Witness:
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Testimony

Good Morning, Mr. Chairman and members of the Committee, my name is Todd Cecil and I am Vice President of Standards Development of the United States Pharmacopeia (USP). USP appreciates the opportunity to provide its scientific expertise and experience on drug importation issues and the impact such issues may have on public health.

USP commends your leadership in convening a hearing on drug importation and acknowledging the important role science has in helping to ensure that the importation of drugs to the United States will not adversely affect public health. The issues surrounding drug importation call into question many scientific issues that merit full consideration. My testimony today will discuss two issues – pharmaceutical equivalence and bioequivalence - that USP believes are key considerations in allowing importation of drugs to the United States. I will also discuss the need for public standards and the public health impact that imported drugs may have on patients and consumers.

USP is a not-for-profit organization that was created in 1820 by eleven (11) practitioners who wanted to establish public standards for pharmaceutical products being used in the United States at that time. The practitioners recognized that by setting public standards for drug products, they would help ensure the consistency and quality of drugs. Ensuring drug quality through public standards remains USP's core mission. Today, USP's drug standards are developed by its Council of Experts and Expert Committees, a group of 650 nationally and internationally recognized scientists and practitioners in medicine, pharmacy, the pharmaceutical sciences and many other healthcare professions. USP's standards are widely recognized in the U.S. and elsewhere because they are authoritative, science-based and developed through a transparent and credible process with established integrity.

USP's standards are made public through the United States Pharmacopeia (USP) and the National Formulary (NF). Together the two compendia are published as a combined text annually (USP–NF) with two Supplements. Originally a book of process standards (recipes for preparations), USP–NF evolved over time into compendia containing primarily product standards. These standards are expressed in public monographs for drug substances, excipients, dosage forms and other articles, and in General Chapters, which are dedicated to procedures widely used throughout the USP-NF.

Closely allied with the public monograph in the USP-NF, and equally important in many respects, is the availability of an official USP Reference Standard. USP Reference Standards are chemical substances used by the pharmaceutical industry to test conformity to the USP-NF. The USP-NF and USP Reference Standards are complementary tools to ensure the strength, quality, and purity of pharmaceutical substances and products.

Over the years, Congress has relied on USP on many occasions and has repeatedly recognized USP's expertise as a standard-setting organization. Initially, in the Import Drug Act of 1848, Congress turned to USP for public standards for imported medicines. Today, principal recognition occurs as a result of Congress' recognition of the USP-NF as official compendia of the United States. The Federal Food, Drug and Cosmetic Act (FDCA) makes the standards found in the official compendia enforceable by the Food and Drug Administration (FDA). Today, the USP science-based and public process for developing an official monograph for the USP-NF and official USP Reference Standards is a well evolved system that works in concert with efforts of U.S. manufacturers and the FDA to assure the public trust.

Based on USP's experience and long history of ensuring the consistency and quality of drugs, USP provides the following observations and recommendations for the implementation of any drug importation program in the United States:

First, USP believes that any medicine imported without benefit of submission of a New Drug Application (NDA), Biologics Licensing Application (BLA), or Abbreviated New Drug Application (ANDA) to FDA and subsequent Agency review must conform to a USP-NF monograph. Lacking this conformity, the imported medicine should indicate where it differs from the public standard and should so state clearly on the label. The science and regulatory basis for these requirements is the foundation for ensuring quality drugs in the United States and has been for 185 years. USP believes that the success of any drug importation program implemented in the United States must recognize the critical role of public standards and require adherence to the official US compendia – the USP-NF. Adherence to the public standards in the USP-NF can achieve, via testing to the standards of a monograph and with the use of USP Reference Standards, the consistency and uniformity sought by the initial founders of USP in 1820 and equally critical today in ensuring good quality pharmaceutical care.

Second, through intense science-based deliberations on the part of USP, FDA, and manufacturers, the United States has led the world in considering the various issues of bioequivalence (BE) for over fifty (50) years. This consideration has many origins, but it certainly began in part with failure of tablets containing cardiac glycosides (digitalis and its congeners) in the early 1970s. These issues led to national efforts to better define BE and to determine appropriate procedures for assessment. In the United States, the Congressional Office of Technology Assessment issued a key report in 1974 (OTA Report). The OTA Report recommended the importance of bioavailability and bioequivalence studies and indicated further steps to ensure that this information became part of the drug development and regulatory processes. Many recommendations of the OTA Report were subsequently adopted by FDA and were published in 1977 as regulations. These regulations set the stage for the passage of the 1984 Drug Price Competition and Patent Term Restoration amendments to the FDCA, which established a comprehensive system of interchangeable multi-source products in the United States.

