to the issue of food safety. China is also consolidating its regulatory approaches for assuring food and food ingredient safety in the Bureau of Safety in the Ministry of Health.

On February 28, 2009, China enacted the *Food Safety Law and Hygienic Standard for Uses of Additives in Food Containers and Packaging Materials* of the People's Republic of China, which became effective on June 1, 2009. The new law consolidates disparate food standards and regulations into one unified national standard. The new law strengthens monitoring and supervisory powers, toughens safety standards, mandates the recall of substandard products, and subjects offenders to severe sanctions.³ The law also includes provisions for third party testing and encourages importers to follow standards that are more strict than the national standards developed by the Ministry of Health. It is too soon to know what

³ *China Legal Developments Bulletin*, Volume 16, No. 2, April – June 2009, Baker & McKenzie (2009).



impact the new law will have in addressing the Chinese government's concerns and in providing assurances of food safety to the global community.

3. EUROPEAN UNION

The European Union (EU) food safety policy is based on a comprehensive and integrated approach mandating traceability through all sectors of the food chain from “farm to fork,” i.e. feed production, primary agricultural and livestock production, food processing, storage, transportation, and retail sale. This approach is also built partly on the principles of Hazard Analysis and Critical Control Point (HACCP), a risk-based prevention and verification model. While food manufacturers and operators are primarily responsible for compliance with EU food and food additive standards, competent authorities appointed by the EU in Member States are responsible for monitoring compliance with the standards.⁴

The EU food safety approach is considered to be one of the more comprehensive approaches practiced by food importing nations. The food additives standards are primarily based on those set by the CAC but may be more stringent. Although the EU officially does not recognize *FCC* standards, some European Commission agencies, such as the European Food Safety Authority (EFSA), are aware of *FCC* and refer to *FCC* standards when setting their own guidelines on new food additives and flavorings.

The EU has mandatory food and food additive standards that apply to domestic and international parties, who grow, manufacture, distribute, and market food products in the EU. The standards are mentioned in various regulations of the European Parliament and Council and directives of the European Commission. All EU Member States are required to follow these standards. The Member States can formulate national laws and standards on food ingredients within the broader framework of the standards and guidelines outlined in the various EU laws.

4. INDIA

In India, several laws deal with food safety. The most important of these laws is the Prevention of Food Adulteration Act, which provides a list of food standards.⁵ The other significant piece of food safety legislation is the Food Safety and Standards Act of 2006 which establishes the Food Safety and Standards Authority of India, the primary standard-setting body for food and food additives⁶. This Indian authority is the counterpart of the U.S. Food and Drug Administration (FDA) for foods.

Although India's Prevention of Food Adulteration Act requires Indian food ingredient standards to be based on international standards, it does not specify or define which international food ingredient standards should be used. Therefore, *FCC* could be used as a resource for developing quality specifications. However, the Ministry of Health and Family Welfare (MHFW), which is in charge of

⁴ European Commission (2000). Council Directive 2000/29/EC.

⁵ MLJ (2004). *The Prevention of Food Adulteration Act & Rules* (as on 10/1/2004). Retrieved from the MHFW website. URL: <http://www.mohfw.nic.in/pfa%20acts%20and%20rules.pdf>

⁶ MLJ (2006). *The Food Safety and Standards Act*. Retrieved from the MHFW website. URL: <http://www.mohfw.nic.in/Food%20Safety%20Standard%20Act.pdf>



setting food additive standards through its Notifications, requires these standards to be based on *Codex Alimentarius*.⁷

In addition to the mandatory standards required by MHFW, the Government of India's Department of Marketing and Inspection (DMI) formulates its own standards on food additives. Compliance with these standards is voluntary for manufacturers, suppliers, retailers, and importers of food ingredients. Those who comply with these standards, receive the Agmark certificate from the DMI, providing a grade for agricultural and related products. The products are tested for compliance with national standards and to discern whether they are adulterated.⁸

5. UNITED STATES: GOVERNMENT

Congress/Food, Drug, and Cosmetic Act

In the U.S., the controlling law for much of the food supply is the Federal Food, Drug and Cosmetic Act (FDCA). Under the FDCA, which applies to food in interstate commerce, "a food shall be deemed to be adulterated if it bears or contains any added poisonous or added deleterious substance ...that is unsafe" or "if it is otherwise unfit for food."⁹ The FDCA defines a "food additive" as "...any substance, the intended use of which results or may be expected to result, directly or indirectly, in it becoming a component or otherwise affecting the characteristic of any food ...if such substance is not generally recognized among experts qualified by scientific training and experience...to be safe under the conditions of intended use." The 1958 Food Additives Amendment requires a strict premarket approval regimen and safety standard. Prior to marketing, new food additives are presumed to be unsafe for their intended uses unless and until they are proven "safe" on the basis of scientific data and information. Safe is defined as "reasonable certainty of no harm." The petitioner bears the burden of proof of safety and must present to the FDA all safety data concerning the proposed uses of the food additive. These data are reviewed by FDA scientists who independently determine if the data support the safe use of the additive.

Congress is currently in the process of amending the FDCA in an attempt to enhance the safety of the U.S. food supply for consumers, provide industry with clear regulatory direction, and develop a funding plan. Congress is keenly aware that the U.S. food economy is dependent on the sourcing of food and food ingredients beyond U.S. borders. Unfortunately, this may mean an elevated safety risk to the U.S. as some food ingredient suppliers are located in countries that practice little or no regulatory oversight, enforcement, or sanitary control over their respective food economies. In addition, the specter of intentional adulteration for economic gain is a constant concern in the global food economy. There is growing recognition that additional regulatory oversight in the U.S. is required to adequately protect the food supply. The FCC, discussed more fully below, is believed by some to merit consideration as part of the solution sought by Congress, by offering through its food ingredient standards a means by which food-related risks could be reduced.

⁷ MHFW (2008). Page on food safety. Retrieved from the MHFW website. URL: <http://mohfw.nic.in/pfa.htm>

⁸ Agmark (Unknown). *Promotion of Standardization and Grading of Agricultural and Allied Produce*, Retrieved from the Agmark website. URL: http://agmarknet.nic.in/agm_std1.htm

⁹ Title 21 United States Code § 342(a).



Food and Drug Administration

The FDA is the federal agency tasked with implementing the statutory provisions set forth by Congress in the FDCA. The FDA protects the public health principally by screening out unsafe or otherwise inadequate products in pre-market review, and by establishing, on the basis of scientific knowledge, general regulatory requirements for the design, manufacture, testing, labeling, and in limited circumstances, advertising of marketed products.¹⁰ The FDA promulgates the Code of Federal Regulations (CFR) containing the rules applicable to food manufacturers, distributors, packagers, and suppliers in the U.S.

Specific provisions of the CFR incorporate, by reference, certain individual *FCC* standards. These references require manufacturers of certain food ingredients to meet the specified *FCC* standards (typically for now-outdated editions) or be out of compliance. This is in contrast to the *USP*, where the general statutory recognition allows for standards to be updated and automatically requires compliance to the current standards. In general, *FCC* standards provide an informational, but not binding, resource of the identity and purity requirements of a majority of substances added to foods. These standards specify food grade material and are thus helpful to suppliers and manufacturers who otherwise would have to develop their own procedures and acceptance criteria.

Food and color additives in the U.S. require pre-market approval; other food ingredients must be Generally Recognized As Safe (GRAS) for their intended use. The FDA may publish or incorporate by reference specifications for food and color additives, which may subsequently be published in the *FCC*.

Unique to the U.S. system is the GRAS concept, which, in essence, is a legal classification of substances added directly or indirectly to food and judged by experts whose “scientific training and experience” (see above) and their examination of the relevant information lead them to conclude that the article is generally safe for consumption at the levels proposed for its intended use. This concept of an expert GRAS review may be carried out under the aegis of the food ingredient producer or user or other interested party. According to 21 CFR 170.30(a), “General recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate safety of substances directly or indirectly added to food.” According to 21 CFR 170.30(b), this general recognition of safety is: based upon scientific procedure; requires the same quantity and quality of evidence as for approval of a food additive; is ordinarily based upon published studies that may be corroborated with unpublished studies and information; and is based on common use in food prior to January 1, 1958. As stated in 21 CFR 170.30(c)(2), information on the history of use must be widely available in the country of use.

It is recommended, but not required, that findings of the GRAS review be submitted along with all relevant data to FDA—known as a “GRAS notification.” In response to the notification, the FDA may issue a letter stating that the agency has no questions concerning the notifier’s determination that a substance is GRAS. The legal status of a food ingredient that went through a GRAS review without the notification of the FDA is referred to as “self-affirmed” or “self-determined GRAS.” In these cases, the seller and buyer of the self-affirmed GRAS substance are relying solely on such determination without FDA’s knowledge or involvement that the article has been self-determined as GRAS. Additionally, while

¹⁰ *A Practical Guide to Food and Drug Law and Regulation, Second Edition*, Food and Drug Law Institute, Page 50, (2002).



a new substance may be determined as GRAS for a particular use, GRAS is a common mechanism for expanding on existing uses of substances.

U.S. Department of Agriculture

Regulatory oversight of the U.S. food industry is split between the U.S. Department of Agriculture (USDA)—responsible for the regulation of meat, poultry, seafood, and grains—and the FDA—responsible for food safety and food defense and for setting standards for certain foods, food additives, packaging, labeling, good manufacturing practices, and GRAS substances, as described above. Jurisdiction over food matters that overlap these two agencies is handled through a Memorandum of Understanding (MOU) that dictates the roles and responsibilities of each agency. For example, the owner of a meat processing plant is required to have a USDA inspector on-site whose job is to assure that the meat is safe for consumption pursuant to the Federal Meat Inspection Act. An FDA inspector can also inspect the plant to determine whether any unsanitary conditions exist in or outside the plant that could cause the meat to be contaminated, adulterated, or unfit for human consumption before, during, or after processing. The jurisdiction of the USDA extends to the actual meat being processed while the FDA exercises jurisdiction over the plant, processing area, and employees to ensure that good manufacturing practices are being followed. The continuing overlap of jurisdiction between USDA and FDA, and the resulting regulatory confusion in the eyes of some, has revived proposed legislation in Congress to create a single food agency with authority over all food activity in the U.S.

States

Every state in the U.S. has enacted a food and drug law, and local authorities conduct the bulk of compliance inspections and enforcement of food facilities in the U.S. The FDA partners with the states through MOUs that prescribe specific regulatory targets and goals for each state and, in return, the states receive federal funding to bolster their food safety programs. The FDA also trains state inspectors and monitors the states' regulatory compliance and enforcement activities. The FDA can exercise its preemption authority and supersede a state's authority to regulate food facilities when state food requirements are in conflict with the FDCA.

UNITED STATES: NON-GOVERNMENT

1. UNITED STATES PHARMACOPEIAL CONVENTION

FCC began in 1961 following passage of the 1958 Food Additive Amendments to the FDCA. Volunteer experts of the Committee on the Food Chemicals Codex of the Institute of Medicine's (IOM) Food and Nutrition Board developed and maintained *FCC* through the 5th edition. In August 2006, the United States Pharmacopeial Convention's (USP) Board of Trustees purchased *FCC* from IOM. *FCC* standards are now the responsibility of the Food Ingredients Expert Committee of USP's Council of Experts. USP published the 6th Edition of *FCC* in February 2008 and the first Supplement to this edition in February 2009. The second supplement was published in August 2009. Public comments to draft *FCC* standards are invited through a freely available web-based publication, the *FCC* Forum (www.usp.org/FCC).



More than 1000 monographs are listed in the *FCC* and many more monographs are needed to cover ingredients and additives that are used globally for food production but not listed in the *FCC*. USP metrology routinely employs reference standards, but only approximately 15% of *FCC* monographs use reference standards. *FCC* contains mostly food ingredient standards to support the authentication of these ingredients and in-process testing; however, there seems to be some reluctance by the food industry for developing reference standards for *FCC* articles—in some cases for proprietary reasons. USP has no authority to compel manufacturers to provide either information to support *FCC* monographs or candidate reference materials.

To the extent that the goal of *FCC* is to create standards for all legally-marketed food ingredients, the U.S. GRAS process adds complexity to the effort. Food ingredients that have gone through the GRAS notification process, and received an FDA response indicating the agency found no objection to the GRAS determination, can readily be adapted for publication of a monograph for the article in the *FCC* as FDA makes a list of all GRAS notices available on its Web site¹¹. However, in most cases this needs the support of a sponsor as technical questions are common, and USP also seeks to establish physical reference standards together with any monograph. In instances where the FDA has not received or issued an opinion of concurrence with the self-GRAS determination, *FCC* will need to rely exclusively on the cooperation of a sponsor to establish a monograph. To reflect the different regulatory status, *FCC* implemented a process to publish such a monograph as a “Provisional Monograph.” *FCC*’s requirements for a provisional monograph are identical to other monographs, except for the lack of notice from FDA or other governmental authority that the item is authorized to be used in food. Therefore, *FCC* will only move those provisional monographs to normal monographs for which the sponsor forwards an official approval by FDA or another governmental authority to *FCC*.

2. AOAC INTERNATIONAL

AOAC International (AOAC) is an independent, not-for-profit association that publishes AOAC® Official Methods. These Official Methods are accepted and recognized by regulatory agencies and organizations worldwide. Some methods are specifically required in the enforcement of some state, provincial, municipal, and local laws and many national food standards worldwide.

In the U.S., AOAC “Official Methods of Analysis” have been defined as “official” by regulations promulgated for enforcement of the FDCA (21 CFR 2.19), recognized in Title 9 of the USDA-FSIS Code of Federal Regulations, and in some cases, by the U.S. Environmental Protection Agency. Furthermore, AOAC has held official observer status in Codex Alimentarius since its inception and a majority of the methods cited in the Codex standards originated from the AOAC “Official Methods of Analysis.”

However, the Official Methods do not establish quality criteria for the identity, purity, and quality of food ingredients and additives. AOAC does not supply any reference standards to accompany a detection method. Although AOAC operates proficiency programs, it does not supply reference standards to support their collaboratively-studied test methods.

¹¹ <http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=grasListing>



DISCUSSION

Through the Council of Experts and staff, USP has shown considerable initiative in developing quality standards in *USP* (and the *Dietary Supplements Compendium*) and *FCC* that can be used by food additive producers and users and conformity assessment bodies. This work has been supported by the USP Convention and recognized as valuable to public health efforts. However, USP's ability to expand the global relevance and recognition of the *FCC* relies on financial resources from the sale of the compendia and reference materials. This model for *FCC* is not yet robust, and to date the food industry has shown little interest in using reference materials in carrying out *FCC* assays. The absence of strong national regulatory recognition, on one hand, does not facilitate the *FCC*'s position globally; however, on the other hand, it provides the flexibility to incorporate food ingredients that are legal in foods in other parts of the world, making the *FCC* more relevant to the global food community.

USP relies on the voluntary donation of information and materials to support monograph and reference material generation. As a result, as with the *USP–NF*, *FCC* lacks a full complement of monographs, and many monographs currently in the *FCC* require updating to move the compendium towards modern metrology while maintaining useful older methods. USP might contribute more significantly to public health by expanding *FCC*'s text to include process standards and ancillary information— for example, general information on adulterants— that could be useful to the food industry while expanding the reach of quality standards geographically. Taken together, the opportunities for advancing food standards and conformity to *FCC* standards through actions of an independent standards-setting body appear to be strong. USP has taken the first steps toward creating a foundation for assuring the quality of food ingredients. The Council of the Convention Section on Quality of Food Ingredients and Dietary Supplements encourages further consideration of ways to amplify these initial efforts. Examples where progress could occur include:

1. REGULATORY FRAMEWORK FOR FOOD INGREDIENTS

FCC quality standards for food ingredients can provide a baseline for quality and a description of their identities, thus increasing food safety by making it easier to identify adulterated products. This will increase overall food safety and protect the consumer from qualitatively inferior and potentially dangerous products. In particular, USP might support the following:

- Updating /expanding reference to *FCC* specifications/monographs in the CFRs, which would strengthen existing regulations and improve domestic food safety by requiring that food ingredients meet acceptable quality levels;
- Supplying food ingredient reference standards to interested parties for procedures in *FCC* monographs to enable all stakeholders in the food supply chain to perform independent tests to ensure identity and quality against a certified authentic and “real” food ingredient;
- If there is sufficient interest, USP could work with all partners as feasible to offer food ingredient reference materials for *FCC* as well as JECFA specifications; and
- Serving as a resource that offers a full range of services, including monographs, reference materials, general chapters, and training courses and workshops, all of which support



regulators, industry, and other stakeholders to increase food quality and better protect the consumer from the potential risks of harm caused by adulterated food.

2. GLOBAL FOOD TRADE

All efforts aimed at protecting public health must take into account complex international supply chains, thus making it critical to develop tools with an eye toward the impact on the international community.

- USP's international presence facilitates the development of monographs relevant to different geographical regions, which in turn enhances the global relevance of the *FCC*.
- USP can facilitate food trade through collaborations with JECFA. Quality standards enable JECFA to perform an expedited safety evaluation while expending fewer resources.
- USP can extend its prominence as a resource to national (e.g., FDA, USDA) and international regulators, and the *Codex Alimentarius*, by increasing *FCC* recognition.



