



WHITE PAPER

USP'S ROLE IN SETTING ENFORCEABLE QUALITY STANDARDS FOR MEDICINES

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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.

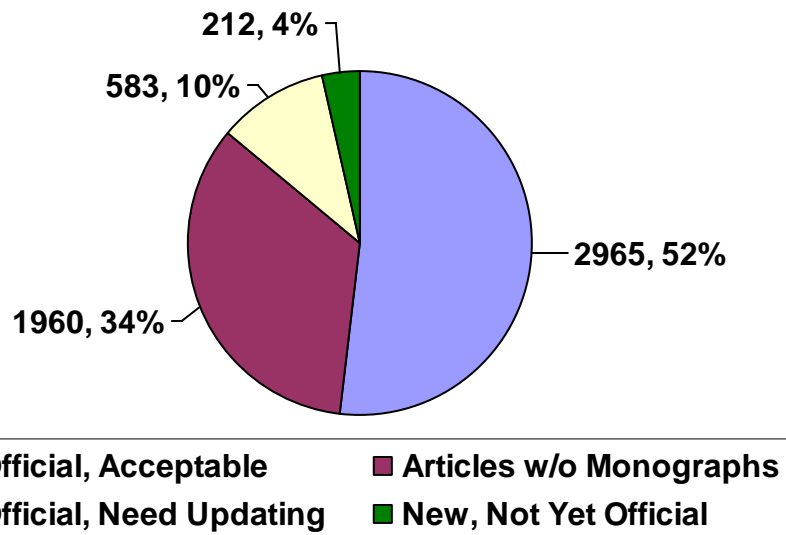
OVERVIEW AND CURRENT STATUS OF USP STANDARDS

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.

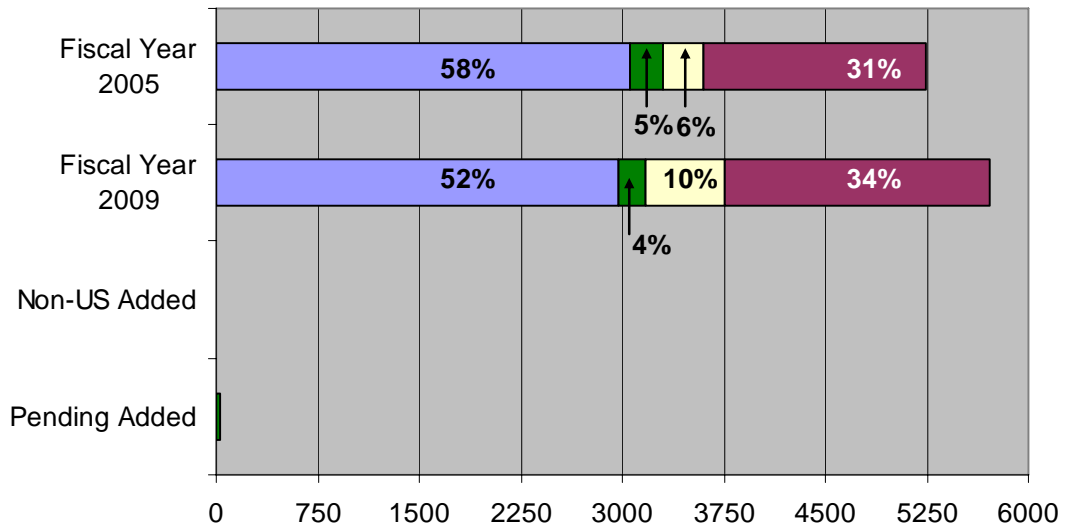
- The *flexible monograph* moves away from a “one size fits all” approach for the monograph's specification to an approach that allows differences in the tests, procedures and acceptance criteria of the monograph depending on routes of synthesis, differences in formulation, or other factors. This approach 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.