Following on these major scientific and legislative advances, FDA published a number of

guidances that further addressed the many and various complicated bioavailability and bioequivalence studies that may be needed both for the pioneer and certainly for the generic manufacturer to allow market access. The end result of these scientific and legal endeavors is a coherent system of interchangeable pharmaceutical dosage forms. USP requests Congress to consider carefully whether this multi-decade effort, beginning with substantial marketplace problems and moving to Congressional action through the Office of Technology Assessment, can be assumed to have occurred in other countries. The U.S. regulatory, academic, and manufacturing communities have worked to great mutual benefit with their counterparts in other countries. However, these collaborative efforts, no matter how successful, do not guarantee that regulatory systems in other countries impose the same rigor for bioequivalence as does the FDA.

Third, USP believes that any drug importation program should carefully consider the public health impact of allowing dosage forms from other markets in the treatment of patients and consumers in the United States. Bioequivalence as a concept is not just a single clinical study performed by a generic applicant as part of the documentation required in an ANDA. Rather, it is a complicated science and policy approach that requires equivalent performance between multiple iterations of both a pioneer and, at the appropriate time, interchangeable multi-source generic products. Both pioneer and generic manufacturers are required under law to initially establish bioequivalence and then assure continuing bioequivalence through careful post-approval change control. USP wishes to emphasize the importance of pre- and post-approval change control to patient health. In today's environment, where appropriate healthcare cost control is critical, substitution of therapeutically equivalent dosage forms can occur frequently as healthcare systems and practitioners try to achieve the most effective treatment at the lowest cost. Given the strength of the FDA regulatory system, patients and their practitioners can be reasonably assured that the patient is getting the same medication time after time and dose after dose. Introducing a dosage form from another market has the possibility of substantially disturbing the finely-tuned equilibrium so that, without some assurance of bioequivalence, the practitioner and patient would have no way of knowing that the patient was receiving a therapeutically equivalent dosage form. Any drug importation program should provide such assurances to the patient and practitioner.

USP looks forward to working with Congress and other stakeholders in the ongoing effort to ensure that patients and consumers are not adversely affected by the importation of drugs into the United States. USP is ready to assist you by making available our scientific expertise and experience. USP believes it can play a leading and helpful role, working with this Committee and Congress, the federal government, and other relevant organizations and stakeholders, in evaluating the scientific issues surrounding drug importation.

Thank you Mr. Chairman and members of the Committee for providing USP the opportunity to provide input on the scientific issues surrounding drug importation.
WRITTEN TESTIMONY OF TODD CECIL, Ph.D.

I. INTRODUCTION.

The United States Pharmacopeia (USP) is a private not-for-profit organization whose mission is to promote the public health by establishing and disseminating officially recognized standards to ensure the quality of medicines and other health care products. USP achieves its mission through the contribution of volunteers representing, pharmacy, medicine, and other health care professions, as well as science, academia, the United States government, the pharmaceutical industry, and consumer organizations.

USP was created in 1820 by practitioners who wished to promote the quality of therapeutic products. The first pharmacopeia was published in 1820 and began as a "recipe" book to promote uniformity in drugs (a drug includes its active ingredient(s) and excipients) that were generally available in the United States at that time. Prior to the publication of the first pharmacopeia, the quality of drugs varied between cities and regions. The practitioners recognized that by setting public standards for drug products, they would help ensure the consistency and quality of drugs used in this country.

Ensuring drug quality through public standards remains USP's core mission. Today, USP's drug standards are developed by its Council of Experts and Expert Committees, a group of 650 nationally and internationally recognized scientists and practitioners in medicine, pharmacy, the pharmaceutical sciences and many other healthcare professions. USP's standards are widely recognized in the U.S. and elsewhere because they are authoritative, science-based and developed through a transparent and credible process with established integrity.