WHITE PAPER

ACCESS TO GOOD QUALITY DIETARY SUPPLEMENTS

SEPTEMBER 23, 2009

COUNCIL OF THE CONVENTION SECTION ON THE
QUALITY OF FOOD INGREDIENTS AND DIETARY SUPPLEMENTS

INTRODUCTION

The 1994 Dietary Supplement Health and Education Act (DSHEA) amendments to the Federal Food, Drug, and Cosmetic Act (FDCA) provided a regulatory framework to allow marketing of vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Now, more than 15 years later, a vast array of dietary supplements in different combinations and amounts are available to United States patients/consumers. Sales of dietary supplements are approaching \$25 billion/year, with about \$4 billion of this amount representing sales of botanicals. While DSHEA was instrumental in providing consumers with easy access to dietary supplements, a recent U.S. Government Accountability Office (GAO) report stated that consumers of dietary supplements are not adequately protected under current U.S. law and regulations.¹ Pre-market oversight and registration of products are recommended in the GAO report.² Outside the United States, dietary supplements are frequently considered as traditional medicines with few standards and conformity assessments to these standards. In this white paper, USP's Council of the Convention Section on the Quality of Food Ingredients and Dietary Supplements provides background information on the topic and advances proposals for consideration by the Convention membership to further improve the quality of dietary supplements.

NATIONAL APPROACHES

1. CONGRESS: PROVISIONS OF DSHEA

Through DSHEA, Congress defined dietary supplements as “foods.” As with all foods, DSHEA provisions in the FDCA do not require pre-market review of a dietary supplement by the Food and Drug Administration (FDA) if the ingredients have a safe history of use in food or supplements prior to 1994. Instead, Congress put in place a notification process for a new dietary ingredient to ensure that ingredients that do not have a safe history of use are reviewed by the FDA prior to entry into the U.S.

¹ Government Accountability Office report. 2009 Dietary supplements. FDA Should Take Further Actions to Improve Oversight and Consumer Understanding <http://www.gao.gov/new.items/d09250.pdf>.

² Ibid.

market. In addition, DSHEA essentially places the burden of proof on the FDA to demonstrate that a dietary supplement presents “significant or unreasonable risk of illness or injury” before it can be removed from the market.

With regard to the *United States Pharmacopeia (USP)*, Section 403(s)(2)(D) of the FDCA states that if a dietary supplement is 1) covered by the specifications (tests, procedures, and acceptance criteria of a monograph) of an official compendium of the United States (*USP, National Formulary [NF]*, or the *Homeopathic Pharmacopoeia*), 2) is represented as conforming to the specifications of an official compendium, and 3) fails to so conform, then the supplement is considered to be misbranded. Accordingly, unlike the provisions relating to prescription drugs (where conformance with USP standards is mandatory, whether labeled as such or not), Section 403(s)(2)(D) of the FDCA makes compliance with the specifications of an official compendium strictly voluntary for dietary supplement manufacturers (unless the manufacturer chooses to represent the product as conforming to *USP*). As a consequence, this statutory reference to official compendia provides legal recognition to *USP*, but effectively creates a disincentive for its use, because it exposes only those manufacturers who so label (and not others who make no reference to USP standards at all) to a potential misbranding violation if found not to conform to *USP*.³

2. THE FOOD AND DRUG ADMINISTRATION

In 2007, the FDA finalized Current Good Manufacturing Practices (cGMPs) for dietary supplements. These regulations allow manufacturers to establish product specifications and to use “appropriate and scientifically valid” methods to determine whether those specifications are met. The cGMPs do not define the words “scientifically valid” nor is validation of analytical procedures required. The FDA has indicated that “a scientifically valid method is one that is accurate, precise, and specific for its intended purpose—in other words, a scientifically valid test is one that consistently does what it is intended to do. As a result, dietary supplement manufacturers develop private procedures, tests, and assays, which may or may not receive regulatory scrutiny. Standards for a dietary supplement under a specified name may not have comparable requirements and thus may be dissimilar in quality, benefit, and safety to consumers. The cGMPs do not require dissolution and disintegration testing, and manufacturers set their own limits for contaminants such as heavy metals, microbial limits, fungal toxins, or pesticides. USP has published an article describing the current regulatory scheme as one that creates “standards without standardization.”⁴

3. UNITED STATES PHARMACOPEIAL CONVENTION

Following enactment of DSHEA in 1994, the 1995 USP Convention adopted Resolution 12 that encouraged the USP to explore the feasibility and advisability of establishing standards and developing information concerning dietary supplements. This resolution was taken up and implemented by USP’s Board of Trustees and Council of Experts, resulting in a well-evolved section of *USP* for dietary supplement monographs, with allied USP Reference Standards offered in USP’s catalogue.⁵ *USP32-*

³ It should be noted that the FDA has indicated that DSHEA will not apply to dietary supplement products intended for use in animals. As such, animal dietary supplements currently are regulated generally as “food” without the additional protection afforded human dietary supplement products under DSHEA. It is generally felt in the veterinary community that the need for evidence of quality, safety, and efficacy are similar for veterinary and human patients alike. For more information, see *Safety of Dietary Supplements for Horses, Dogs and Cats*, Committee on Examining the Safety of Dietary Supplements for Horses, Dogs and Cats, National Research Council, National Academic Press, 2008.

⁴ Miller RK, Celestino C, Giancaspro GI, Williams RL. 2008. FDA’s dietary supplement CGMPs: Standards without standardization. *Food and Drug Law Journal* 63 (4), 929-942+iv.

⁵ More information on USP dietary supplements Expert Committees is available through <http://www.usp.org/support/products/uspNewslettersRequest.html>

NF27 now contains approximately 430 dietary supplement and ingredient monographs and general chapters, which cover a large percentage ($\pm 90\%$) of the dietary supplements commonly marketed in the United States. USP's Council of Experts Dietary Supplement Information Expert Committee applies admission criteria together with a safety review guideline to allow exclusion of some dietary supplements from USP, even though they may be legally marketed in the United States. This approach mirrors the work of the Scope Committee of the Committee of Revision (the predecessor of the Council of Experts) that ended in the 1990s. USP also includes a General Chapter on *Manufacturing Practices for Dietary Supplements* <2750>, which was developed prior to finalization of FDA's cGMPs and is generally more stringent and specific than those regulations. In June 2009, USP introduced a separate *USP Dietary Supplements Compendium* that includes official text from USP (monographs and general chapters relating to dietary supplements) as well as authorized explanatory text and graphics intended to provide useful information to dietary supplement manufacturers.

INTERNATIONAL APPROACHES

While vitamins, minerals, amino acids, botanicals, and other plant and animal substances are available in the U.S. as dietary supplements, they are variably regulated as health products, traditional medicines, or drugs in other countries. This varied international approach on the regulation of dietary supplements provides different paradigms for consideration and exploring options for domestic regulatory oversight. Quality standards also are quite variable around the globe. Issues of quality are present in the international commerce of dietary supplements, which is evident in cases such as protein adulteration with melamine or dietary supplements containing toxic metals, high levels of pesticides or unapproved drugs. Information from the World Health Organization (WHO) details the widespread consumer misconception that "natural" always means "safe," and a common belief that remedies from natural origin are harmless and carry no risk.⁶ Also of concern is that healthcare providers are frequently unaware of the dietary supplements their patients are taking; either because they do not ask, or patients do not offer the information.⁷ Under the current law and regulations, there is no way of knowing the quality standards to which each product is held, and thus, there is no way to determine whether two products with the same dietary supplement ingredients are the same or different.

PROPOSALS

The Council of the Convention Section on Food Ingredients and Dietary Supplements suggests for consideration the following opportunities for possible USP Convention action and improvement in the regulation of dietary supplements.

1. PUBLIC MONOGRAPHS AND REFERENCE MATERIALS

The universe of products in the market is constantly expanding, creating gaps where monographs and reference materials are missing. To the extent feasible, documentary standards and reference materials offered by USP should expand to cover all the products in the dietary supplements market.

⁶ WHO. 2004. Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance systems. WHO Department of Essential Drugs and Medicines Policy: Geneva. <http://apps.who.int/medicinedocs/index/assoc/s7148e/s7148e.pdf>

⁷ Gardiner P, Sarma DN, Low Dog T, Barrett ML, Chavez ML, Ko R, Mahady GB, Marles RJ, Pellicore LS, and Giancaspro GI. 2008. The state of dietary supplement adverse event reporting in the United States. *Pharmacoepidemiology and Drug Safety*. 17: 962–970.



2. ADHERENCE TO PUBLIC STANDARDS

Public quality standards arising from the open and participatory process conducted by USP conserve both regulatory and manufacturer resources. They work to achieve consistency in the quality of a dietary supplement both within and between manufacturers, and allow updating. This consistency is more likely to be achieved if manufacturers are required to comply with public standards. Thus, USP might consider informing and engaging in discussions with Congress about the desirability of strengthening section 403(s)(2)(D) of the FDCA to require dietary supplements and dietary supplement ingredients to conform to the standards established in *USP-NF*, where such standards exist. USP also might consider making Congress aware of the benefits of strengthening the adulteration provisions of the FDCA to ensure that all dietary supplements conform to the relevant standards promulgated in *USP-NF*. However, it is not clear, at this time, that industry supports such mandatory standards.

3. INTERNATIONAL HARMONIZATION

Amidst the increasingly complex global supply of dietary supplement ingredients and products, ensuring quality and harmonization of standards is important, irrespective of how dietary supplement products are labeled and regulated—whether as traditional medicines, drugs, or supplements. Global harmonization of public standards would ensure quality, identity, and label uniformity in international commerce, and could facilitate international commerce of good quality dietary supplements. To start its work in this area, USP standards and analytical methods could complement the descriptions of quality, dosage, safety, and pharmacological activity of botanical monographs offered by other standards setting bodies of the world.⁸ For these reasons, USP should cooperate with international health organizations to promote standards for traditional medicines that are also dietary supplements in the United States. Examples of such organizations include the WHO, the Canadian Natural Health Products Directorate in Health Canada, the European Directorate for the Quality of Medicines and HealthCare (EDQM), and the Indian and Chinese Pharmacopoeia Commissions.

4. EDUCATION

There is a dearth of unbiased dietary supplement information for consumers and practitioners. Gaps in practitioner training and consumer education are clear impediments to the safe use of dietary supplements. Practitioners should receive training on proper counseling of consumers on the use of dietary supplements and consumers should be educated about the importance of disclosing such usage to healthcare providers. In this way, practitioners and consumers can monitor and prevent possible adverse effects that may occur from the combined use of certain dietary supplements and drugs.

USP could expand its educational programs to meet the needs of practitioners and patients/consumers with respect to dietary supplements. The USP Dietary Supplements Information Expert Committee earlier recommended education of practitioners regarding suitable practices for safe use and prevention of interactions with other therapeutic agents.⁹ USP should consider developing Pharmacopoeial Education courses for practitioners and consumers in this regard, and additional courses on compendial approaches to quality standards for dietary supplements to help manufacturers, testing labs, and regulators understand the value of USP public standards and reference materials.

⁸ Ko RJ. 2004. A U.S. perspective on the adverse reactions from traditional Chinese medicines. *J Chin Med Assoc.* 67(3):109-116.

⁹ Gardiner et al, 2008 (see reference 5 above).



5. VERIFICATION

USP Verification Programs could also be used to increase confidence that ingredients and products moving in the international market comply with the quality specifications to help ensure public safety, including absence of known/identified adulterants and contaminants. Although FDA has not endorsed the use of third party certifications of dietary supplements, it has recognized the value of third-party certifications in its recent guidance on foods.¹⁰ Broad implementation of USP's Verification Programs for dietary supplements and dietary supplement ingredients could assist in raising supplement quality, help patients make informed decisions, restore consumer confidence, and allow healthcare practitioners to recommend verified dietary supplements with some level of confidence. The various elements of USP's Verification Programs (audits, testing, document review, and market surveillance) would act synergistically with the cGMPs already in place, thus helping conserve FDA resources. Because cGMPs provide minimum requirements, implementation of USP Verification Programs would add value for greater assurance of the quality of supplements.

The concern about the quality and purity of ingredients moving in the international market also could be addressed through a system of USP Verification Programs' inspecting companies and testing products overseas. With sites in China, India, and Brazil, USP is very well positioned to contribute worldwide to raising the quality of dietary supplements. It is also possible that the challenges faced by regulatory differences with other countries could be addressed through credible USP Verification Programs.

6. REGULATORY OVERSIGHT

Dietary supplement product registration or pre-market notification might be considered as a means of monitoring the number and type of dietary supplements moving in commerce in the U.S. and helping to assure the safety of dietary supplements prior to sale to the consumer. To accomplish this, the FDA would need sufficient resources to adequately assess and address the safety of dietary supplement products, and the FDCA would need to be amended to provide the FDA with authority in this area.

The Council of the Convention Section on Food Ingredients and Dietary Supplements welcomes input on these proposals from the Convention, as well as additional comments on how USP might build upon its past efforts and expand its work to help assure the quality and appropriate use of dietary supplements worldwide.

¹⁰ Third-party verification – The FDA is endorsing third party verification of foods through its Guidance for Industry on Voluntary Third-Party Certification Programs for Foods and Feeds. 2009.
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm125431.htm>



WHITE PAPER

OPPORTUNITIES FOR DRUG INFORMATION AND USE STANDARDS

SEPTEMBER 23, 2009

COUNCIL OF THE CONVENTION SECTION ON QUALITY OF PATIENT CARE

INTRODUCTION

As a standards-setting organization for medicines and other healthcare articles, the United States Pharmacopeial Convention (USP) has contributed broadly and deeply to the provision of information supporting rational therapeutic decision-making and safe medicine use. In this white paper, USP's Council of the Convention Section on the Quality of Patient Care provides a situation analysis of these and allied contributions, focusing on the general topic of drug information and use standards. A separate white paper will consider safe medication use.

Standards generally apply to people, processes/practices, and/or products. USP now provides an extensive array of product standards for drug and food articles in the *United States Pharmacopeia (USP)*, *National Formulary (NF)*, *Food Chemicals Codex (FCC)*, and allied compendia. These product standards support testing to assure identity, strength, quality, and purity of foods and drugs. Beyond these product standards lie others that support rational therapeutic use—process and practice standards—and perhaps clinical practice standards as well that can be associated with education and training. Process/practice standards also might promote improved operations of healthcare teams and systems. This paper uses the term *drug information and use standards* to define collectively the concept of standards to promote rational and cost-effective therapeutic decision-making for medicines. Such standards could be applied in the paradigm that moves from diagnosis to treatment. Once a diagnosis is made, many therapeutic guidelines exist; many are maintained on an Agency for Healthcare Research and Quality (AHRQ) web page at <http://www.ahrq.gov/clinic/>, that speak to multiple treatment interventions ranging from the extremely simple to the highly complex. Use of medicines also ranges from the simple to the complex, and the complexity in an era of biomolecules and molecular medicine is increasing by the year. Typically, information and use standards for medicines begin with Food and Drug Administration (FDA)-approved efficacy and safety information in drug labeling. This information is amplified over time with further studies and clinical usage.



How this further information is generated and applied is a subject of considerable societal interest. It relates not only to rational therapeutic decision-making but also to payor and quality of care needs and decision-making. Such information is needed more critically now than ever before. The cost to provide continuing information and standards about a medicine is borne primarily by the private sector—and increasingly the information itself is a web-based commodity. Multiple compendia provide a basis for reimbursement, and many hundreds, if not thousands, of pharmacy and therapeutic committees provide administrative decisions to support cost-effective treatment for defined populations. USP's foray into drug information and use standards might build on the organization's ongoing responsibility for maintenance of the Medicare Model Guidelines. Many other organizations also are involved in such standards, and USP would necessarily ally with them in its "neutral convener" role in any further standards-setting attempts. Increasingly, as a dominant payor, the United States Federal government is involved, and a public-private model of some sort might be optimal. If such a model is considered, financing, scope, governance, and many other questions and challenges will arise.

With the exception of the every-three-year Medicare Model Guidelines updates, or the most part, USP has exited activities associated with the provision of drug information and use standards. The larger question for the organization now relates to its specific role as a practitioner-based, volunteer-driven, standards-setting organization. USP can do anything it wishes in the way of drug information and use standards, being bound only by resource constraints. The issues for consideration in this white paper might thus be:

- In an era of health care crisis and reform, what are the societal needs for drug information and use standards to support rational therapeutic decision-making?
- If these needs can be defined and USP, by virtue of its structure and history, can uniquely fulfill them—with availability of adequate resources—does it have a responsibility to do so?

USP'S HISTORY IN DRUG INFORMATION

1. UNITED STATES DISPENSATORY

When the first *United States Pharmacopeia (USP)* appeared in 1820, it deliberately excluded most explanatory material regarding preparation techniques, which the authors considered to be too rudimentary. However, a need did exist for a Dispensatory—a volume that would not only select official drugs and provide recipes for preparations, but would also give full descriptions and indications of the drugs and explain applicable practitioner techniques. George B. Wood and Franklin Bache, two of USP's founding physicians, produced the first *Dispensatory of the United States of America (USD)* in 1832. They viewed its purpose as both instructional (for poorly trained physicians and pharmacists) and as a means to solidify the national authority of the *USP*, to which the *USD* deferred. The *USD* went on to become one of the most popular American medical reference books of the 19th century, overshadowing the *USP* itself in terms of everyday usage. The *USD* continued to be popular well into the 20th century, but started to lose its authority with the rise of the Food and Drug Administration and other sources of drug information as they emerged. Its link to the *USP* was formally severed in 1880. The last (27th) edition of the *USD* was published in 1973.

2. USP DI SERIES

The *USP Drug Information* resource (*USP DI*) was created in 1980 as a complete, unbiased compilation of clinically relevant information about therapeutic products, for the use of practitioners (physicians, nurses, pharmacists) and patients. *USP DI* was recognized in the Social Security Act as an authority for reimbursable off-label use under Medicare and Medicaid. It comprised three volumes—*USP DI Volume I: Drug Information for the Health Care Professional*; *USP DI Volume II: Advice for the Patient*, and *USP DI Volume III: Approved Drug Products and Legal Requirements*. Originally produced in print format only, a *USP DI* product line extension in the form of an interactive laser disk focusing on a single disease (About Your Diabetes) was attempted in the late 1980s. Maintenance proved a costly and time-consuming hurdle, and the disk was discontinued in the mid-1990s.

Another attempt to move the *USP DI* into the increasingly important online delivery mode was attempted in 1994, when USP acquired the Drug Evaluations database from the American Medical Association (AMA-DE). The goal was to integrate the AMA-DE data into the *USP DI* database. Again, technical complexity and the difficulty and expense of maintenance led to the project's termination. A third attempt to develop a *USP DI* relational database was launched in the mid-1990s, this time contracting with Carepoint, a provider of pharmacy management software. Yet again, the program was abandoned due to technical complexity and costs. In 1998, USP sold the *USP DI* database and licensed the *USP DI* trademark to Thomson Healthcare, but retained editorial oversight of the off-label use material in the publication. In 2000, Thomson launched the *USP DI* Desktop Series CD ROM, capturing a “large share” of healthcare web portal and hospital web site segments with *USP DI* branded content. However, changes in some state pharmacy regulatory requirements in 2001 resulted in a sharp decline in the number of pharmacies ordering the product. In addition, the chain pharmacy market was demanding a single vendor for all electronic solutions, which the Thomson *USP DI* could not provide. USP and Thomson explored a variety of strategic options over the next few years, but ultimately it made the most financial and operational sense for USP to exit the business completely. In 2004, the *USP DI Volume I* and *Volume II* became the responsibility of Thomson Healthcare. Under the agreement, Thomson could edit, create content, and publish these texts under the *USP DI* name until the 2007 edition, after which Thomson's right to use the name ceased. *USP DI Volume III* continued to be owned in its entirety by USP. Thomson continues the *USP-DI* product under the name *DrugPoints*.

Many other entities have provided drug information in various compendia to support sound therapeutic decision-making. An analysis of these types of compendia appeared in a series of three articles earlier this year in the *Annals of Internal Medicine*; a summary editorial references the three articles.¹ Overall these articles and summary editorial are generally critical of the various compendia in terms of their currency, consistency, and other factors.

3. MODEL GUIDELINES

The Medicare Modernization Act (MMA) of 2003 defines the role of USP (Section 1860D-4(b)(3)(C)):

(ii) MODEL GUIDELINES – The secretary shall request the United States Pharmacopeia to develop, in consultation with pharmaceutical benefit managers and other interested parties, a list of categories and classes that may be used by prescription drug plans under this paragraph and to revise such classification from time to time to reflect

¹ Sox, HC. 2009. Editorial: evaluating off-label use of anticancer drugs. *Annals of Internal Medicine*, Volume 150, Number 5



changes in therapeutic uses of covered part D drugs and the additions of new covered part D drugs.

In addition, Section 1860D-11(e)(2)(D) creates a “safe harbor:”

(ii) USE OF CATEGORIES AND CLASSES IN FORMULARIES – The Secretary may not find that the design of categories and classes within a formulary violates clause (i) if such categories and classes are consistent with guidelines (if any) for such categories and classes established by the United States Pharmacopeia.

With this legislative mandate and on behalf of the Secretary of the Department of Health and Human Services, the Centers for Medicare and Medicaid (CMS) awarded USP a cooperative agreement to develop and revise the Part D Prescription Drug Benefit Model Guidelines. A new Model Guidelines Expert Committee was formed to accomplish the task. While the MMA did not specify the frequency of updates to the Guidelines (“...from time to time...”), the Expert Committee and CMS agreed that an annual update was appropriate given the rapidly evolving nature of pharmaceuticals. Version 1.0 was a large effort, involving a review of how other formularies are categorized and presented.

At its highest usage (2006), 74% of health plans were using the USP Model Guidelines (Version 1.0). The Model Guidelines Categories and Classes provided a formulary structure that helped ensure beneficiary access while preserving needed flexibility for pharmacy benefit managers (PBMs) and health plans. USP developed an additional component to the Model Guidelines: Formulary Key Drug Types (FKDT), which offered additional protection for beneficiaries and a useful tool for CMS in reviewing formularies. Although not mandatory, the FKDT have been utilized by CMS as part of its Formulary Review Guidance, and serve as standards that promote consistency, fairness, and ease of administration. Usage of the Model Guidelines lessened in subsequent years, primarily due to plan consolidation and a broader use of internal classification systems due to plans’ comfort with the CMS process. Nevertheless, the guidelines contributed substantially to the availability of a comprehensive, yet affordable, benefit. As with all its standards, USP actively solicited and welcomed participation and input on Guidelines development from interested stakeholders, including manufacturers, drug plans, practitioners, and patients. USP’s experience with the Model Guidelines was summarized in a report published in *Annals of Internal Medicine* in 2006.² Its work on behalf of the Federal government followed a primary activity where USP participated in a consortium of interested organizations to produce a document entitled “Principles of a Sound Drug Formulary System” (2000).³

By 2008, CMS decided that the Guidelines had achieved a significant level of success and stability. Based on this, USP and CMS agreed to move from an annual revision timeline to a three-year cycle. CMS continues to use the current Model Guidelines and FKDT through plan year 2011, and USP is maintaining the current versions on its web site. The goal is for USP to start work on Version 5.0 in 2010.

² Narrative review: the US Pharmacopeia and Model Guidelines for Medicare Part D Formularies. USP Model Guidelines Expert Committee, USP Staff [Williams, RL] *Ann Intern Med* 145, 448–453 (2006)

³ <http://www.usp.org/hqi/patientSafety/resources/soundFormularyPrinciples.html> 2009



EXPLORATION OF NEW OPPORTUNITIES

1. DRUG INFORMATION CONSULTATIONS

In 2005 and again in 2006, USP convened special meetings, called Drug Information Consultations, where individuals and organizations gathered to discuss the feasibility and advisability of developing practice standards associated with drug information. In these meetings, USP sought a clear understanding of the current gaps in drug information and where its standards-setting expertise might be used to augment information used by practitioners, plans, and patients in decision-making about rational drug use. At the time of these meetings, USP was engaged in the development of Model Guidelines for the Medicare Prescription Drug Benefit and was considering how that activity might also be supported with additional drug information for the healthcare community. Despite a number of useful suggestions from a broad range of participants, these consultations did not generate any specific activity (notes of meetings are available). A Board Task Force (2005-2010) was formed to monitor USP's interests in the topic.

2. APPLIED DRUG INFORMATION RESOURCE

Working with the American Medical Association, the American Nurses Association, and the American Pharmacists Association, USP led a series of meetings that explored the concept of an Applied Drug Information Resource (ADIR). The general idea for the ADIR was to advance “personalized medicine” concepts, in which general information about a medicine would be adjusted by patient-specific characteristics. The product would yield information directed to diverse practitioner and patient constituencies. The opportunity did not progress.

3. COMPARATIVE EFFECTIVENESS

Comparative effectiveness (CE) studies of specific treatment approaches—including various pharmacotherapies, lifestyle changes, imaging procedures, and surgical interventions—have great current and potential value. They add to the body of knowledge that helps health care practitioners, as well as patients and their families, make treatment decisions. The infusion of funds (through the American Recovery Reinvestment Act of 2009, also known as the “Economic Stimulus” Legislation) that will support additional research is a welcome development. The bill provides \$1.1 billion for CE research:

- \$300 million to the Agency for Healthcare Research and Quality (AHRQ);
- \$400 million to National Institutes of Health (NIH); and
- \$400 million to the Department of Health and Human Services (DHHS).

Observations about this funding that are relevant to USP include:

- Organizations can make proposals for CE project funding (the process is still being determined by agencies).
- According to the conference report, funding is not to be used to mandate coverage decisions, but instead is for generating useful research comparing clinical outcomes.

- The law also establishes the Federal Coordinating Council for Comparative Effectiveness Research, made up of high-level government officials, for the purpose of coordinating healthcare research across the Federal government.
- IOM has engaged the community in a better understanding of the types of CE studies needed.⁴
- AHRQ has conducted workshops and engaged in other tasks to generate evidence-based information and engage the community in understanding how database analyses can generate useful CE information.⁵

CE studies *per se* will be valuable and must, more frequently, become one of the inputs used by practitioners and patients to guide therapy following diagnosis, despite the fact that CE is sometimes linked in public discourse to rationing of healthcare. Diagnosis and treatment can be aided by development of a treatment model—captured and presented as a generally applicable set of process standards—that addresses key aspects of the decision-making process that are often considered in an ad hoc fashion, if at all. In turn, these process standards support treatment programs (protocols) to guide the practitioner and patient/consumer alike. These treatment programs themselves are also process standards that are frequently lacking for the individual patient when he or she leaves the immediate healthcare provider's setting.

4. PHARMACOTHERAPY GUIDELINES

Comparative Effectiveness results could be put into action through extended pharmacotherapy treatment standards. USP could serve as a convener of organizations to 1) develop an innovative, multidisciplinary, patient inclusive approach for integrating CE research study outcomes into pharmacotherapy standards/guidelines—treatment program standards—and 2) apply this approach to two separate, established, model standards or guidelines for particular disease treatments.

Aspects/features of the approach include:

- AHRQ-funded evidence-based studies, including CE studies;
- Conferences and Webinar(s); and
- Disease/condition candidates for which a wide range of treatment therapies exist, the cost of therapies varies widely, and which are part of a discrete patient population that would be affected.

In all cases, transparency of work would be emphasized, partners would represent the interdisciplinary health care team (including patients and payors), and USP committees and members would be part of the process.

5. SPECIALTY MEDICINES

Specialty medicines are the product of innovative technologies (often, but not solely, biotechnology engineered molecules) that target unmet medical needs and are expensive because of limited patient populations, high cost of manufacture, and the increased risk and cost of development programs. In

⁴ www.iom.edu/cepriorities (July 2009)

⁵ <http://www.ahrq.gov/clinic/outcomix.htm> (July 2009)



addition, the forced evolution of the pharmaceutical industry business model from reliance on historically successful but fading “blockbusters” to larger numbers of innovative specialty medicines requires higher prices to fuel growth.

Exacerbating the cost problem is that, as a consequence of structural and financial realities in the approval process and the costs and risks of development, these medicines are often used for unapproved indications for which evolving data sets are suboptimal when compared with data supporting their use in approved indications. Such use is generally for chronic, inadequately treated diseases with high morbidity and mortality, creating compelling demand for utilization and making it difficult to deny access. Access may seem arbitrary, depending upon the sophistication of the practitioner and patient in confronting the payor, which contributes to a growing sense of unfairness.

The payment for these medicines varies considerably among plans. Medicare covers specialty pharmaceuticals under Parts B and D, depending upon seemingly unrelated factors, including the route and place of administration. Therefore, care may be driven by reimbursement rather than clinical considerations. Both private and public (Medicare) payors use tier structures (essentially a cost shift to patients) to reimburse for these medicines. Since Medicare Part B (and most private plans) lacks out-of-pocket maximums and these medicines can cost tens of thousands of dollars per year, they are simply unaffordable for many under the current system.

To effectively allocate scarce health care resources, standards are needed to support rational therapeutic use of specialty medicines. These standards are now left to individual pharmacy and therapeutics committees, their health plans, and/or individual practitioner and patient decision-making. The question arises whether a national process could lead to standards to better inform these decisions.

The sensitive and inevitably controversial nature of these standards requires that this process be inclusive, transparent, and objective. USP possesses a structure and history that uniquely position it to achieve these objectives.

6. INFORMATION STANDARDS

USP’s Information Expert Committee chairs have advocated that USP provide information standards rather than the information itself. Such standards would serve as a framework within which others could create information. This concept relates directly to USP’s standards-setting and practitioner-based character and links the quality of patient care to the quality of the information used by healthcare professionals and patients. Examples of information standards (as distinct from information) could include the adequacy of research study design, methodology, analysis, and communication of results. Other standards could include:

- Linguistic competency for verbal or aural messaging and comprehension targeted at specific audiences, e.g., level of language used, languages available, visual depictions, words presented per minute;
- Cultural sensitivity in messaging: ethnicity, gender, age, etc.;
- Ethics in targeting vulnerable populations: elderly, children, terminally ill;
- Competency in decision-making: use of duress, undue influence, physical and mental capacity, etc.;



- Patient–provider relationships and conflicts of interest;
- Direct to patient advertising: "free" samples; and
- Requirements for post-regulation marketing surveillance.

7. NATIONAL AND INTERNATIONAL APPROACHES

Through its Essential Medicines List, the World Health Organization (WHO) has sought to provide a limited list of medicines to decrease inappropriate prescribing and promote rational use.⁶ The WHO Essential Medicines List is used by many nations throughout the world to create national formularies that expand and/or contract the WHO list to meet local needs. In principle, USP's Model Guidelines provides a "table of contents" for a U.S. national formulary. Combining the approach with the AMA-DE in evaluating individual medicines within each category and class of the Model Guidelines further supports a U.S. national formulary, which does not now exist. The opportunities and challenges of such an approach are generally well known. An essential medicines list speaks to the best medicines within a country, region, or even the globe. In this context, it speaks to official medicines in the *United States Pharmacopeia*, which were always intended to be the best medicines. The *National Formulary* in the United States provided quality standards for non-official medicines. It was adopted by USP in the 1970s and has evolved into a book of excipient monographs. A seminal paper by T. Donald Rucker, Ph.D., argued that USP should advance a "true" national formulary in the U.S.⁷

SUMMARY

At the outset, this white paper asked the following questions:

- In an era of health care crisis and reform, what are societal needs for drug information and use standards to support rational therapeutic decision-making?
- If these needs can be defined and USP, by virtue of its structure and history, can uniquely fulfill them—with availability of adequate resources—does it have a responsibility to do so?

The U.S. Federal government has turned to USP's standards-setting activities and expertise on many occasions over more than 100 years, not only when it recognized *USP* and *NF* as official compendia of the United States, but also for purposes of reimbursement on two occasions⁸ and, more recently, to assure beneficiary access in the Medicare Part D legislation. In these cases, USP was recognized as a trusted, neutral organization that could bring together diverse stakeholders and make objective, science-based decisions through an open and transparent process. In the current state of healthcare reform and crisis, it may be time

⁶ Reidenberg, MM. Can the selection and use of essential medicines decrease inappropriate drug use?. 2009. *Clinical Pharmacology and Therapeutics*, Volume 85, Number 6.

⁷ Rucker, TD. November 15, 1999. A public-policy strategy for drug formularies: preparation or procrastination?. *American Journal of Health-System Pharmacists*, Volume 56.

⁸ Omnibus Budget Reconciliation Act of 1990 (Public Law 101-508) signed into law November 5, 1990 and The Omnibus Budget Reconciliation Act of 1993 (Public Law 103-66) 107 Stat. 312, enacted August 10, 1993. http://assembler.law.cornell.edu/us-cgi/get_external.cgi?type=publ&target=103-66), (<http://www.answers.com/topic/united-states-statutes-at-large>)



to call upon USP again. There is a deep logic, expressed in many countries over many years, for governments to seek non-governmental practitioner experts to achieve a public health good, such as drug information and use standards. But even if the U.S. Federal government does not turn to USP at this juncture, this does not mean that USP should not act. While USP has a need for sufficient financial resources to set drug use and information standards, it has access to the greatest resource of all: a cadre of healthcare experts from around the world who have, can, and could set, through activities of the Council of Experts, drug information and use standards in ways that would speak profoundly to patients and practitioners in a time of great need. The Council of the Convention Section on the Quality of Patient Care seeks creative thinking about a strengthened role for USP in setting drug use and information standards.



WHITE PAPER

USP'S ROLE IN PATIENT SAFETY

SEPTEMBER 23, 2009

COUNCIL OF THE CONVENTION SECTION ON QUALITY OF PATIENT CARE

INTRODUCTION

For the last four decades, the United States Pharmacopeial Convention (USP) has relied on spontaneous reporting information to support creation of safe medication use and quality of care standards in the *United States Pharmacopeia (USP)* and allied reports. For the most part, these are standards and supporting information that speak to how practitioners within healthcare systems should adjust their processes and practices to promote safe medication use. At times, USP product standards call for the adjustment of labels and labeling to reduce the likelihood of error.¹

As a volunteer-driven, practitioner-based, standards-setting organization, USP provides an important and unique pathway for practitioners to set standards they use in daily life. USP is not itself a regulatory body and does not enforce its standards; however, conformity assessment bodies may recognize USP standards in ways that enhance their value, impact, and at times make them mandatory. Irrespective of their voluntary or mandatory character, standards provide a safe harbor for practitioners and support optimum health care outcomes.

While beyond the scope of this white paper, USP acknowledges—and has always supported—the remarkable work of academia, the Institute of Medicine (IOM), highly involved standards- and conformity-assessment organizations (many of whom are Convention members), and many others who have worked tirelessly to develop information and provide evidence-based approaches to promote patient safety, safe medication use, and optimal quality care. Much of this effort culminated in the seminal reports of the IOM beginning in 1999 and follow-on activities in the IOM and elsewhere.

The Council of the Convention Section on the Quality of Patient Care presents this white paper as a means of reviewing USP's prior efforts in this area and to encourage the Convention to consider future patient safety opportunities for USP.