USP's standards are made public through the United States Pharmacopeia (USP) and the National Formulary (NF). Together the two compendia are published as a combined text annually (USP–NF) with two Supplements. Originally a book of process standards (recipes for preparations), USP–NF evolved over time into compendia containing primarily product standards. These standards are expressed in public monographs for drug substances, excipients, dosage forms and other articles, and in General Chapters, which are dedicated to procedures widely used throughout the compendia. The USP-NF monographs contain specifications (tests, procedures, and acceptance criteria) that help ensure the strength, quality, and purity of the named items. The purpose of the USP-NF is to provide a single standard for medicines used in the United States to ensure product uniformity and quality.

Closely allied with public monographs in USP-NF, and equally important in many respects, is the availability of an official USP Reference Standard. USP Reference Standards are chemical substances used by the pharmaceutical industry to test conformity to the USP-NF. USP Reference Standards are highly characterized chemical materials used in quality control laboratories to carry out tests for strength, quality, and purity described in the USP-NF. USP Reference Standards and USP-NF monographs are complementary tools to ensure these critical attributes for pharmaceutical substances and products.

Over the years, Congress has relied on USP on many occasions and has repeatedly

recognized USP's expertise as a standard-setting organization. Initially, in the Import Drug Act of 1848, Congress turned to USP for public standards for imported medicines. Today, principal recognition occurs as a result of Congress' recognition of the USP-NF as official compendia of the United States. The Federal Food, Drug and Cosmetic Act (FDCA) makes the official compendia, the USP-NF, enforceable by the Food and Drug Administration (FDA).

For over 185 years, USP's activities have supported the availability of safe, effective, good quality therapeutic products for patients and consumers. USP believes it can play a leading and helpful role, working with this Committee and Congress, the federal government, and other relevant organizations and stakeholders, in evaluating the scientific issues surrounding drug importation and continuing to help ensure the availability of safe, effective, good quality therapeutic products.

II. SCIENCE ISSUES.

USP commends Congress for its efforts in attempting to address the issues of drug importation and acknowledging the important role science has in helping ensure that the importation of drugs to the United States will not adversely affect public health. The issue surrounding drug importation calls into question many scientific issues that merit full consideration. This testimony will discuss two science issues – pharmaceutical equivalence and bioequivalence - that USP believes are key considerations in allowing importation of drugs into the United States. USP will also address the need for public standards and the public health impact that imported drugs may have on patients and consumers.

A. Public Monographs in USP-NF and Official USP Reference Standards.

USP believes that any medicine imported without benefit of submission of a New Drug Application (NDA), Biologics Licensing Application (BLA), or Abbreviated New Drug Application (ANDA) to FDA and subsequent Agency review must conform to a USP-NF monograph both for its ingredients, including and most importantly the drug substance and the dosage form. Lacking this conformity, the imported medicine should indicate how it differs and should so state clearly on the label. The general approach accords with the FDCA, which states that a drug shall be deemed to be adulterated 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 standards set forth in such compendium. Such determination regarding strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium.

The science and regulatory basis for these requirements is the foundation for ensuring quality drugs in the United States and has been for over 185 years. Specifically, in the Import Drug Act of 1848, the U.S. government turned to the United States Pharmacopeia for public standards for imported medicines. With passage of the Pure Food and Drug Act in 1906 and in the following almost 100 years, USP has provided public monographs for ingredients and dosage forms, working collaboratively with the FDA and

manufacturers of medicines legally marketed in the U.S. With passage of the Federal Food, Drug and Cosmetic Act in 1938, USP and subsequently NF were named as official compendia of the United States.

The USP science-based and public process for developing an official monograph for the USP-NF and official USP Reference Standards is a well evolved system that works in concert with efforts of U.S. manufacturers and the FDA to assure the public trust. Speaking simply, the public monograph in the USP-NF for a dosage form and its ingredients is the public Quality document, which allies with the Safety and Efficacy information expressed in product labeling. In offering a USP–NF monograph and, where needed, official USP Reference Standard, USP is part of a comprehensive quality system that helps assure practitioners and patients—and the public at large—that a medicine is "fit for purpose," i.e., is safe and/or effective in the maintenance of health and treatment of disease. Testing to a public monograph in USP-NF supports the nation's historical objective, through many laws and through actions of FDA itself, in ensuring the identity of an article via the test procedures and other standards of the monograph, regardless of who is manufacturing the article, who is testing it, and when or where it is tested.