¹ For the most part, USP does not provide clinical practice standards, which are the responsibility of practitioner associations, state practice boards, and other certifying bodies.



USP'S LABELING AND NOMENCLATURE RESPONSIBILITIES IN LAW

In the United States, under the Federal Food, Drug, and Cosmetic Act (FDCA), the *United States Pharmacopeia (USP)* and *National Formulary (NF)* are recognized as official compendia. A drug with a name recognized in *USP-NF* must comply with compendial identity standards or risk being deemed adulterated, misbranded, or both. Drugs must also comply with compendial standards for strength, quality, and purity, unless they are labeled to show all respects in which the drug differs. These Federal requirements arise under the adulterated drugs provision of the FDCA at §501(b) as well as the misbranding provisions at §502. The role of nomenclature is particularly important, since the link to drugs “recognized in an official compendium” at §501(b) arises in the statutory provision that addresses the designation of drugs by “established names” at §502(e).

As explained in 21 CFR §299.4, the Food and Drug Administration (FDA) has statutory authority to designate “official” or “established names,” yet it rarely does so. Instead, while continuing to review *proprietary* (brand) names as part of the drug approval process, FDA defers to USP’s Nomenclature Expert Committee in the Council of Experts and to the U.S. Adopted Names (USAN) Council, in which USP plays a key role, to provide *established/nonproprietary* drug product and drug substance names. Accordingly, the term “established name” means an article recognized in *USP-NF* (see FDCA §502(e)(3)), and drugs with such names must meet *USP-NF* standards for identity as well as (unless labeled otherwise) strength, quality, and purity.

The FDA has extensive authority regarding the labeling of drugs, ranging from the package insert, dispensing, and containers, to advertising and promotional materials. The FDCA provides that a drug with a name recognized in an official compendium—including *USP* or *NF*—will be considered misbranded unless it is packaged and labeled as prescribed therein (FDCA §502(g)). Monograph requirements for packaging and labeling are noted in the *USP-NF* General Notices at 4.10 and are reflected in various monographs and General Chapters.

CURRENT ACTIVITIES

1. THE USP NOMENCLATURE EXPERT COMMITTEE

USP’s Nomenclature Expert Committee establishes nonproprietary names for drug substances, drug products, excipients, biologics, dietary supplements, and medical devices for humans and animals. It also promotes uniformity and consistency among the official titles in the *USP* and *NF*. The Committee is concerned with nomenclature for dosage form monographs and other aspects of the language used in the prescription, dispensing, sale, or manufacture of drugs. The Committee works in a collaborative fashion with the USAN Council, and USP has committed to using the USAN as the title of a drug monograph for that substance. The Committee’s authority to develop official nonproprietary names is identified in section 502(e) of the FDCA. The section indicates that a drug is misbranded if its label does not include the “established name” of the drug and each ingredient. It further specifies that the established name of a drug or ingredient is the official title used for the drug or ingredient in an official compendium such as *USP* or *NF*, as long as the FDA has not designated an official name in accordance with section 508 of the FDCA. In early 2006, a federal appeals court decision confirmed that the nonproprietary names



assigned by the USP Nomenclature Expert Committee take precedence over the names informally approved by the FDA during regulatory review. Taken together, the public-private partnerships created through Congressional authority have provided U.S. practitioners with coherent non-proprietary drug substance and product names, and these good naming conventions promote safe medication use and quality of care.

2. SAFE MEDICATION USE EXPERT COMMITTEE

The Safe Medication Use Expert Committee (SMU EC) began its work in the 2000-2005 cycle and continued in the 2005-2010 cycle. The nineteen members of the 2005-2010 SMU EC were drawn from the professions of medicine, nursing, and pharmacy, and include representatives from academia, research, government, and consumer interest. In this cycle, the SMU EC has reviewed and analyzed medication error reports submitted to USP, and from those, the Committee established recommendations for revision and development of standards in *USP-NF* and made recommendations to the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) discussed later in this white paper. It also developed guidelines, recommendations, a General Chapter, and publications related to safe medication practices and patient safety. The SMU EC's members provided support to USP's two reporting programs—MEDMARX® and the Medication Error Reporting (MER) Program. The SMU EC's focus has been on policy-level priorities for the safe use of medications and patient safety initiatives. Examples of initiatives appear below:

- Total Dose per Total Volume — The SMU EC developed crosscutting support for a requirement to change labeling to indicate total dose per total volume for parenteral packages of 100mL or less. The recommendation was based on errors in which health professionals mistakenly administered the entire vial content in error—published in *Pharmaceutical Forum (PF)* 31(4) [July-Aug 2005]: Strength and Total Volume for Single – and Multiple-Dose Injectable Drug Products.
- Neuromuscular Blocking Agents — An article, “Improving the safety of neuromuscular blocking agents: A statement from the USP Safe Medication Use Expert Committee” was published in the *American Journal of Health-System Pharmacists*, Vol 63, Jan 15, 2006. The work stimulated a new policy statement from the American Society of Health-System Pharmacists (ASHP) on the use of neuromuscular blocking agents. The publication of this article followed the standard instituted by USP that required the warning, “Warning – Paralyzing Agent,” on the closures of neuromuscular blocking agents.
- Patient Safety Stakeholder Forum — A cross-disciplinary Patient Safety Stakeholder Forum was convened on October 11, 2006 to discern the need for the creation of a new USP publication: “Safe Medication Practices Compendium.” This forum was followed by a USP white paper, “Exploring a Strategic Proposal for the Concept of a Compendium of Safe Medication Practices.” It was eventually concluded that additional exploration was needed to develop such a compendium.
- “Error Avoidance Recommendations for Tubing Misconnections When Using a Luer-Tip Connector: A Statement by the USP Safe Medication Use Expert Committee” was published in the *Joint Commission Journal on Quality and Patient Safety*. May 2008. Volume 34, Number 5: pp. 293-296.

- Physical Environments that Promote Safe Medication Use — General Chapter <1066> *Physical Environments that Promote Safe Medication Use* was created to provide safe medication use standards for all health care settings.
- Guidelines or Standards for Computerized Prescription Order Entry and Other Technologies — The SMU EC is working with Dr. Andrew C. Seger and Dr. Gordon Schiff from Brigham and Women's Hospital on an analysis of computerized prescription order entry (CPOE) errors from the MEDMARX® database to develop guidelines/standards.
- "High Alert Drugs by Location" is being drafted by the Medication Error Data Analysis Advisory Panel of the SMU EC.
- Health Literacy and Prescription Container Labeling — The Health Literacy and Prescription Container Labeling Advisory Panel of the SMU EC is working on recommendations for the development of standards regarding simplifying language; using explicit text to describe dosage/intervals, including purpose for use; organizing the label in a patient centered manner; improving readability; and including supplemental information.
- Standardized Intravenous Concentrations — The SMU EC completed analysis of a Standard Intravenous (IV) Concentrations survey of health system pharmacy directors in order to determine the standard drip and flush concentrations being used in their respective facilities for the treatment of neonates, pediatrics, and adults. The goal is to standardize product concentrations to help decrease medication errors. The SMU EC will recommend standard concentrations for ten High Alert Drugs as a follow-up to an IV SMU survey (and an IV Summit held at USP) and publish an article identifying standard IV concentrations for ten High Alert Drugs by patient type.
- Tall-Man Lettering — The SMU EC will publish an article based, in part, on a research survey titled "Tall Man"/ Enhanced Lettering for Medication Name Differentiation. The survey on Tall Man Lettering was conducted in an effort to better understand the current landscape regarding use of and experience with enhanced lettering as a safety tool. Based on the survey results, the USP Nomenclature Expert Committee will consider the advisability of developing standards. A significant number of responses (1,788) were received from pharmacists (60%), nurses (16%), and physicians (16%), with the remainder coming from pharmacy technicians, nurse practitioners, and other healthcare providers. Cooperation in disseminating the survey was obtained primarily from the American Society of Consultant Pharmacists, the ASHP, the Institute for Safe Medication Practices (ISMP), the Joint Commission, and the National Alliance of State Pharmacy Associations.
- Harmonization with WHO Label Standards for Vincristine and Other Vinca Alkaloids — Three component changes were recommended to reduce the chance of vincristine (and other vinca alkaloids) being administered by the intrathecal route (which is universally fatal). Through a reworded cautionary statement, the recommendation would change to overwrap alert labeling and add a cautionary statement on the cap and



ferrule of the vial. (This proposal is currently under consideration by the Nomenclature Expert Committee.)

3. THE NATIONAL COORDINATING COUNCIL FOR MEDICATION ERROR REPORTING AND PREVENTION

USP serves as the Secretariat for the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP/The Council), an independent body comprised of numerous national organizations. The Council was formed in 1995 through the efforts of its member associations and agencies to focus on ways to enhance patient safety through a coordinated approach and a systems-based perspective.

An interdisciplinary group of 15 organizations and agencies held its first meeting in July 1995. In the past 14 years, the Council has grown to 26 member organizations and two individual members. The five goals that continue to direct the Council's activities are:

- Stimulate the development and use of reporting and evaluation systems by individual health care organizations;
- Stimulate reporting to a national system for review, analysis, and development of recommendations to reduce and ultimately prevent medication errors;
- Examine and evaluate the causes of medication errors;
- Increase awareness of medication errors and methods of prevention throughout the health care system; and
- Recommend strategies for system modifications, practice standards and guidelines, and changes in packaging and labeling.

Council Accomplishments—1995 to Present:

- Defined a “medication error” and encouraged all stakeholders to use this definition to provide a uniform basis for medication error reporting and analysis.
- Developed a medication error taxonomy, index and algorithm for categorizing medication errors
- Issued a statement on calculating medication error rates
- Promulgated recommendations for:
 - Prescribing
 - Labeling and packaging
 - Dispensing
 - Administration



- Verbal medication orders
- Standard bar codes on medication packages and containers
- Reducing medication errors in non-health care settings
- Reducing at-risk behaviors
- Bar coding labels to reduce medication errors
- Promoting safe use of drug suffixes
- Avoiding medication errors with drug samples

The Council has had national and international impact through its multidisciplinary conferences on bar coding, drug nomenclature, and suffix use. Continuing activities and other accomplishments include:

- 1) Developing and disseminating standardized definitions for terms such as *adverse drug event, adverse drug reaction, harm, preventable event*;
- 2) Establishing a dedicated Web site for organizations, government, and practitioners to reference The Council's recommendations and other information;
- 3) Developing a solid oral dosage forms article for broad dissemination;
- 4) Endorsing the ISMP *Safety Self-Assessment for Community/ Ambulatory Pharmacy*;
- 5) Establishing consumer information links to The Council's Web site;
- 6) Developing and disseminating a white paper on the use of bar codes;
- 7) Signing on to a set of *General Principles* supporting legislation to uphold, as privileged, information submitted to error reporting programs (These *General Principles* were incorporated into the Patient Safety and Quality Improvement Act of 2005 that was signed into law on July 29, 2005.);
- 8) Recognition with the 2007 American Pharmacists Association Foundation Pinnacle Award; and
- 9) Receipt of the 2008 Eisenberg Award.

In the coming years, The Council will continue to focus on key issues impacting the safe use of medications. With the help of new and enthusiastic member associations and agencies, The Council will address medication reconciliation as well as geriatric and long-term care issues. The members of The Council are recognized at www.nccmerp.org.



PRIOR ACTIVITIES: USP'S REPORTING PROGRAMS TO SUPPORT STANDARDS

1. DRUG PRODUCT PROBLEM REPORTING PROGRAM

Because of concern with the quality of drug products on the market, in 1971, the USP and the FDA co-founded the Drug Product Problem Reporting Program (DPPR). This was a national program in which health professionals voluntarily reported problems and defects experienced with drug products marketed in the United States. Often, product problems or defects had to do with inadequate packaging or labeling that could lead to errors or confusion on the part of health professionals. Other problems such as inclusion of foreign matter, suspected contamination, questionable potency, and "bioinequivalence" based on observed therapeutic response were also reported among the more than 100,000 observations gathered in DPPR. USP terminated the DPPR contract with the FDA in 1987, but continued a USP Drug Reporting Program until August 2000.

2. MEDICAL DEVICE AND LABORATORY PRODUCT PROBLEM REPORTING PROGRAM

Together with the DPPR Program, USP operated the Medical Device and Laboratory Product Problem Reporting Program (PRP) under contract with the FDA Center for Devices and Radiological Health (CDRH). In this program, USP collected reports on defective medical devices and shared that information with both CDRH and the manufacturers involved in incidents. This program had a major impact on the use of breast implants, dental implants, and marijuana testing kits. It was the precursor to the FDA's MedWatch program. This contract with the FDA was terminated in September 1995.

3. VETERINARY REPORTING PROGRAM

In 1994, USP established a Veterinary Reporting Program (VRP) to assist the FDA's Center for Veterinary Medicine (CVM), the Environmental Protection Agency, and the Department of Agriculture in obtaining information about adverse events with veterinary products. Reports were shared with the appropriate government agency and with the manufacturers of the products involved in the reports. The program was terminated in April 2003.

4. MEDICATION ERROR REPORTING PROGRAM

In 1991, USP established its first Medication Error Reporting Program (MER) in conjunction with the ISMP. MER was designed to obtain spontaneous reports both for the medicine itself and the system in which the medicine was prescribed, dispensed, administered, and used. Between 1991 and 2008, MER received more than 6,000 voluntary reports of actual and potential medication errors. MER identified errors in various health care delivery environments, including hospitals, nursing homes, physicians' offices, pharmacies, emergency response vehicles, and home care. The reports documented that errors are multi-disciplinary and multi-factorial and that they may be made by experienced as well as inexperienced health professionals, support personnel, interns, students, and even patients and their caregivers. Medication errors can and regularly do occur anywhere along the continuum from prescribing to transcribing to dispensing and administration. The causes of errors may be attributed to human error, to product names or designs, and to the medication handling and delivery systems in which the products are used and in which individuals operate and interact. USP submitted MER reports to the FDA as a



MedWatch partner, including adverse drug reactions that came to MER but were not evaluated. MER reports were also shared with the relevant manufacturers.

Examples of important changes USP made to its standards as a result of MER reports appear below:

- Potassium Chloride — Reported deaths due to the accidental misadministration of concentrated Potassium Chloride Injection led to: 1) changing the official USP name to Potassium Chloride for Injection Concentrate to give more prominence to the need to dilute the product prior to use; 2) requiring that labels bear a boxed warning with the words "Concentrate: Must be Diluted Before Use;" 3) requiring that the cap must be black in color (the use of black caps is restricted to this drug product only); and 4) requiring that the cap must be imprinted in a contrasting color with the words "Must be Diluted."
- Vincristine Sulfate — Reported deaths due to confusion and the resultant injection of the anticancer drug, Vincristine Sulfate for Injection, directly into the spine instead of the vein resulted in changes in the requirements for packaging by pharmacies and manufacturers preparing ready-to-use doses. Each dose, whether prepared by the manufacturer or the pharmacist, must now be wrapped in a covering labeled "FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES" and that covering may not be removed until the moment of injection.
- Amrinone/Amiodarone — Reported deaths due to the confusion of similar names Amrinone and Amiodarone led USP and the USAN Council to change the nonproprietary name and official title of Amrinone to Inamrinone.
- Neuromuscular Blocking Agents — Reported deaths due to the inadvertent mix-up of neuromuscular blocking agents (which paralyze the respiratory system) with other drugs led to recommended changes in standards for labeling and packaging of the therapeutic class of neuromuscular blocking agent products.

5. MEDMARX®

MEDMARX® was developed by USP in 1998 as an Internet-accessible, anonymous reporting program that enables hospitals to voluntarily report, track, and trend data, incorporating nationally standardized data elements (i.e., definitions and taxonomy). These standardized elements were drawn from the work of the MER Program, the FDA, NCC MERP, and the ASHP. MEDMARX® is structured to support an interdisciplinary, systems-approach to medication error reduction and fosters a non-punitive environment for reporting. USP created MEDMARX® with the intent to broaden the model to include other health care settings, e.g. long-term and ambulatory care settings, and to include other types of reporting such as medical error and adverse drug reactions.

Hospitals are encouraged to use MEDMARX® as part of their internal quality improvement processes, thereby extending their "peer-review" to other hospitals in the program. Hospitals can review errors entered by other institutions in "real time" and also see any reported action taken by another institution in response to an error in an effort to avoid similar errors in the future.



This feature affords institutions the opportunity to examine errors in a proactive manner. For example, the institution can review the error profile of a drug or class of drugs to determine if certain risk prevention measures or training programs should be established within the institution before a product is added to the institution's formulary. If the error profile is significantly serious, a determination may be made not to stock the drug. MEDMARX[®] supports the performance improvement standards of the Joint Commission, which requires institutions to look outward at the experiences of others in order to reduce risk.

USP transferred its reporting programs, MEDMARX[®] and MER, to Quantros and ISMP, respectively, in 2008. USP will continue to use data from these and other programs to enhance its standards-setting activities to promote patient safety and safe medication use. In the interest of public health and to assist practitioners and patients, USP has posted eight annual reports on its Web site free of charge, ensuring full access to this clinically important information.

FUTURE OPPORTUNITIES

1. NOMENCLATURE, SAFETY, AND LABELING EXPERT COMMITTEE FOR THE 2010-2015 CYCLE

In the next cycle, a new expert committee—Nomenclature, Safety, and Labeling Expert Committee— will combine the work of the Nomenclature and Safe Medication Use Expert Committees from the 2005-2010 cycle. This new Expert Committee will build on the work of its predecessors by continuing to develop guidelines, recommendations, General Chapters, and publications related to safe medication practices and patient safety, as well as by linking these efforts to drug naming and the labeling of medications. Via Expert Panels, specific standards-setting activities can be addressed on a broad range of safe medication use and quality of care standards.

2. INSTITUTE OF MEDICINE

In 2007, the IOM published *Preventing Medication Errors*, a report by its Committee on Identifying and Preventing Medication Errors. The report called on USP to work with the FDA and others in several areas related to drug naming, labeling, and packaging. The IOM posited that there are many ways that basic information about a specific drug is communicated to providers and patients and identified some of the more obvious problems:

- Brand names and generic names that look or sound alike
- Different formulations of the same brand or generic drug
- Multiple abbreviations to represent the same concept
- Confusing word derivatives, abbreviations, and symbols
- Unclear dose concentration/strength designations



- Cluttered labeling—small fonts, poor typefaces, no background contrast, overemphasis on company logos
- Inadequate prominence of warnings and reminders
- Lack of standardized terminology

The proposed IOM action plan focused on two overarching principles: 1) product naming, labeling, and packaging should be designed for the end user—the provider in the clinical environment and/or the consumer; and 2) safety should always take precedence over commercial interests. In addition, Recommendation #4 of the IOM report included USP in a list of organizations that should work together to address labeling, packaging, and the distribution of free samples.

CONCLUSION

Based on its nomenclature and labeling recognition in the FDCA and exhortations from the community, the need for USP's involvement in standards to promote safe medication use and quality care is as strong as ever—and may increase in an era of health care crisis and reform. One of USP's greatest strengths lies in its ability to convene a broad and diverse group of stakeholders around issues common to all, and USP can leverage this role by helping to advance standards related to medication safety that are beyond the scope of a single health profession or professional organization. For many years, USP has devoted substantial resources and energy to its safe medication use and quality of care standards-setting activities, but has struggled to find a sustainable financial and public health model for these activities. Convention Delegates must now ask: What is the appropriate role for USP in setting standards related to medication/patient safety, and how will this role be financially supported? The Council of the Convention Section on the Quality of Patient Care calls on the Convention membership to articulate ways in which a standards-setting body such as USP can continue its work based on USP's historical contributions, unique capabilities, and current and possible future positions in law.



WHITE PAPER

USP'S ROLE IN ASSURING GLOBAL ACCESS TO QUALITY MEDICINES

SEPTEMBER 23, 2009

COUNCIL OF THE CONVENTION SECTION ON GLOBAL PUBLIC HEALTH

INTRODUCTION

Today, global access to quality medicines increasingly is threatened by many factors, including the presence of both substandard and counterfeit medicines. Substandard medicines¹ can occur even when they are manufactured according to quality standards and Good Manufacturing Practices (GMPs). Counterfeit medicines², on the other hand, which account for a larger percentage of poor quality medicines in resource-limited countries, occur because there is a deliberate intention to mislead. In both instances, however, the result is poor quality medicines that deny practitioners and patients of achieving expected health outcomes. Poor quality medicines can be especially burdensome in developing countries where they not only fail to produce needed results, but also absorb limited resources, undermine faith in already tenuous health systems, and may promote antimicrobial resistance to devastating infectious diseases such as HIV, malaria, and tuberculosis. Poor quality medicines represent a failure of standards and conformity assessments to standards, and such failures can and do arise at multiple points in the medicines continuum; from discovery, to development, to registration, through manufacturing and distribution, to utilization. The globalization of pharmaceutical markets has exacerbated this growing problem of poor quality drugs, particularly in countries that lack strong drug regulatory systems and oversight. Whatever standards and conformity assessments there are for medicine supply chains—from suppliers to manufacturers, and thereafter from practitioners to patients—these supply chains are becoming increasingly fragmented and fragile.

The United States Pharmacopeial Convention (USP) offers standards that help ensure the quality of processes and products. The process standards include good manufacturing practices and supply-chain management standards. Product standards are offered in monographs with tests, procedures, and acceptance criteria to allow ingredient and product testing. End product or in-process testing at key points along manufacture and supply continua are key components in the series of safety nets that result in quality medicines. For medicines, including natural source and rDNA biologicals, USP's compendia are the *United States Pharmacopeia (USP)* and *National Formulary (NF)* for excipients. While not regulated in the U.S. as medicines but rather as foods, dietary supplements are included in USP's compendial approaches, and *USP* is alluded to as a source of standards in the Dietary Supplement Health and Education Act (DSHEA)

¹ Legally registered product that does not meet official USP standards for identity, quality, purity, strength, packaging and labeling.

² Product that is deliberately mislabeled for identity and/or source. Usually there is no active ingredient or a different active ingredient than stated on the label.



amendments to the Food, Drug and Cosmetic Act (FDCA). Recently, USP published a *Dietary Supplements Compendium* for dietary supplements and their ingredients (known as traditional medicines outside the United States). Although USP is not a conformity assessment (enforcing) body, it offers conformity assessments through third party verification programs for dietary supplements and their ingredients as well as medicinal ingredients. USP also provides programs to support training and education in compendial and allied standards. These programs, in turn, can support certification activities for compendial and health professionals.

In this white paper, the USP Council of the Convention Section on Global Public Health presents background information and proposals to stimulate Convention discussion on the roles and responsibilities of a volunteer-driven, practitioner-based standards setting body in promoting global public health through its standards-setting and allied public health activities.

BACKGROUND AND STATUS OF USP'S GLOBALIZATION EFFORTS

1. BURDEN OF COUNTERFEIT, SUBSTANDARD, OR ADULTERATED MEDICINES

Approximately 15% of all drugs in circulation are believed to be substandard or counterfeit, with the clinical and financial burdens falling most heavily on developing countries. In some parts of Africa and Asia, as much as 50% of the medicines in commerce may be counterfeit.³ More than one-third of chloroquine-containing and antibacterial medicines collected in Nigeria and Thailand were found to be below compendial standards as a result of degradation and poor manufacturing.⁴ Countries with limited resources face many challenges that can result in poor quality medicines, including weak regulatory systems, poorly staffed and equipped national drug control laboratories (official medicines control laboratories), and poor enforcement due to corruption or lack of political will. Heat and humidity common to many developing countries can reduce quality during manufacture, storage, and distribution. In recent years, many countries—irrespective of their development—have been challenged by episodes of economically-motivated adulteration. Melamine, diethylene glycol, and over-sulfated chondroitin sulfate have created morbidity and mortality within countries and across regions of the globe.

2. USP AND ADULTERATION

As the United States entered the 20th Century, the state of its supply of medicines was poor and deteriorating. This was the era of Dr. Harvey Wiley (a President of the USP Convention) and his poison squad.⁵ And it also was an era in which Congress, in 1906, first established a statutory role for USP in helping to assure drug quality. By 1938, Congress had established the modern role we know today for USP-NF as official compendia under the FDCA. Under the FDCA, a drug with a name recognized in USP-NF must comply with compendial identity standards or be deemed adulterated, misbranded, or both. Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs.⁶ Although USP-NF standards have an important

³ Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ. The Global Threat of Counterfeit Drugs: Why Industry and Governments Must Communicate the Dangers. *PLoS Med* 2005;2(4): e100. Accessed on June 1, 2009: <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0020100>.

⁴ Shakoor O, Taylor RB, Behrens RH. Assessment of the incidence of substandard drugs in developing countries. *Tropical Medicine and International Health*. 1997;2:839–845.

⁵ <http://www.fda.gov/AboutFDA/WhatWeDo/History/CentennialofFDA/HarveyW.Wiley/default.htm>

⁶ *Federal Food, Drug, and Cosmetic Act* §201(j), §§501(b), 502(e)



role in federal law, the enforcement of compendial standards is the responsibility of the U.S. Food and Drug Administration (FDA) and other governmental authorities.

3. USP AND GLOBALIZATION

Historically, USP's Convention membership has been sympathetic to international public health opportunities⁷ and has always strongly supported the work of the World Health Organization (WHO) and its regional offices (particularly the Pan American Health Organization) and other international organizations that work to promote global public health. In the 1990s and the first decade of the 21st Century, USP accelerated its international efforts. A key decision occurred in the first year of the 2005-2010 cycle when the USP Board of Trustees endorsed development of overseas sites, first in Europe, then in India, China, and finally, in Brazil. Subsequently, the Board advanced a new strategic plan that emphasized the importance of working internationally, which resulted in USP defining key regions and countries of the world for special focus (Attachment 1). USP's overseas sites were located where USP could have the greatest public health impact—in countries where the largest amount of active pharmaceutical ingredient and dosage form manufacturing is occurring.

This effort has accelerated with more focused initiatives, including language translations; increased global availability of USP's products and services; and technical assistance provided to ministries of health, regulatory agencies, and national drug control laboratories. USP's international effort has been forging closer ties with governmental agencies, resulting in the potential for increased cooperation in standards development. At the same time, USP's standards-setting role and allied financing model (sale of books and reference materials to support its work) at times limits understanding of its broader public health service role and creates the perception that USP is too commercial in nature.

USP's dependence on revenue from the sale of its books and reference materials stems from the fact that, unlike other pharmacopeias in the world, USP is non-ministerial and receives no government funding for its standards activities. While other pharmacopeias receive financial support from their governments and may also sell their products and services to manufacturers as an additional means of support, USP must rely solely on self-generated income to fund its activities.

USP's regional focus usually allies well with this traditional financing model, which brings products and services directly to first parties (manufacturers of medicines and pharmaceutical ingredients) who wish to demonstrate adherence to quality standards by use of the *USP* and *NF* marks—a traditional value of USP irrespective of whether *USP* and *NF* are recognized in national law. However, only a small fraction of the world's ~200 countries have a significant number of manufacturers whose purchases of USP's products and services can help finance USP's other public health activities. For regions without a significant manufacturer presence, USP must find additional resources to support its work in promoting access to quality medicines.

USP's international initiatives have met with other challenges as well. For example, an attempt to create monographs for articles legally marketed outside of the U.S. (non-U.S. authorized monographs) failed because of constraints on the opportunity (monographs only for neglected infectious diseases) and also in execution (staff were challenged to understand the differentiation in monograph stipulations needed to control the same article in different countries).

⁷ Resolutions: Standards for Non-USA Articles (1985, 1995); International Harmonization (1990, 2000, 2005); Global Scope – Information (1995); and International Presence (2005).



Many organizations in the United States have advanced successfully into global activities. In some ways, USP came somewhat late to these opportunities and, despite impressive success in a few short years, it remains to be seen whether the organization can advance from its national base to act successfully on the world stage in a way that has real impact on global health.

4. USP'S INTERNATIONAL PROGRAMS

The following summarizes USP's specific international activities and initiatives that, along with the development of its overseas sites, have been part of its globalization.

a) *The USP Council of Experts: International Health Expert Committee*

In the 2005-2010 cycle, the USP Council of Experts formed an International Health Expert Committee (IHEC) that met at least yearly to consider key issues and opportunities to promote access to quality medicines. In addition, the Expert Committee formed advisory panels to cover key topics. A brief summary of the work of the Expert Committee and its advisory panels appears below:

- CIPIH Advisory Panel – This advisory panel, led by committee member Stan N. Finklestein, M.D., developed a paper entitled *How Does the Regulatory Framework Affect Incentives for Research and Development?* in response to a request by the WHO's Commission on Intellectual Property Rights, Innovation, and Public Health (CIPIH).
- African Health Advisory Panel – This advisory panel, led by committee member Andrew Walubo, M.D., conducted a study on the issues of the healthcare system in Sub-Saharan Africa, including the drug distribution system, drug regulatory authority, and drug quality-control laboratories. Dr. Walubo developed a paper entitled *The Drug Situation in the Sub-Saharan Africa* that identified major problems such as widespread killer diseases (malaria, HIV and TB), counterfeits, lack of skilled personnel, and weak regulatory mechanisms. Following a suggestion from the IHEC, Dr. Walubo also wrote two business proposals for strengthening the quality control laboratories and drug regulation's personnel skills in South Africa, and drug quality testing in rural Uganda using Mini Laboratory tools.
- Spanish Translation Advisory Panel – This advisory panel, led by committee member Dr. Enrique Fefer, Ph.D., and supported by staff member Mr. Damian Cairatti, has provided oversight to the translation of the *USP-NF* into Spanish, now in its third consecutive official edition, including Supplements and corresponding online versions. The panel has also undertaken translation of the 4,400 redesigned monographs that will be part of the 2010 revision of *USP-NF*.
- Russian Translation Advisory Panel – This advisory panel, led by committee member Roman Koslov, M.D., Ph.D., completed the publication of the *USP-NF* Russian Edition (unofficial) with plans to publish updates in 2009 and 2010 to bring the book to official status. An electronic version is under consideration.
- Chinese Translation Advisory Panel – This advisory panel was led by committee member Professor Zhong-Yuan Yang. A Memorandum of Understanding (MOU) between USP and the Chinese State Food and Drug Administration specifies four areas



of collaboration including *USP-NF* Chinese translation and third party verification of pharmaceutical ingredients.

- Collaboration with WHO – The IHEC provided comments on WHO Guidances (normative documents), which are developed by WHO staff with input from experts from around the world. The guidances most relevant to USP are advanced through two WHO Expert Committees: the Expert Committee on Specifications for Pharmaceutical Specifications and the Expert Committee on Biological Standardization.

b) *USP Drug Quality and Information Program*

The USP Drug Quality and Information Program (USP DQI) is a cooperative agreement with the United States Agency for International Development (USAID) in which USP is funded to provide technical assistance to developing countries. The program was begun in 2000 as a follow-on to the Rational Pharmaceutical Management Plus program. The agreement was extended in 2005 and, more recently, is on track for extension and expansion in 2009. While the program initially focused on drug information, drug quality initiatives were added in 2003 and have become the primary objective. Through staff located in USP's Rockville headquarters, USP DQI works with governments in more than 30 countries, USAID missions, WHO, and other partners to evaluate a country's readiness and capacity to provide quality medicines. Working through in-country mechanisms, USP DQI obtains targeted funds to develop or strengthen drug registration processes, drug quality assurance systems, national drug quality control laboratories, and postmarketing surveillance systems. USP DQI also assists manufacturers in developing countries to improve their good manufacturing practices (GMP) to reach WHO prequalification status. The USP DQI program has established a presence in USAID-priority countries on four continents, advancing strategies to improve drug quality and the appropriate use of drugs. Examples of current work appear in Attachment 2.

c) *John Snow, Inc. and Population Services International*

In 2007, USP received funding outside its USAID cooperative agreement to support additional activities in developing countries. This included sub-contracting awards with John Snow, Inc. (JSI) and Population Services International (PSI). JSI implements DELIVER, a separate USAID Project. USP's role in the project is to provide technical services (i.e., development of standard operating procedures, GMP audits, and laboratory testing) to ensure the quality of antimalarial medicines being procured for and/or by developing countries. USP has also partnered with PSI in the ACT Watch project, a study funded through a private grant from the Bill and Melinda Gates Foundation. USP's objective in this initiative is to assess the quality of Artemisinin-based Combination Therapy (ACT) antimalarial medicines in developing countries in sub-Saharan Africa and Southeast Asia.

d) *USP's Verification Programs*

In the early years of the 21st Century, USP began third party verification programs designed to fill regulatory gaps for dietary supplements and their ingredients and medicinal ingredients. As conceived, the program was designed to mimic a regulatory process for articles, with careful document review, testing, GMP audits, and post-market surveillance. The status of articles that have been verified appears below. The program has had slower than expected uptake for several reasons, including cost of execution and the absence of regulatory and/or consumer recognition. Yet, it remains an opportunity that might be useful in developing countries, perhaps with suitable



modifications and with adequate funding, to assist in promoting access to quality medicines. USP's program was adapted successfully as part of the USAID cooperative agreement to independently qualify an artesunate-amodiaquine combination medicine from China for use in Liberia. Its use in developing countries might be especially valuable where good manufacturing and supply chain process standards and conformity assessments to these and other standards are weak or non-existent. It might also be used to prepare manufacturers for more stringent regulatory assessments, including WHO's prequalification program.

| Verification Program | Number of Companies | Verified Products/Ingredients | Number of Products/Ingredients Undergoing Verification |
|-----------------------------|---------------------|-------------------------------|--|
| Dietary Supplements | 10 | 175* | 15 |
| DS Ingredients | 13 | 38 | 10 |
| Pharmaceutical Ingredients: | | | |
| • Drug Substances | 7 | 16 | 3 |
| • Excipients | 3 | 52 | 0 |
| Total | 33 | 281 | 28 |

* This number represents over 296 million labels on over 800 unique SKUs of products represented by various label brands, such as Nature Made, Kirkland Signature, Sunmark, B&J, Yourlife, Equaline, Longs, etc.

e) USP's Pharmacopeial Education Programs

At USP's 2000 Membership Meeting, a resolution was adopted encouraging USP to consider creating an educational program to further the understanding and optimal use of the robust standards, monographs, and information contained in the USP-NF. An education program was launched in 2002 and has grown into a unique department capable of offering over thirty different continuing education courses that are taught in various countries across the world. During the past year, USP's Pharmacopeial Education Department has conducted over 100 programs reaching nearly 3,000 science professionals in 20 countries. These educational programs provide highly useful information to manufacturers, purchasers, retailers, healthcare professionals, and government testing laboratories. As USP creates new standards or revises existing standards, corresponding educational courses are created to help inform and train the world's science community on these changes. USP strives for increased access to its educational offerings by developing Internet-based courses and by working with international organizations and governments to offer educational programs at national, regional, and local levels. Despite some success, USP's education and training programs remain in some ways "pilot" approaches that need careful consideration in the coming years to make them as value-added and robust as they can be. In many developing countries, these programs could be amplified with courses on GMPs, supply chain management, and registration topics. Partnering with ministries, agencies, academia, manufacturers, practitioners, and their associations—aided by revolutions in information technology that support distance learning—add further opportunities for success.