In establishing a drug importation program, it is critical for the U.S. government and other independent testing laboratories to have the capability to test the medicine and its ingredients. The most transparent and effective way this testing can be achieved is via a public monograph in USP-NF, allied with an official USP Reference Standard when needed. Without this capability, the U.S. will ultimately be relying on testimonials from manufacturers vending their products in other countries or on private and/or public specifications that have not undergone the stringent analytical processes conducted either by FDA or USP.

The USP-NF has for 185 years provided public standards for medicines. These standards provide information on the quality, strength, and purity of the ingredient or product and ensure consistency in the medicines taken by the public. USP feels strongly that the success of any drug importation program implemented in the United States must recognize the critical role of public standards and require adherence to the official US compendia – the USP-NF. Adherence to the public standards in the USP-NF can achieve, via testing to the standards of a monograph and with the use of USP Reference Standards, the consistency and uniformity sought by the initial founders of USP in 1820. The failure of such recognition will result in the lack of consistency and uniformity that existed prior to 1820.

B. Pharmaceutical Equivalence

A critical part of the legislation speaks to the definition of pharmaceutical equivalence (PE). The definition alludes to when the drug substance in two duplicate dosage form is the same or not. Assurance of 'sameness' can be readily demonstrated through conformance to a modern monograph in USP-NF. Thus, if the drug substance meets the specification (tests, analytical procedures, and acceptance criteria) specified in the monograph, its identity is established, irrespective of the source of the drug substance,

and pharmaceutical equivalence for this specific substance is established.

A modern monograph in USP-NF must account for important characteristics of the drug substance and its impact on safety and efficacy. The drug substance includes impurities and physical characteristics such as particle size. The active pharmaceutical ingredient (API) is itself only one component in the drug substance. Furthermore, the API can take on many forms that at times affect—dramatically—the safety and efficacy of the dosage form containing the drug substance. The active pharmaceutical ingredient may differ in terms of crystalline form (different arrangements and/or conformations of the molecules in the crystal lattice), amorphous forms (disordered arrangements of molecules that do not possess a distinguishable crystal lattice), and solvates (crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent, such as water). Critical risks to public health have arisen based on U.S. experience for virtually all these important characteristics of the drug substance. These risks have related to both sub- and super-potency, risk from impurities, risk from changes in polymorphic form, and risk from change in particle size. Although less well studied, many of these risks are likely to extend to a dosage form's excipients, given that these ingredients frequently form the major part of a dosage form.

C. Bioequivalence

Through intense science-based deliberations on the part of USP, FDA, and manufacturers, the U.S. has led the world in considering the various issues of bioequivalence (BE) for over fifty (50) years. This consideration has many origins, but it began in part with failure of tablets containing cardiac glycosides (digitalis and its congeners) in the early 1970s. These issues led to national efforts to define BE and to determine appropriate procedures for assessment. In the United States, the Congressional Office of Technology Assessment issued a key report on July 15, 1974 (OTA Report). The OTA Report recommended the importance of bioavailability and bioequivalence studies and indicated further steps to ensure that this information became part of the drug development and regulatory processes. Many recommendations of the OTA Report were subsequently adopted by FDA and were published in 1977 as regulations entitled Part 320-Bioavailability and Bioequivalence Requirements, which contain Subparts A (General Provisions) and B (Procedures for Determining the Bioavailability or Bioequivalence of Drug Products). These regulations were themselves a seminal event and have stood the test of time, with only minor revisions, and have established firmly the general approach to assuring PE and BE for all dosage forms over time. The regulations set the stage for the passage of the 1984 Drug Price Competition and Patent Term Restoration amendments to the FDCA, which established a comprehensive system of interchangeable multi-source products in the U.S. This legislation has also stood the test of time, again undergoing only relatively minor revisions.

Following on to these major scientific and legislative advances, FDA expended considerable energies in the 1990s and thereafter to come to a better understanding of how to document interchangeability for many different types of ingredients and dosage forms. The general approach is established in FDA guidances that address the many and

various complicated bioavailability and bioequivalence studies that may be needed both for the pioneer and certainly for the generic manufacturer to allow market access. They ally with the scale up and post approval change (SUPAC) documents created by FDA in the same time frame. While this work is incomplete, it remains a beacon to the world on the information needed to assure a system of fully interchangeable pioneer and generic dosage forms.