SUMMARY AND PROPOSALS FOR CONSIDERATION

USP advanced its international presence and activities vigorously in the 2005-2010 cycle based on decisions of the USP Board of Trustees and supported by Convention members through resolutions adopted at the 2005 Convention (as well as prior Conventions). This progress complemented the ongoing work of the USP DQI cooperative agreement with USAID. Together, the joint efforts bring USP into all parts of the world.

While USP's offerings are small relative to need, USP has experienced resistance at times from other public health bodies whose missions appear to mimic those of USP. As discussed above, this resistance comes from confusion between USP's standards-setting activities and its public health mission to promote access to quality medicines throughout the world. Also, USP's role as a non-governmental, non-profit, standards-setting body and its associated freedom of action is confusing to many. For the most part, USP believes the issues arising in this context are readily resolved through better understanding and communication, evolving with recognition that there is far more than enough work and "space" for all parties to make a valuable contribution.

USP's own resources must always be husbanded carefully, and the organization's financial situation no longer allows funds to support non-core compendial activities, including activities in developing countries. Nevertheless, USP's scarce financial resources should not overshadow the rich resources reflected in the knowledge, skills, and commitment of its volunteers—Convention delegates, the Board of Trustees, and the Council of Experts—or the expertise of its staff and stakeholder groups. Bolstered by its existing products and services, USP could have a significant impact working with others in developing countries. Funding alternatives such as cooperative agreements, grants, and contracts would allow USP to expand its work to improve global access to quality medicines.

With these challenges and limitations in mind, this white paper from the Council of the Convention Section on Global Public Health calls on all USP volunteer experts and their cumulative wisdom to consider ways to marshal USP's forces internationally for the next cycle in accordance with USP's mission. Ideas for consideration include:

- 1) Global approaches to registration and control of medicines through both ministerial and non-ministerial approaches. An example of an approach to global registration and control appears in Attachment 3.
- 2) Special programs to advance regional networks of activity and interest to promote access to quality medicines. A summary of a white paper from the African Health Advisory Panel of the IHEC appears in Attachment 4.
- 3) Approaches that lead to the availability of "global comparator pharmaceutical products" (in the U.S., the reference listed drug) and global primary reference materials coupled with any acceptable procedure to achieve sound measurements of medicines and their ingredients to assure their identity, strength, quality, and purity.⁸

⁸ Williams, R.L. & Shah, Vinod (2008). Continuing equivalence: is there an end to the story? *Journal of Generic Medicines*, July 5(4), 297-304.



- 4) Approaches that support continuing equivalence of all medicines relative to a comparator pharmaceutical product using life cycle management, quality by design, and harmonized compendial approaches.
- 5) Approaches that support drug control laboratories to promote market access, market surveillance, and compendial updating. An example of a regional network approach appears in Attachment 5.
- 6) Compendial approaches that rapidly advance harmonization to avoid duplicative testing, reduce cost of medicines, and promote quality medicines irrespective of country or region.
- 7) Spectral libraries using multiple portions of the electromagnetic spectrum coupled with advanced informatics and instrumentation for all materials (food and drug products, ingredients, and impurities, together with their packaging), along with global surveillance networks to signal outbreaks of substandard, fake, and/or adulterated medicines. Libraries of acceptable materials and products would also include known or likely adulterants for drugs and contaminants for foods.
- 8) Approaches using modern informatics including Web based systems to bring useful information to practitioners and patients throughout the world—in their languages and at a level where comprehension is possible—to allow understanding of the importance of quality medicines used rationally to maintain health and treat disease.
- 9) Expanded activities, alternately funded, that advance the types of products and services that USP DQI can offer. Examples of areas of focus and opportunity appear in Attachment 6.

Taken together, the opportunities are immense for USP's cadre of volunteers and staff, working through appropriate partners and with suitable funding, to promote global access to quality medicines rationally used. The Council of Convention Section on Global Public Health is pleased to offer this white paper to Convention members for their consideration.



ATTACHMENT 1

USP'S INTERNATIONAL ACTIVITIES

“Where”

| USP World Region | North America | Latin America | West Europe | East Europe | Middle East, North Africa (MENA) | Sub-Saharan Africa | South Asia | Asia Pacific |
|---|-------------------|------------------|-------------|--------------------------------------|----------------------------------|--|--------------------------|---|
| Partners | USP Rockville HQ | Brazil Site | Basel Site | | | | India Site | China Site |
| Ministries of Health | MOU-Health Canada | | | | | | | |
| Regulatory Agencies | FDA | PAHO MOU-FEUM | MOU-NIBSC | MOU-Russia ROSZDR AVNADZ OR | MOU-Jordan FDA | African Medicines Regulatory Harmonization Initiative (Developing) | | MOU-China SFDA MOU-Singapore HSA ASEAN (Developing) |
| Official Medicines Control Laboratories (OMCLs) | | PANDRH | | | | | | |
| Pharmacopeial Agencies | | | | | | | MOU-Indian Pharmacopoeia | MOU-NICBPB |
| Manufacturers | | MOU-Sindusfarma | | | | | MOU-PHARMEXCIL | |

“Who”

“How”

- Headquarters and Sites
- Relationships with Networks
- Memorandums of Understanding (MOUs)
- Annual Science Meetings (ASMs)/Stakeholder Forums
- Marketing & Sales
- USAID/Contracts



ATTACHMENT 2

USAID-FUNDED USP ACTIVITIES (CURRENTLY USP DQI)

GENERAL OVERVIEW OF HOW USP DQI WORKS IN ALL COUNTRIES

When USP DQI is invited into a country by USAID, staff first establishes a cooperative working relationship with the country leadership including the Ministry of Health, national steering committee, drug regulatory agency (DRA), drug quality control laboratory, infectious disease programs, pharmacists associations, related pharmacy schools, and provincial health authorities. The first step is to assess the current QA/QC situation, determine gaps in their programs, and propose how USP DQI can assist them. The goal is to strengthen their QA/QC capacity by addressing drug registration, good manufacturing and good laboratory practices (GMPs and GLPs), laboratory testing capability, post-marketing surveillance, as well as good storage and distribution practices. USP DQI partners with international organizations (IOs) and Nongovernmental Organizations (NGOs) working in the region by coordinating efforts and shaping activities to meet individual needs of the country. USP DQI published “Ensuring the Quality of Medicines in Resource-Limited Countries: An Operational Guide,” which discusses all aspects of drug quality; four co-authors were from DRAs of developing countries; others were partners from World Health Organization (WHO), Management Sciences for Health (MSH), PATH and other organizations.

ASIA AND NEAR EAST REGION

USP DQI has worked in the Mekong sub-Region since 2003, primarily in **Cambodia, Laos, Thailand, and Vietnam**, specifically targeting antimalarial medicines. USP DQI staff has provided technical assistance by:

- Supplying essential lab supplies and equipment;
- Conducting laboratory and surveillance training—lab set-up, GLP, basic and advanced testing, equipment maintenance, Minilab®¹ use, sampling procedures, documentation, and data analysis and reporting;
- Establishing surveillance programs in 39 sentinel sites.

Surveillance in Cambodia, Thailand, and Vietnam covers antimalarial and other anti-infective medicines, including selected antibiotics, anti-tuberculosis and antiretroviral drugs. The results allow local, national and regional governments to take law enforcement action and to alert health professionals and the public to problems.

¹ Minilab® is a small portable (suitcase) laboratory equipped to do basic drug quality testing in the field.

USP DQI also collaborates with INTERPOL and WHO to thwart counterfeit medicines production in Southeast Asia. Data from the medicines monitoring programs in Cambodia, Laos, Thailand, Vietnam, and the Philippines has been used in covert operations that have led to arrests and seizures of fake medicines. Within this collaboration, USP DQI staff also trained customs, drug regulatory, and police officials on how to identify fake medicines using Minilabs®, as well as on proper sampling techniques.

Vietnam and **Laos** each hosted a “Training on the Quality, Safety and Rational Use of HIV/AIDS Medicines,” a seminar to inform pharmacists about managing the treatment of HIV/AIDS, in September 2008. USP DQI organized and facilitated the seminars.

Laos and **Cambodia** recently received training on good practices for medicines procurement, distribution, storage, and dispensing, focusing on antiretrovirals. **Cambodia** and **Vietnam** were recently trained on expanding quality monitoring to anti-infective medicines.

Cambodia has filmed public service announcements on the importance of drug quality and the danger of counterfeit medicines as part of its public awareness campaign, which will air in local languages in Cambodia, Laos, Thailand, and Vietnam. The campaign also featured articles in Health Messenger and the WHO DVD Dealers in Death. USP DQI organized a workshop and offered technical assistance to help the Cambodian Department of Drugs and Foods establish a pharmacovigilance center, which has since been awarded associate membership in the WHO International Drug Safety Monitoring Program. Analysts in the national drug quality lab were also trained on bioavailability and bioequivalence.

Cambodia/Thailand are cooperating to conduct a study of antimalarial drug quality in Cambodian/Thai border provinces using randomized sampling methodology to document possible links to antimicrobial resistance and drug quality.

Thailand has received training in Good Manufacturing Practices to improve skills for the Center of Excellence and Minilab® training for sentinel site staff.

The **Asian Network of Excellence in Quality Assurance of Medicines** (ANE/QAM) comprising three institutions was established with USP DQI/USAID assistance to share their expertise in drug quality to serve the needs of the region. The institutions include Mahidol University Faculty of Pharmacy and Chulalongkorn University/Pharmaceutical System Research and Intelligence (PSyRIC), which are located in **Thailand**, and the University of Santo Thomas Center for Drug Research, Evaluation & Studies, which is located in the **Philippines**. USP DQI helps strengthen the unique capabilities of each Center through training and technical consultation. PSyRIC is building a public drug quality database to centralize results of surveillance testing.

Philippines began monitoring the quality of antimalarial drugs at two sentinel sites in 2005. Recently, a five-day Minilab® training was conducted at the Bureau of Food and Drugs in Manila for six selected sentinel sites targeting antituberculosis medicines in the Filipino market.

Bangladesh is now able to manufacture zinc tablets locally; USP DQI has assessed three company facilities and is providing technical guidance to two to help them meet WHO prequalification status to provide medicines for UNICEF.

Nepal recently had three manufacturers assessed by USP DQI for GMPs on zinc tablets in order to become UNICEF-prequalified. In 2009, a chlorhexidine manufacturer was also assessed. Nepal was one of the first countries in which USP worked in the early days of the USAID agreement. In that work, a network of eight drug information centers was established.

USP DQI assessed three companies in **India** for GMPs for the manufacture of antituberculosis drugs and also has begun reviewing dossiers that manufacturers will submit to WHO for pre-qualification status.

For Avian Influenza, USP DQI developed monographs for oseltamivir and testing guidelines compatible with the Minilabs® capability. A quality monitoring system for oseltamivir has been established in the **Asia and Near East Region**, with mapping all suppliers and distributors in an attempt to improve the quality of stockpiled and circulated oseltamivir.

SUB-SAHARAN AFRICA

Many of the activities in the Sub-Saharan African (SSA) region focus on antimalarial drugs and countries making the transition to Artemisinin Combination Therapies (ACTs) as first-line treatment. USP DQI and WHO are collaborating on a Study of the Quality of Antimalarials in Sub-Saharan Africa (QAMSA) which will establish baseline data on the quality of ACTs in select African countries.

Phase 1 countries include **Benin, Cameroon, Ethiopia, Ghana, Kenya, Madagascar, Nigeria, Senegal, Tanzania, and Uganda**. In Ethiopia in February 2008, USP DQI staff conducted initial training for two representatives from each country on Sampling Procedures and Basic Tests using the Minilab®; staff then traveled to Madagascar in June 2008 to validate the first round of sampling. USP DQI financially sponsors Madagascar, Senegal and Uganda by supplying Minilabs®, lab ware, reagents, and reference standards; WHO sponsors the remaining seven. USP DQI will continue to provide technical oversight, train additional country reps and lab analysts, oversee sample analyses, and disseminate the data obtained to all countries involved in the QAMSA study. Data will be available in early 2009.

While in Ethiopia for the QAMSA training, USP DQI staff also conducted an assessment of the country's QA/QC capabilities in preparation for establishing a Drug Information Center (DIC) and a postmarketing surveillance system. The final disposition of these activities will depend upon obtaining sufficient funding from USAID/Ethiopia. In August 2008, staff conducted a training course on Basic Tests and Sampling Procedures for Establishing Antimalarial Drug Quality Monitoring in the Oromia region. If done correctly, these tests can evaluate the quality of antimalarials as a component of establishing a sustainable system of medicines quality control in the country. In January 2009, staff conducted a training workshop on Good Laboratory Practices and compendial analytic methods for the Drug Administration and Control Authority (DACA) and its Drug Quality Control and Toxicology Laboratory (DQCTL). Beginning in 2009 and going through 2012, USP DQI has proposed a plan to assist DACA DQCTL become WHO pre-qualified and achieve ISO/IEC 17025:2005 accreditation.

USAID obligated funds in the Fall of 2008 for USP DQI to conduct QA/QC assessments of **Mali, Benin, and Liberia**. In summer 2008, USP DQI staff began evaluating the drug regulatory authorities' (DRA) capacity for drug registration and quality control in order to establish a postmarketing surveillance program for antimalarials in these countries. Staff assessed Benin in July, Mali in September, and Liberia in November. USAID and USP DQI staff also traveled to Liberia in February 2009 to provide technical assistance in finalizing draft legislation relating to quality assurance issues in the country.

USP DQI has been working in **Ghana, Senegal, and Madagascar** since 2003 assessing QA/QC capabilities, as a way of helping to strengthen the institutions in charge of medicines in their countries, and establishing drug monitoring programs for antimalarial medicines. Each country has received priority equipment, reagents, and pharmacopeial references, and has been provided with Minilabs® for testing at sentinel sites. Each has been trained in lab set-up, GLP, basic testing, equipment maintenance, and Minilab® use; Senegal and Madagascar have been trained in advanced testing methods. The three countries are in different stages of their programs contingent, primarily, on the diligence of the DRA and cooperation of all key players.

- **Ghana** has been instructed in good registration procedures and trained on the use of SIAMED drug registration software. WHO experts also assessed their registration division and issued recommendations to improve the DRA's registration of medicines. In February 2009, USP DQI conducted a training in sampling and testing of antimalarials using Minilabs®.

- In **Senegal**, USP DQI facilitated cooperation among agency partners to advance their work; the current work plan includes establishing a pharmacovigilance program focused on adverse drug reaction (ADR) reporting of ACTs.
- **Madagascar** has made particular progress with training and monitoring activities, as well as with acting on problems that have been discovered. USP DQI helped install SIAMED drug registration software and trained staff in good registration practices, and trained national drug quality control laboratory (NDQCL) analysts in testing for Bacterial Endotoxins. With the Malaria Action Coalition, USP DQI assisted in establishing a national pharmacovigilance program focusing on ADRs for ACTs; USP DQI returned to Madagascar in June 2008 to collect and assess the pharmacovigilance data that had been obtained. During that visit, USP DQI helped establish a DIC in Antananarivo, Madagascar—the first in the country. The DIC will provide drug information to health professionals as well as to consumers.

USP DQI conducted a GMP assessment of Shelys Pharmaceuticals in **Tanzania** for the manufacture of Zinc sulfate tablets (for treatment and prevention of acute diarrheal disease in children), and returned in 2007 to assess their progress toward WHO pre-qualification status. In Fall 2008, USP DQI traveled to Tanzania to conduct a GMP assessment of a second pharmaceutical manufacturer, Zenufa.

Uganda was one of three countries initially selected to receive funds in 2005 from the President's Malaria Initiative. USP DQI staff conducted a QA/QC assessment in 2006 and has provided lab equipment and trained NDQCL staff on GLP and major testing methods. In May 2008, USP DQI established a drug quality monitoring program in five provinces in Kampala, and in December 2008, trained staff on new drug applications on SIAMED drug registration software. In 2009, USP DQI will help Uganda establish a pharmacovigilance program in the country.

In 2006, USP DQI conducted an assessment of the existing drug information unit of Kenyatta National Hospital of **Kenya**; however, USAID funding was not made available and no additional action has been proposed.

During 2001-2004, USP DQI worked with USAID-**Mozambique** to provide technical assistance and support to the Center for Drug Information (CiMed).

USP has presented, co-organized, sponsored and/or led and facilitated meetings on drug quality and pharmacovigilance in **Egypt** (2006), **Morocco** (2007), and **Tanzania** (2006).

LATIN AMERICA AND THE CARIBBEAN (LAC)

Currently, USP DQI participates in two initiatives to help combat AMR in the LAC region: Amazon Malaria Initiative (**AMI**) and South American Infectious Disease Initiative (**SAIDI**).

Since 2002, USP DQI has partnered with USAID, Pan American Health Organization (PAHO), Centers for Disease Control and Prevention (CDC), Management Sciences for Health/Strengthening Pharmaceutical Systems (MSH/SPS), and eight country members – **Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru, Suriname, and Venezuela** – to participate in the Amazon Malaria Initiative. USP DQI collaborates with local drug regulatory authorities and existing national drug quality control laboratories to assure the quality of antimalarials by strengthening the laboratories and advancing drug registration procedures. Following USP DQI training, each country develops antimalarial drug quality monitoring systems of sampling, testing, and data reporting.

In 2008, USP DQI sponsored two interns from the OMCLs of Colombia and Peru to participate in an “Internship on the Application of USP’s Quality Management System to its Laboratory Operations.” USP DQI plans to host another intern in 2009.

The AMI program began to reach out to Central American countries in 2008. At a July 2008 workshop on “Gas Chromatography, Headspace, and Residual Solvents” held in Colombia, representatives from the national labs of **Guatemala** and **Panama** participated. Representatives from **Honduras** first participated in an AMI workshop in Ecuador in August 2008, where GLP, HPLC, UV, and dissolution techniques were taught; Guatemala and Panama also participated. The first USP DQI activity to be hosted in Central America was the November 2008 “Workshop to Improve Management of Supply and QA Systems for Malaria Medicines in Central America,” held in Guatemala and attended by representatives from **Costa Rica, El Salvador, Honduras, Nicaragua, and Panama**. During that trip, USP DQI staff also performed a Rapid Assessment of **Guatemala’s** national laboratory.

Beginning in 2004, USP DQI has partnered with USAID, CDC, MSH/SPS, PAHO, Alliance for Prudent Use of Antibiotics (APUA), Links Media, and three country members – **Paraguay, Peru, and Bolivia** – to participate in **SAIDI**. SAIDI assesses the current drug quality capacity at the national level and helps each country develop effective, sustainable interventions to contain AMR. USP DQI trains analysts from local, regional, and national quality control laboratories to create a sampling plan for collecting and testing samples of antibiotic and anti-tuberculosis medications. That data is used to help DRAs take action to improve the quality of medications in the market.

Following an audit by ACLASS, **Peru** was recommended in January 2009 for ISO/IEC 17025:2005 accreditation for 5 laboratory tests.

EUROPE AND EURASIA

USP DQI – through the Rational Pharmaceutical Management program – began working in Europe/Eurasia in 1993, focusing on the spread of AMR, drug-resistant TB, HIV/AIDS, and more recently, avian influenza.

- DICs located in medical schools, hospitals, and other institutions were set up in **Russia, Moldova, and Romania**. With initial assistance from USP DQI, the DICs provide current, reliable drug and therapy information to healthcare professionals and patients. A major goal was reached in 2006 when all the DICs became self-sustaining.
- In **Russia, Belarus, Ukraine, and Kyrgyzstan**, USP DQI established Continuing Education Distance Learning Centers in cooperation with the Institute of Antimicrobial Therapy, the Department of Clinical Pharmacology of Smolensk State Medical Academy, and the regional DICs. Courses are intended to improve the qualifications of doctors and focus on antimicrobial therapy, socially important diseases, and DIC management.
- Developed by a group of Russian scientists in 2001, the Infectious Diseases Textbook provides Russian and Newly Independent States healthcare professionals with information on antibacterial, antiviral (including HIV/AIDS), antifungal, antiprotozoal, and antihelminthic drugs. The third edition of the Textbook, published in 2007, also provides information on HN51 avian influenza and the quality of antimicrobials and other new drugs on the market. In 2008-2009, USP DQI plans to design and implement a study to assess the impact of the Textbook and the distance learning programs in Russia.
- In 2003, USP DQI and the Institute of Antimicrobial Therapy published a Russian translation and adaptation of the 2002 Guide to Infection Control. This manual explains guidelines for reducing the rate of nosocomial infections and describes practical measures intended to improve quality of care, minimize risk, save lives, and reduce costs.

- In an effort to improve the implementation of the DOTS strategy and reduce the spread of MDR-TB, in 2003 USP DQI helped collect samples of anti-TB drugs from **Kazakhstan** and followed up with a training workshop on drug quality. In 2005, USP DQI and RPM Plus conducted a training workshop on how to use Minilabs® for representatives from the drug regulatory agencies and national quality control laboratories of **Kazakhstan, Kyrgyzstan, Tajikistan, and Uzbekistan**.

In 2009, USP DQI plans to conduct training courses to expand drug quality monitoring in **Russia**, focusing on anti-TB drugs. After translating the Minilab® Manual into Russian, USP DQI will provide the necessary Minilabs®, reference standards, and lab supplies for its Russian counterparts.



ATTACHMENT 3

THE WAY FORWARD: A GLOBAL HEALTH CARE SECRETARIAT

EXCERPT FROM RESPONSE PREPARED BY USP'S ADVISORY PANEL OF THE INTERNATIONAL HEALTH EXPERT COMMITTEE IN RESPONSE TO WORLD HEALTH ORGANIZATION'S COMMISSION ON INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH (CIPIH)

Despite what now can only be described as a deeply challenged set of systems to treat neglected diseases in developing countries, much has occurred that offers hope. Opportunities relate to transnational collaborative activities, such as WHO's Pre-Qualification program and the EDQM Certificate of Suitability, that advance beyond information exchange and harmonization to collaboration for action. These initial efforts to move beyond national decision-making, which can be flawed and resource-constrained, set the stage perhaps for a truly global regulatory and practitioner/patient enterprise. By means of enhanced collaboration, public and private officials and regulators of developing countries may be in a remarkable position to advance basic research, discovery, drug development, registration, utilization, and related approaches for medicines (with allied activities) to prevent and treat diseases that have plagued humankind for centuries—and to develop medicines to treat other conditions as well. In the past several years, national, sub-regional, regional, trans-regional, and global activities for collective action have appeared and offer hope. These not only have yielded needed registration and other standards but also have engaged regulators in the conduct of bilateral and multilateral conformity assessment activities. They have thus moved beyond information sharing and harmonization to yield useful results; i.e., they are action oriented.

The concluding theme of this paper is that regional and global collaboration efforts should be strengthened and, when possible, expanded and consolidated. Further consolidation is based on a vision of a collaborative global health care secretariat with multiple components, involving representatives from all countries, and yielding decisions suitable for national adoption. The components would focus on a) discovery; b) research and development; c) sound regulatory decision-making and, when appropriate, rapid registration decisions; d) optimal pricing/payment strategies; e) evidence-based health care delivery based on outcomes/pharmacoeconomic studies, f) quality of care and g) safe medicine use.

As a further proposal, this paper argues for close involvement of practitioners and patients throughout the overall process and urges for them a dominant role after registration. Specifically, it proposes a consortium of practitioners and patients to advance optimal health care, including pharmaceutical care, based on continually updated drug information. Independent, credible, authoritative practitioner and consumer experts would transform prospectively and retrospectively designed research studies and observational data into knowledge-based information monographs and wisdom-based brief summaries and alerts, following the paradigm of :

data → information → knowledge → wisdom.

An overarching theme is the need for action. With sufficient (but not exorbitant) resources, a collective effort based on this shifting duality of inputs (regulators to the community and community to regulators) may promote, as overarching strategic objectives, rational use of medicines and good, cost effective health care delivery practices. An overall structure is shown in Figure 2. The secretariat is imagined to operate in close cooperation with the World Health Organization, relying on frequent and continuing input from governmental and practitioner/consumer experts from all countries of the world and in particular from developing countries. This input would yield science and policy decisions that would be suitable for national adoption, based on local acceptance and modification if needed.

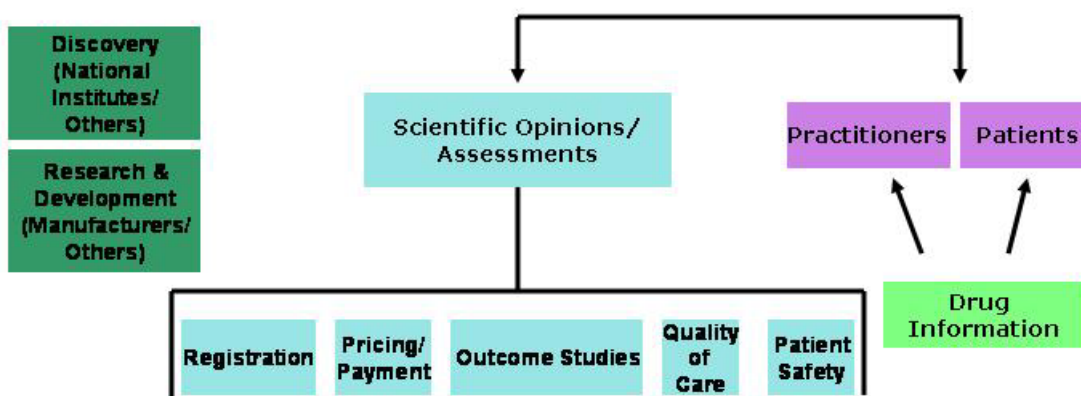


FIGURE 2

Such a secretariat could evolve over time into even stronger authorities and alliances, working to establish procedures that ensure transparency and trust and rely on advancing skills and shared values. Indeed, the vision perhaps leads to a world medicines agency with participants from experts from around the world, managed by a secretariat, and yielding scientific opinions on many topics suitable for national consideration and adoption. While not small, the expense of such a venture is almost certainly minimal compared to costs encountered today, which leave many if not all actors in civil societies at the mercy of fragmented, duplicative, and poorly coordinated approaches that are encumbered by inertia, misinformation, and perhaps even incompetence and corruption. A particular feature of the approach is that it consolidates and focuses the skills and wisdom of experts from developing countries themselves. Nonetheless, partnering with science and technical experts from developed countries is encouraged, so that skills and wisdom of all contributors are enthusiastically welcomed and shared.

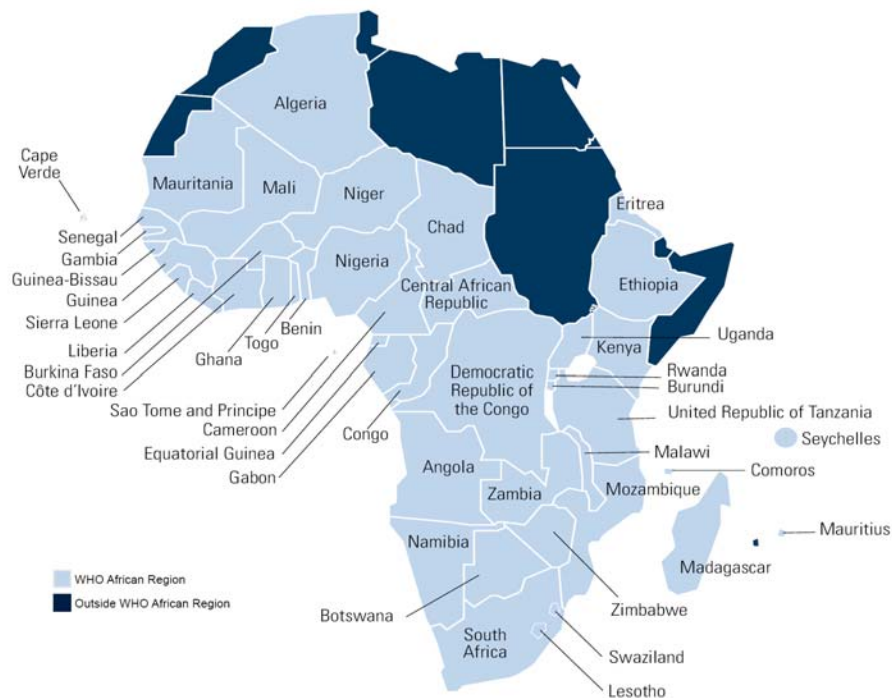


ATTACHMENT 4

THE DRUG SITUATION IN THE SUB-SAHARAN AFRICA

EXECUTIVE SUMMARY

PREPARED FOR USP BY
THE USP AFRICAN HEALTH ADVISORY PANEL
MARCH 2008



CONTRIBUTORS

- USP African Health Advisory Panel
- USP Staff
- USP International Health Expert Committee

Since the United States Pharmacopeia (USP) is seeking to extend its activities to the sub-Saharan Africa, it was necessary to determine which activities within its ambit are most important to introduce into Africa. Therefore, the aim of this study was to identify the major health and pharmaceutical problems in a sample of African countries. This information was gathered by use of a questionnaire and literature search. It is hoped that this position paper will provide information that will be useful to the USP and all those who want to rescue Africa's pharmaceutical situation.

1. From Table 1, it was observed that:

- Most African countries have a District Referral Health Care System as well as a Centralized Medicines Distribution System with an open tender procurement policy for most drugs.
- Although most countries have established drug regulatory authorities, pharmacy councils and drug control laboratories, most of these are inexperienced as they were established less than 10 years ago.

Table 1: The health system and pharmaceutical regulatory structures in some African countries.

| Region | SADC | | ECOWAS | | UEMOA CEMAC | | EAC | |
|--------------------|------|------|--------|---------|-------------|------|-------|------|
| Country | SA. | Zim | Ghana | Nigeria | Mali | Cam | Kenya | Tanz |
| Pop. (millions) | 42.6 | 12.4 | 22.9 | 142 | 13.5 | 17.2 | 32 | 37 |
| Health system | DRS | DRS | DRS | DRS | DRS | DRS | DRS | DRS |
| Med. Distrib. | CDS | CDS | CDS | CDS | CDS | CDS | CDS | CDS |
| Regulatory Agency | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Pharmacy Council | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Drug. Control Lab. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

DRS = District Referral System; **CDS** = Centralized Distribution System

Regions: **SADC** = Southern Africa Development Community; **ECOWAS** = Economic Community West African States; **UEMOA** = West African Economic, Monetary Union; **CEMAC** = Economic and Monetary Community of Central Africa.; **EAC** = East African Community.

Countries: **SA** = South Africa; **Zim.** = Zimbabwe; **Cam.** = Cameroon; **Tanz** = Tanzania

2. From Table 2, it was observed that:

- a) The top 3 killer diseases were:
 - Malaria,
 - HIV/AIDS
 - TB
- b) The major drug quality issues are:
 - Counterfeits (CFI)
 - Lack of skilled personnel (LTP)
 - Inadequate regulatory mechanisms (IRM)

- c) The major Medicines' problems are:
- Limited access
 - Inefficient distribution/drug supply systems
 - Weak monitoring of products on the market

Table 2: The top three health and pharmaceutical indicators in some African countries.

| Region Country | SADC | | ECOWAS | | UEMOA CEMAC | | EAC | |
|--|---------|---------|---------|---------|-------------|---------|----------|---------|
| | SA. | Zim | Ghana | Nigeria | Mali | Cam | Kenya | Tanz |
| a) Top 3 diseases | | | | | | | | |
| 1. | HIV | Mal. | Mal. | Mal. | HIV | HIV | Mal. | Mal. |
| 2. | TB | HIV | HIV | HIV | Mal. | Mal. | HIV | Diarr. |
| 3. | CVD | TB | URTI | TB | TB | TB | TB | URTI |
| b) Top 3 on Quality & Product | | | | | | | | |
| 1 | CTF | CTF | LTP | CTF | LTP | CTF | CTF | LTP |
| 2 | LTP | LTP | CTF | LTP | CTF | LTP | LTP | CTF |
| 3 | IRM | IRM | IRM | IRM | IRM | IRM | IRM | IRM |
| c) Top 3 Medicine Problems | | | | | | | | |
| 1 | Access | Access | Access | Access | Import | Access | Import | Access |
| 2 | Distrib | Distrib | Distrib | Distrib | Distrib | Distrib | Dist/Ac. | Distrib |
| 3 | Monit. | Monit. | Monit. | Monit. | Monit. | Monit. | Monit. | Monit. |

CTF = Counterfeit; **LTP** = Lack of trained personnel; **IRM** = Inadequate Regulatory Mechanism; **Access** = Limited Access to Essential Drugs; **Distrib** = Ineffective distribution System; **Monit.** = Inadequate monitoring of drug quality on a continuous basis.

Regions: **SADC** = Southern Africa Development Community; **ECOWAS** = Economic Community West African States; **UEMOA** = West African Economic, Monetary Union; **CEMAC** = Economic and Monetary Community of Central Africa.; **EAC** = East African Community.

Countries: **SA** = South Africa; **Zim.** = Zimbabwe; **Cam.** = Cameroon; **Tanz** = Tanzania

3. From Table 3, it was observed that the pharmaceutical market characteristics indicate that:
- Foreign-based multinationals account for over 70% (median) of the market share, while about 30% is by domestically-based subsidiaries of the multinational companies and/or local manufacturers.
 - 80% of the products in all the countries studied are generics.
 - Counterfeits remain a big problem and it was estimated by WHO to range between 10 -30% of the products (UNICRI 2007).
 - There is wide inter-country variation in the number of products on the market.

Table 3: Characteristics of the pharmaceutical market in some African countries.

| Region | SADC | | ECOWAS | | UEMOA CEMAC | | EAC | |
|------------------------|--------|------|--------|---------|-------------|-----|-------|-------|
| Country | SA. | Zim | Ghana | Nigeria | Mali | Cam | Kenya | Tanz |
| M-Nat. outside | 73% | 15% | 70% | 32% | 98% | 99% | 50% | 20% |
| M-Nat. inside | 27% | 5% | 30% | 14% | 2% | 1% | 40% | 0% |
| Generics | 80% | 70 | 70% | 80% | ? | 90% | 80% | 80% |
| Counterfeits | 10% | ? | 8% | 16% | 15% | ? | 20% | ? |
| No. products | 25,000 | 1500 | 5200 | 13,632 | 3,027 | ? | ? | 4,030 |
| Pharm. GDP (\$) | 10.0 | < 1 | 1.0 | 2.0 | 4 | < 1 | 1.0 | 2.0 |

M-Nat. outside = Multinational from outside the country; **M-Nat. inside** = Multinational (%) based inside the country; **No. products** = Number of products in market (estimated); **Pharm. GDP (\$)** = Per capita drug expenses on pharmaceuticals (US \$).