The end result of both these seminal scientific and legislative endeavors discussed above is a coherent system of interchangeable pharmaceutical dosage forms. This system has worked to great success, based on sound legislative, regulatory, and scientific approaches involving a broad constellation of stakeholders. USP requests Congress to consider carefully whether this multi-decade effort, beginning with substantial marketplace problems and moving to Congressional action through the Office of Technology Assessment, can be assumed to have occurred in other countries. The U.S. regulatory, academic, and manufacturing communities have worked to great mutual benefit with their counterparts in other countries. However, these collaborative efforts, no matter how successful, do not guarantee that regulatory systems in other countries impose the same rigor for bioequivalence as does the FDA.

D. Patient Care Issues.

USP believes that any drug importation program should carefully consider the public impact of allowing dosage forms from other markets in the treatment of US patients and consumers. Bioequivalence as a concept is not just a single clinical study performed by a generic applicant as part of the documentation required in an ANDA. Rather it is a complicated science and policy approach that requires equivalent performance between multiple iterations of both a pioneer and, at the appropriate time, interchangeable multi-source generic products. Thus, bioequivalence per se exists as a challenge that must be documented for dosage form continuously throughout the life of any medicine irrespective of the company that is manufacturing it. To gain a glimpse of the general challenge, USP wishes to review briefly an entire and comprehensive series of pre- and post-market series of regulatory and compendial controls.

(i) Pre- and Post-Market Change Control

For the first-entry pioneer manufacturer, a careful series of approaches are needed to assure that the clinical trial material on which safety and efficacy are based is equivalent to the to-be-marketed dosage form. This is a highly resource intensive enterprise executed by U.S. innovator companies who must satisfy FDA requirements for careful product development in a regulatory filing. Many laws, regulations, and guidances provide specific and detailed requirements and recommendations for a pioneer manufacturer in this endeavor. It is a risk based approach that can intensify even for relatively simple, orally administered dosage forms, depending on the complexity of the drug substance—the active pharmaceutic ingredient, excipients, and the dosage form itself.

After approval, the NDA holder must provide continuing assurance to FDA that the approved dosage form remains both pharmaceutically equivalent and bioequivalent to the originally marketed dosage form—even in the presence of multiple changes in method of manufacturing, components, and composition. These same approaches are also critical for US generic manufacturers who have, in principle, the same requirements to initially establish bioequivalence and then assure continuing bioequivalence through careful post-approval change control. Compliance with the general requirements for both pioneer and generic manufacturers over time is a daunting task. The general manufacturing and regulatory set of approaches even now, after many years of study, is not fully resolved for all dosage forms. Below is a chart that sets forth the science and regulatory process for drug approval (Figure One).

FIGURE 1 – Process for Drug Approval

While much remains to be done in this area, USP commends FDA and the U.S. pharmaceutical industry for coming to a much clearer understanding of how to assure, in the presence of pre- and post-approval change, stable quality and performance characteristics of a dosage form and its ingredients over time. These tasks are critical to the U.S. patient and the consumer. The U.S. Congress itself emphasized the importance of post-approval change control with passage of the Food and Drug Administration Modernization Act in 1997, which legislates three types of changes and the need for associated filing requirements. This legislation was subsequently adopted by FDA in changes in regulation at 21 CFR 314.70 and associated regulatory guidance. This important legislation followed on to the FDA's careful delineation of the types of information needed by dosage form in the presence of certain changes (SUPAC documents). Again while much more work needs to be done, the SUPAC documents and the FDA's subsequent revisions of both regulation and guidance put the US and FDA and its regulated industry in the forefront of post-approval change control.

USP has a long and honorable history of supporting approaches that assure optimal dosage form performance. This is expressed most prominently in the USP dosage form monograph, which frequently includes a Performance test such as dissolution or disintegration. Dissolution acceptance criteria are usually set in private negotiations between an applicant and a regulatory agency. These subsequently can enter the public dosage form monograph in USP-NF based on decisions of the USP Council of Experts. Based on the relationship between the regulatory decisions and information voluntarily submitted by a pharmaceutical manufacturer to USP, the USP dissolution procedure links to the regulatory judgment about bioavailability and bioequivalence and, ultimately, to a judgment about safety and efficacy. For imported medicines, conformance to a USP dissolution test would be critical to an understanding of product performance.