Regions: **SADC** = Southern Africa Development Community; **ECOWAS** = Economic Community West African States; **UEMOA** = West African Economic, Monetary Union; **CEMAC** = Economic and Monetary Community of Central Africa.; **EAC** = East African Community.

Countries:: **SA** = South Africa; **Zim.** = Zimbabwe; **Cam.** = Cameroon; **Tanz** = Tanzania

4. Conclusion (Tables 4a, 4b, & 4c)

Overall, African countries have put in place the necessary regulatory drug policies and agencies, distribution systems, and drug control laboratories, but these systems are in dire need of assistance to be effective. Such assistance should address counterfeits, lack of skilled personnel and strengthening of the regulatory mechanisms. It is advised that the USP establishes facilities by which it can support Quality Control Laboratories as well as undertake training for laboratory and drug regulatory staff in Africa, and that this should be in collaboration with the existing stake-holders and plans in the region.

Table 4a: USP questions—Where in sub-Saharan Africa should USP establish a facility?

| SADC | | EAC | | ECOWAS | | CEMAC | UEMOA |
|--|--|--------------|---|--|--|-----------------|--|
| South Africa | Zimbabwe | Kenya | Tanzania | Nigeria | Ghana | Cameroon | Mali |
| <p>a) South Africa: well established and functioning regulatory system which has exemplary success. Also, has established marketing channels to the rest of Africa through its diverse business contacts. Indeed, 40% of the South African pharmaceutical exports are to the rest of Africa.</p> <p>b) Nigeria/Ghana: well established and functioning regulatory system. The high population adds promise to growth in the pharmaceutical industry. Of note, the facility is not for one country, as such, there is a need to establish communication with the East African region, which is expensive.</p> | <p>South Africa – They have a strong pharmaceutical manufacturing industry</p> | <p>Kenya</p> | <p>In Tanzania due to conducive investment environment, political stability and strong government support to ensure availability of safe and efficacious medicines of acceptable quality.</p> | <p>It is best established in Nigeria. Any assistance given to Nigeria will permeate to all the other countries being the most populated Member State. Nigeria has about ¼ of the SSA population. We have been sharing strategies and carrying other countries along in the West African Drug Regulatory Authorities Network (WADRAN) which we sponsor and supervise .</p> <p>We have carried positive international advocacy campaigns against drug counterfeiting which have led to the establishment of the International Medical Products Anti-Counterfeiting Task Force (IMPACT). Prof. Akunyili is the Chairperson WADRAN and the Vice Chairperson of IMPACT.</p> | <p>Ghana</p> <p>Ghana is a stable democracy with a very low crime rate. Has easy air traffick access to most cities in West, East, Central and Southern Africe. Has an efficient and well functioning MRA that initiated, sustained and facilitated the harmonization process in the ECOWAS region since 2001.</p> | <p>Cameroon</p> | <p>In Africa sub- Saharan USP should establish a service in Mali, to reinforce the activities of quality control of the drugs. Namely the formation; the information and the equipment of the technical and lawful structures. Because, here in Mali the only tool for detection of embezzlement and fraud on the level of the drugs is the lawful quality control as well as technical.</p> |

SADC = Southern Africa Development Community; **ECOWAS** = Economic Community West African States; **UEMOA** = West African Economic, Monetary Union; **CEMAC** = Economic and Monetary Community of Central Africa; **EAC** = East African Community.

Table 4b: USP questions continued—What should USP do in the following areas?

| | SADC | | EAC | | ECOWAS | | CEMAC | UEMOA |
|----------------|--|---|---|---|---|--|--|--|
| | South Africa | Zimbabwe | Kenya | Tanzania | Nigeria | Ghana | Cameroon | Mali |
| Quality | Establish a second quality control laboratory and this should add value to the current situation. Support government and relevant bodies to fight against counterfeit products | Assist laboratories implement quality management systems | Establish a regional Drug Quality Control reference laboratory | Support in provision of laboratory reference standards and reagents and laboratory equipment and instruments. | <ol style="list-style-type: none"> 1. Support the provision of adequate infrastructure, human resources and sufficient funds for Quality Control Laboratories. 2. USP should conduct an assessment of capacities and identify existing gaps in Quality Control Laboratories; 3. USP should put in place structured mechanisms to enable exchange of QC and regulatory officials to bring about better understanding of processes adopted in Sub Saharan Africa. 4. USP should support the documentation of best practices to be replicated in other member countries with Nigeria as a starting point; | Train and Set up an accreditation system for QCL in West Africa. Periodic Quality Monitoring of most essential medicines required. | Support medicines control laboratory with regard to reference standards and reagents and laboratory equipment and instruments. | To reinforce the technical and lawful structures of quality control of the drugs in documents qualities and formation. |
| Access | Support government departments in developing models by which to distribute drugs to the people. | Assist laboratories access competitively priced equipment and reagents so they can be empowered to improve access to quality medicines in their countries | Support Drug regulatory authority in establishing and monitoring ethical distribution by qualified personnel through registered outlets | Support government efforts to improve quality of pharmaceutical services in rural and peri-urban areas. | <ul style="list-style-type: none"> • USP should support the establishment of a strong and operational drug distribution system based on the Drug Mart Strategy. • Encourage the establishment of Public Private Partnership in the drug Procurement and Distribution programs of governments. • Encourage the establishment of Pharmacy chains e.g CVS and Walgreen in USA to improve access to quality and affordable medicines. • Support Government to expand the National Health Insurance Scheme (NHIS) to cover States and Local Governments. Currently only Federal Institutions and a few states have subscribed. | The issue of Health Insurance must be vigorously pursued. | Advice on effective distribution systems and storage of medicines | To reinforce the structures of supply drugs in material and formation. |

SADC = Southern Africa Development Community; **ECOWAS** = Economic Community West African States; **UEMOA** = West African Economic, Monetary Union; **CEMAC** = Economic and Monetary Community of Central Africa; **EAC** = East African Community.

Table 4c: USP questions continued—What should USP do in the following areas?

| | SADC | | EAC | | ECOWAS | | CEMAC | UEMOA |
|---------------------------------|--|--|--|--|---|--|--|---|
| | South Africa | Zimbabwe | Kenya | Tanzania | Nigeria | Ghana | Cameroon | Mali |
| Surveillance | Support government in establishing and running the drug and poison information centers. | Establish a network of laboratories in the region who can share information on surveillance and quality issues. | Establish post – marketing and Post – registration surveillance in liaison with national drug regulatory authority | Assist in developing surveillance strategies to ensure effective market control including pharmacovigilance. | <ul style="list-style-type: none"> USP should support the institutionalization of a Post Marketing Strategy and a robust Pharmacovigilance (PVG) system in member countries. Nigeria is registered as the 74th member and have received up to 630 reports which has resulted in the ban and restriction the use of some drugs. Enhance the establishment of self regulation by the industry and pharmaceutical associations. | Models for safety monitoring and Quality Surveillance must be developed, training organized and pilot schemes implemented in selected countries. | Support the setting up of pharmacovigilance centres in Cameroon. | To reinforce the technical and lawful structures of quality control of the drugs in substances of reference, apparatus of analysis and information. |
| Education & Training | Establish a permanent training facility in Africa where different courses can be offered all year around. Such courses should aim at training of not only workers, but also producing new local trainers. | Assist personnel from laboratories to access appropriate graduate training programs to strengthen their own institutions. Consider working with a regional training institution to offer such graduate programs. | Establish Consumer education & feedback systems of reporting drug related issues | Train laboratory staff in modern analytical techniques, training of drug dossier evaluators on evaluation of new medicinal products with special focus to medicines for malaria, HIV/AIDS, vaccines and biologicals, inspection techniques for suspect counterfeit products. | <ul style="list-style-type: none"> USP should develop Training modules in common languages and should designate two training centers, one in Nigeria and the other in SADC or EAC for building capacity within the region; The capability & skill of staff should be continuously upgraded through adequate training in specific regulatory areas of quality control, inspection and investigation. USP/WHO should coordinate the Technical Assistance to be provided in the region to avoid duplication and overburdening member countries. | It is recommended strongly that the ECOWAS framework is used for training. Expert groups in various areas of medicines regulations could be set up as the basis for creating training centers and faculty. | Train laboratory staff (laboratory and regulatory) | To reinforce the formation continuing and qualifying trainings |
| Other | USP should support the formation and/or functioning of regulatory authorities in the different countries or regions. USP should support the relevant government department in the managing and maintaining drug supply chains. | Provide reference materials, access to information, and technologies to improve the efficiency of the laboratories in the region. | | To establish long term co-operation and collaboration in developing the capacity of medicines regulation in the EAC. | <ul style="list-style-type: none"> USP should embark on an effective Advocacy towards harmonization of QC, Inspection and Drug regulatory control within the Sub-Saharan Africa. WADRAN can provide a supporting platform. Advocacy and Public Enlightenment materials should be developed and harmonized for use within the SSA region. | Liaise with the West African Health Programme (ECOWAS/EU project) for maximum impact | | |

SADC = Southern Africa Development Community; **ECOWAS** = Economic Community West African States; **UEMOA** = West African Economic, Monetary Union; **CEMAC** = Economic and Monetary Community of Central Africa; **EAC** = East African Community.



ATTACHMENT 5

MIDDLE EAST NORTH AFRICA OFFICIAL MEDICINES CONTROL LABORATORIES ALLIANCE

DRAFT PROPOSAL: OCTOBER 8, 2008

While this proposal focuses on the MENA region, the basis for such an alliance could be adapted for other regions throughout the world.

BACKGROUND

Based on increasing regional trade, the challenges of counterfeit and substandard medicines, advances in measurement science, economic integration and other factors, this proposal suggests establishing an alliance of official medicines control laboratories (OMCLs) in the Middle East North Africa (MENA) region.

PROPOSAL

1. EMRO/AFRO/MINISTRIES

WHO's EMRO works in 22 countries in the region. WHO's AFRO works in 44 African countries – including Algeria and Sudan, which are usually classified as MENA countries. Both EMRO and AFRO's governing bodies are based on representation from national Ministries of Health from these countries. The ministries in turn have departments/agencies that have regulatory responsibility for medicines (drug regulatory agencies/DRA). DRAs usually have oversight for the OMCLs. Beyond the national institution, some countries may also have state or provincial drug laboratories that may be part of the Network. EMRO and AFRO, which serve as the WHO Regional Offices for the MENA region, function in a coordinating role for many activities.

2. ALLIANCE STEERING COMMITTEE

Strategy for the proposed Alliance will be handled by a Steering Committee composed of representatives from the national drug laboratories in the MENA region, representatives from WHO Regional Office(s), involved pharmacopoeias, and industry stakeholders. The Steering Committee

will be responsible for developing the strategic direction for the Alliance and related governance activities, taking into account roles and responsibilities of participants. The Alliance will have no regulatory authority, which is reserved to parent drug regulatory agencies. Strategy and tactic implementation activities of the Alliance will be consonant with corresponding requirements of involved organizations.

3. PROCESSES

The Alliance members will meet every year at a frequency and a venue determined by the Steering Committee. Work plans to meet the strategic objectives will be considered at each meeting with updates on goals and achievement of goals. Working groups may be established to execute against specific goals.

ACTIVITIES

- Laboratory standards development
- Conformity assessments to applicable standards
- Ingredient and product quality standards
- Training, education, certification of staff
- Proficiency testing
- Marketplace surveillance
- Anti-counterfeiting activities
- Capacity-building (e.g., equipment)

COSTS

Costs of the Alliance activities will be funded through available mechanisms. Additional funding may be sought from NGOs and other donor bodies. Costs will cover: secretariat support, meetings, web support, other.



ATTACHMENT 6

ADVANCING OPPORTUNITIES FOR INTERNATIONAL TECHNICAL ASSISTANCE

BACKGROUND

1. MANUFACTURING QUALITY

Because people in developing countries often do not have access to quality medicines, attempts to remedy the situation have included the use of generics and a tiered-pricing scheme.¹ Supporters hoped that generic competition would drive prices down and, where generics were not available, establishing a tiered-pricing scheme effectively positioned developed countries or private companies to subsidize drugs for developing countries. Both approaches, however, have been undermined by manufacturers that lack the technical capacity to comply with industry-standard Good Manufacturing Practices (GMP). A larger pool of manufacturers that are GMP-compliant would potentially result in the increased production and availability of essential medicines prequalified by the World Health Organization (WHO) Prequalification Programme. Currently, there are 16 WHO-prequalified antimalarial medicines, ten of which are Artemisinin-based Combination Therapies (ACTs).² As developing countries have increasingly replaced monotherapies with ACTs as their first-line treatment, the availability of prequalified ACTs has become a point of concern. Each of the 18 antimalarial medicine dossiers now under WHO evaluation is awaiting additional data from the manufacturers to fulfill the quality review. The same is true for many other essential medicines.

2. MEDICINE REGULATION

Medicine regulation in developing countries falls on governments with limited resources and/or technical capacity. Failure to strengthen regulations and inadequate enforcement against noncompliance has allowed substandard medicines to be manufactured and distributed. Such poor quality medicines pose an immediate and long-lasting threat to public health. Currently, only 20% of WHO's 191 member states have well-developed regulation, only 50% operate at varying levels of regulation and capacity, and 30% have weak regulation or none at all.³ The variation in the capacity of the regulatory framework can be attributed to the lack of enforcement of existing regulations, regulation that does not address drug registration, incorrect use and interpretation of the USP-NF, and the lack of standards and procedures to perform conformity assessments.

Medicine Regulatory Authorities (MRAs) must be provided with the capacity to conduct: medicine evaluation and registration; inspection and licensing of manufacturers; and postmarketing surveillance. Official Medicines Control Laboratories (OMCLs) often operate below internationally-recognized

¹ Bate, R. Local Pharmaceutical Production in Developing Countries: How economic protectionism undermines access to quality medicines. Occasional Paper Series, Institute of Public Affairs, Melbourne Australia. January 2008; p. 3. Accessed on June 1, 2009: <http://www.ipa.org.au/library/Local%20Pharmaceutical%20Production%20web.pdf>.

² The six other antimalarial medicines are monotherapies, four of which, when combined, form an ACT.

³ World Health Organization (WHO). General Information on Counterfeit Medicines. Accessed on June 1, 2009: <http://www.who.int/medicines/services/counterfeit/overview/en/index.html>.

standards (ISO/WHO) for analytical methodologies and interpretation of monographs to assess compliance, and they need access to monographs and reference standards for neglected diseases.

3. TRAINING

Ultimately, systems that can ensure access to quality medicines require skilled personnel to perform testing, dispensing, policymaking, and enforcement. Yet for developing countries with limited resources, training is often overlooked. The lack of appropriately-trained personnel leads to ineffective quality assurance systems for medicines. MRA and OMCL personnel require continuous training to sustain their ability to ensure drug quality, but the lack of resources to acquire such training further jeopardizes medicine quality in the region. In addition, there is a need to provide unbiased medicine information to healthcare practitioners for dissemination to patients. Gaps in patient and practitioner information need to be addressed to ensure proper and safe medication use.

DISCUSSION/PROPOSAL

With funding from others, USP could expand activities that advance the types of products and services that the current USP Drug Quality and Information (DQI) program offers, which could play a pivotal role in increasing access to quality medicines in developing countries. USP recognizes the work of others in developing countries and would seek to collaborate on the following:

- 1) Assisting in the preparation of manufacturers' product dossiers for submission to the WHO Prequalification Programme in a manner that fulfills the specified requirements.
- 2) Guiding manufacturers on site to comply with WHO-qualified GMP standards and helping strengthen their GMP capabilities.
- 3) Training regulators in developing countries in GMP standards and building capacity in quality assurance systems.
- 4) Develop monographs for new antimalarial drugs, especially those utilizing active pharmaceutical ingredients (APIs) available from various plant sources or those resulting from different manufacturing processes. USP addresses this issue through its flexible monograph approach.
- 5) Develop monographs and reference standards for non-U.S. and WHO essential medicines.
- 6) Providing verification programs to manufacturers in developing countries that would help to improve ingredient quality.
- 7) Evaluate the quality assurance capacity of MRAs to determine if at least minimal functions are being met in the essential operations of medicine evaluation and registration, inspection and licensing of manufacturers, and postmarketing surveillance.
- 8) Evaluate the quality assurance capacity of OMCLs. Depending upon results of the assessment, USP may provide the necessary laboratory resources to conduct medicine quality control testing. USP or DQI staff could conduct training on Good Laboratory Practices, sampling, and analytical methods to test antimalarial and other essential medicines for content, identification, purity, and dissolution. Training might also include interpretation of drug quality data, as needed.
- 9) Provide additional technical support as required via the USP Pharmacopeial Education program to address specific compendial education needs of MRAs and OMCLs.

- 10) Provide regional educational and training programs aimed at improving the ability of local chemists, scientists, and healthcare practitioners to implement standards and best practices for the development, manufacture, regulation, testing, storage, and dispensing of medicines and their appropriate use.
- 11) Establish centers of excellence for the training of regulators and other stakeholders.
- 12) Establish Medicine Information Centers (MICs), organized and led by specially-trained pharmacists, to provide comprehensive drug information services to patients and healthcare professionals. In developing countries, pharmacists more commonly play the role of patient-care providers, and MICs are now recognized as an integral part of a successful and functional health care service.