(ii) Importance to the Patient

USP wishes to emphasize the importance of pre- and post-approval change control to the patient and consumer. The US system generally allows interchangeability based on the ratings set forth in FDA's Approved Drug Products with Therapeutic Equivalence (also known as the "Orange Book"). The Orange Book identifies drug products approved on the basis of safety and effectiveness by the FDA under the FDCA and provides guidance on drug interchangability. This means that in all 50 states and territories, substitution of appropriately rated (e.g., AB rated oral dosage forms) may occur at the pharmacy level. In today's environment, where appropriate healthcare cost control is critical, substitution of therapeutically equivalent dosage forms from one manufacturer to another can occur frequently, as healthcare systems and practitioners try to achieve the most effective treatment at the lowest cost. In practice, this might mean that a patient would receive a dosage form from many different manufacturers over the course of a year's treatment. Given the strength of the US system, this patient—and his/her practitioner team—can be reasonably assured that the patient is getting the same medication time after time and dose after dose. But this assurance is based on FDA's rigorous control of both pharmaceutical equivalence and bioequivalence through careful pre- and post-approval change. Introducing a dosage form from another market has the possibility of substantially disturbing this finely-tuned equilibrium so that, without some assurance of bioequivalence, the practitioner and patient would have essentially no assurance that at any point in time they were receiving a therapeutically equivalent dosage form. For both the patient and practitioner, this is an especially critical point. Health and disease have their own inherent progression. Medicines are not like cars, where breakdowns are usually readily apparent but rather may be attributed to the course of a disease or other factors. This challenge in assessing causality impedes understanding that absence of progress or unexpected toxicity may in fact be attributed to the failure of a medicine.

Through careful safety, efficacy, and quality pre-market studies, the U.S. system requires a pioneer to gain some understanding of the dose/response relationship for a medicine. This dose/response relationship allows the concept of a therapeutic window, as demonstrated by the following figure (Figure Two).

FIGURE TWO – Optimal Dose Therapeutic Window

The therapeutic window refers to the point at which efficacy begins to be lost, if the dose administered is too low or too high or is unacceptably toxic. A dosage form should deliver the same amount of drug at the same rate to a patient with each dose time after time to maintain optimal safety and efficacy. If a dosage form under- or over-performs, as may happen with bioinequivalent products, then the optimal safety/efficacy profile may be lost. It is important also to note that concepts of bioequivalence and therapeutic equivalence are applicable to the individual. Thus a patient/consumer must receive a dosage form that reliably delivers the right amount of the drug at the right time, day after day, in order to assure optimal safety and efficacy over time.

Furthermore, while all regulatory systems produce drugs based on population studies, the concept of generic substitution relates also to the therapeutic window for a single patient.

At this time we have little or no understanding of this therapeutic window in an individual or how it might change in different populations such as the elderly, children, women, or the infirm. As a specific example, the therapeutic window for a narrow therapeutic range drug such as warfarin might range between 2 and 10 or more milligrams/day in the population. But in an individual, such a wide dose range would produce intolerable loss of efficacy, manifested in excessive coagulation, or unacceptable toxicity, manifested by bleeding. Careful attention to bioequivalence both within and between manufacturers is designed to prevent such occurrences. Even small differences between bioinequivalent dosage forms—in terms of amount of drug delivered and the rate at which is delivered--can thus produce dangerous outcomes in individual patients.

Congress, FDA, USP, the pharmaceutical industry, and many other stakeholders have been addressing the issue of bioequivalence and its impact on patients for over fifty years in the United States. The result is a vigorous regulatory process that provides reasonable assurances to patients and practitioners. Any drug importation program must provide patients and practitioners in the United States the equivalent assurance in order to not to adversely impact public health. USP believe that adherence to public standards in the USP-NF is one mechanism to help achieve such assurances.

III. CONCLUSION

USP commends Congress for its efforts in attempting to address the issues surrounding drug importation. USP looks forward to working with Congress and other stakeholders in the ongoing effort to ensure that patients and consumers are not adversely affected by the importation of drugs into the United States. USP is ready to assist you by making available our scientific expertise and experience. Specifically, USP believes it can play a leading and helpful role, working with this Committee and Congress, the federal government, and other relevant organizations and stakeholders, in evaluating the scientific issues surrounding drug importation.

Thank you Mr. Chairman and members of the Committee for providing USP the opportunity to provide input on the scientific issues surrounding drug importation.

ANNEX 1 – USP and its Public Health Mission

1. History.

USP is a not-for-profit organization that was created in 1820 by eleven practitioners who wanted to promote the quality of therapeutic products. The first pharmacopeia was published in the United States in 1820 and began as a “recipe” book to promote uniformity in drugs (a drug includes its active ingredient(s) and excipients) that were generally available in the United States at that time. Prior to the publication of the first pharmacopeia, the quality of drugs varied between cities and regions. The practitioners recognized that by setting public standards for drug products, they would help ensure the consistency and quality of drugs. Ensuring drug quality through public standards remains USP’s core mission.

2. Volunteer Based Organization.

USP's governing bodies include its Convention, which meets every five years, and a Board of Trustees, which provides direction to staff in the years between Convention meetings. Standards-setting activities are conducted by the USP Council of Experts. Membership in the Convention (representing approximately 400 associations), on the Board (11 members representing Convention constituencies), and on the Council and its Expert Committees (approximately 650 members) is entirely voluntary. To support the activities of these bodies, USP maintains a staff of approximately 350 in its Rockville offices.

3. Public Monograph in the USP-NF and Official USP Reference Standards.

USP’s drug standards are developed by its Council of Experts and Expert Committees, a group of 650 nationally and internationally recognized scientists and practitioners in medicine, pharmacy, the pharmaceutical sciences and many other healthcare professions. USP’s standards are widely recognized in the U.S. and elsewhere because they are authoritative, science-based and developed through a transparent and credible process with established integrity.

USP provides standards for more than 4,000 prescription and non-prescription drugs, dietary supplements, veterinary drugs, health care product, and excipients. These standards are presented in a combined text consisting of two compendia – the United States Pharmacopeia (USP), to which the National Formulary (NF) was added in 1975. Together the two compendia are published as a combined text annually (USP-NF) with two Supplements.

USP’s standards, which are presented in monograph form, contain specifications (tests, procedures, and acceptance criteria) that help ensure the strength, quality, and purity of the named articles. Closely allied with public monograph in the USP-NF, and equally important in many respects, is the availability of official USP Reference Standards. USP Reference Standards (chemical specimens) are used in the pharmaceutical industry to test conformity to such monograph standards. USP provides approximately 1,750 USP Reference Standards that are specifically required in many Pharmacopeial assays and tests.

USP's official Reference Standards are highly characterized materials used in a quality control laboratory to carry out tests for strength, quality, and purity described in the USP–NF. Such tests help to determine whether a batch being released to the market conforms to its USP–NF specification as required by law and will continue to conform throughout its shelf life. The Reference Standards are typically used to conduct the analytical procedures set forth in the USP–NF.

USP Reference Standards also are used as calibrators—for dissolution, particle count, melting point, and standardization of titrants and as blanks and controls (negative control plastic, lanolin, and methylcellulose). Reference Standards are used for measurements

required to obtain accurate and reproducible results in chromatographic and spectrophotometric procedures. USP has Reference Standards for drug substances, dosage forms, dietary supplements, excipients, impurities, and degradation products, as well as performance calibrators.

4. Reference Standards Development Process

When USP identifies the need for a new Reference Standard (based on monographs in the USP–NF that require its use), it requests bulk materials from pharmaceutical manufacturers. USP subjects the candidate materials it receives from manufacturers to rigorous analysis and review. USP tests the materials in its own laboratories, and requests collaborative testing by FDA and independent laboratories. The goal of the collaborative testing is to confirm the identity and assess the purity of the material, to confirm its homogeneity, to determine its suitability for use in the official applications, to provide the user with all the necessary information and directions for use, and to acquire time-zero information for future continued-suitability-for-use studies. USP compares and analyzes the results of this collaborative testing and prepares a report for its Reference Standards Expert Committee (RS-EC). The RS-EC comprises experts from industry, government agencies, and academia from the US and from abroad. The RS-EC determines whether the candidate material is suitable to be established as an official USP Reference Standard. USP Reference Standards are established and released under the authority of the USP Board of Trustees upon recommendation of the USP RS-EC.

5. Public Process.

During the past 185 years, USP has played an important role in developing standards for medicines, including drugs, devices, biologicals, and dietary supplements. USP standards are developed and continuously revised by a unique public process, involving expert volunteers from academia, industry, government, trade associations, and consumers, and are subject to public comment

USP’s public comment process occurs via the Pharmacopeial Forum (PF) and is similar to the federal government’s Federal Register. The PF is the working vehicle of the USP Council of Experts (CoE). The PF provides interested parties the opportunity to review and comment as the CoE develop and/or revise standards for the USP-NF.

6. Legal Recognition

The USP-NF is recognized in federal laws regulating drugs, food, devices, and dietary supplements. Initially, in the Import Drug Act of 1848, Congress turned to USP for public standards for imported medicines. Thereafter, the USP was incorporated in the 1906 Pure Food and Drug Act, which stated that drugs included all those medicines and preparations in the USP and stated that a drug was considered adulterated if it differed from the standard of strength, quality, or purity described in the USP. The current law, the Federal Food, Drug, and Cosmetic Act (FDCA), was enacted in 1938 and recognizes the USP-NF in several sections. The FDCA defines the USP-NF as official compendia,

specifically stating that “official compendium” includes the United States Pharmacopeia, the National Formulary or any supplement to any of them. The FDCA also incorporates the 1906 adulteration provision, by stating that a drug is adulterated if it is recognized in the USP-NF and fails to meet the strength, quality, or purity set forth by compendial standards. In addition, the FDCA integrates USP-NF standards in the misbranding provisions for drug products, saying that drugs are considered misbranded if they fail to adhere to USP-NF standards for packaging and labeling. Section 502(e) requires that the established name of a drug appear on the label and states that the established name of a drug or ingredient is the one designated by the Secretary of the Health and Human Services or the name appearing in the USP-NF.

Congress also has recognized USP-NF standards for dietary supplements but has made adherence to them voluntary. Specifically, § 402(s)(2)(D) provides that a dietary supplement is considered misbranded if it states conformance to an USP-NF monograph and fails to so conform. Thus, if a dietary supplement manufacturer asserts conformance to the USP-NF monograph, the product must conform to the monograph requirements or the product will be deemed misbranded.

The Social Security Act (SSA) recognizes the USP-NF in the provisions regarding Medicare. According to the SSA, Medicare provides reimbursement for drugs that cannot be self-administered, such as those drugs administered in a physician’s office. The SSA then defines drugs to be those that are included or approved for inclusion in the USP, NF, United States Homeopathic Pharmacopeia, or in New Drugs or Accepted Dental Remedies or approved by the pharmacy and drug therapeutics committee. As a practical matter, drugs administered in a physician’s office are generally not subject to approval by a pharmacy and drug therapeutics committee so the drugs must be in the USP-NF or approved for inclusion in them. USP has a process whereby a drug can be readily approved for inclusion into the pharmacopeia.

Most recently, under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, the Secretary of the Department of Health and Human Services is required to request USP 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 in developing their formularies. USP is to revise this classification from time to time to reflect changes in therapeutic uses of covered drugs and addition of new covered drugs. In December 2004, USP provided the Centers for Medicare and Medicaid Services (CMS) the USP Model Guidelines as set forth under the MMA. USP is working with CMS to determine the revision process for the USP Model Guidelines.

7. Other Related USP Activities.

a. USP-International

The international market for manufactured pharmaceuticals is changing at a rapid pace, leading to an especially challenging global environment where the likelihood of counterfeit and substandard drugs is of increasing concern. Like early practitioners in the

US, modern practitioners in many parts of the world beyond the US may confront a bewildering array of poorly named therapeutic ingredients and products, with uncertain safety, efficacy, and quality. In a recent publication, USP proposed the creation of a separate official USP compendium, clearly distinguished from USP-NF, to support international needs and, as feasible, national interests as well. The approach allows availability of useful public analytical information to all constituencies of USP throughout the world. USP believes this general approach to assure optimal quality of medicines irrespective of their market sphere of authority might be especially useful in considering issues of importation.

b. USP's Verification Programs

USP has established a Dietary Supplement Ingredient and Product verification program. USP is considering expansion of the approach to excipients, drug substances and perhaps even dosage forms. USP believes that this type of program could be used by the Federal government to help assure the quality of medicines entering the U.S. market from another country or region. USP has enclosed additional information on its Verification Programs.