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Impact of USP on the Regulatory Approval of the Drug

Arjun Pande*, Rudra Chowdhury

Department of Pharmaceutics, Sri Satya Sai College of Pharmacy, Sehore - India

Introduction

The purpose of this article is to introduce the reader to the United States Pharmacopeia/National Formulary (USP/NF) and to its formal and legal role in the Food and Drug Administration's (FDA) drug regulatory process in the United States[1]. It is important to notice the concurrent development of key events in the history of U.S. food and drug law with the development of the USP and NF, two drug standards compendia that originated from different parts of the health care delivery system[2,3]. Since their founding in 1820 and 1888, respectively, the United States Pharmacopeia (USP) and the National Formulary (NF) have worked to create public standards for the purity, quality, and strength of medical products, as well as compounding information. In addition to its other regulatory responsibilities, the Food and Drug Administration (FDA), which was formally established in 1938, has always been involved in enforcing purity and potency standards for drug materials, a role that dates back to the Bureau of Chemistry of the Department of Agriculture in 1862[2,3]. Public standards for the strength and purity of medications have been enforced by the federal government since at least 1848, when the USP, a private, nongovernmental organization, first interacted with the government on the matter. To stop the entry of spurious or substandard medications into the country, Congress created the Drug Importation Act in 1848. Drugs that do not meet the "standard established in the United States Pharmacopoeia, and therefore improper, unsafe, or dangerous to be used for medicinal purposes, the articles shall not pass the custom house" are not allowed to enter the United States[4].

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*CORRESPONDING AUTHOR: Arjun Pande
E- Mail: arjun_p@yahoo.com

The United States Pharmacopeia/National Formulary (USP/NF) is currently recognized in Federal statutes as a drug standards setting body.

When a pharmaceutical product fails to meet the requirements set forth in the USP/NF monograph, we consider it to be adulterated. When products with known safety issues are sold, the company may face compliance actions from the Food and Drug Administration (FDA).

Acceptability of Standards from Alternative Compendia (BP/EP/JP)

Even though the monograph is still the standard for quality and purity, the FDA Office of New Drug Quality Assessment released guidance for new drug development submissions to the FDA, MAPP 5310.7 Rev.1, "Acceptability of Standards from Alternative Compendia (BP/EP/JP)" (Acceptability of Standards from Alternative Compendia (BP/EP/JP)). This document is effective as of October 13, 2017. This policy covers Investigational New Drug Applications (INDs), New Drug Applications (NDAs), and Abbreviated New Drug Applications (ANDAs). Sponsors and applicants for new drugs are given permission to rely on criteria from alternative compendia if they are at least as stringent as those in the USP/NF monographs or equivalent. Pharmaceutical fillers, active pharmaceutical ingredients, and finished pharmaceuticals all fall under this category. Furthermore, if the drug product submission uses an article that does not have a corresponding USP/NF monograph but does have a corresponding BP/EP/JP monograph, the drug sponsor may use the alternative compendial procedure, so long as it is at least as good as the corresponding procedures stipulated in the USP general chapters. All drug substances, inactive components (excipients), drug products, and other official articles are covered by the information found in the General Notices and Requirements and General Chapters portions of USP/NF, in addition to the formal monographs[5].

Legal Basis of USP

Finally, it should be mentioned that the United States Pharmacopeial Convention (USPC) formed in the District of Columbia, with a written constitution and bylaws, in 1900, giving the USP legal status. An elected Board of Trustees is responsible for the day-to-day management of the USPC. There are currently around 750 employees and over 640 volunteers supporting USP/NF operations. The participants include representatives of professionals from almost all fields involved in health care delivery systems around the world. Accredited medical and pharmacy schools, state medical and pharmacy associations, national and international scientific and industry trade associations, consumer organizations, public interest groups, U.S. governmental and international pharmacopeial agencies, and other sectors of the healthcare industry are all represented among the volunteers who participate in USP activities.

Origin of the USP and NF

The USP has been around since 1820. During the years following the American Revolution, medical professionals in the United States relied on foreign texts for guidance on how to prescribe, store, and prepare medicines for their patients. Leading doctors in practice at the time saw the necessity for a standardized national pharmacopeia. Numerous formularies and pharmacopeias, tailored specifically to meet the demands of specific regions, evolved. Dr. Lyman Spalding took the initiative and played a pivotal role in convincing the medical community that a comprehensive national formulary was necessary. In January of 1820, the nation's leading medical institutions gathered at a national "conference" in Washington, D.C. to lay the groundwork for what would become the "national formulary." The first USP was compiled, prepared, and published on December 15, 1820, under the auspices of the convention due to his foresight, work, and leadership[6]. Title page of the first edition of USP states that the text was provided by the Medical Societies and Colleges. Both the primary and secondary lists of medications (totaling 221) may be found in the pharmacopeia. The "materia medica" was a list of drugs that scientists and physicians of the time agreed were necessary to treat the population.

An accurate Latin and English name for the medicine and a detailed description of the substance were the primary goals of the first USP. Through the "United States Adopted Names" (USAN) Council and the "USP Dictionary of USAN and International Drug Names," USP continues to play an important role in this area of "nomenclature"[1]. The original compendia for the official USP articles lacked explicit criteria and quality specifications. The recipes in the "Preparations" sections showed the reader how to make various product. There were a variety of dosage forms available at the time, including solid, semisolid, and liquid versions. The ultimate goal of the USP is to allow physicians all around the country offer their patients with standardized, well-defined medicines without having to rely on foreign imports. When a medicine was included in the USP, it was the same as if it were an "official" medicine. Beginning in 1820, when the USP was still a small organization, a revision process was set in place to update the compendia to incorporate the most up-to-date medicines available at the time. Moreover, it was decided that obsolete items would be deleted from the compendium. Since 1840, when the United States Pharmacopeia (USP) was established, the USP monographs have included standardized tests for determining the identity and quality of pharmaceuticals[4,6]. In 1852, as the USP continued its development and update, the nation's pharmacists joined together to form the American Pharmaceutical Association (APhA). Their main focus was finding a solution to the ongoing issue of low-quality pharmaceutical products entering the U.S. from Europe. As a means of combating this issue, the APhA developed quality criteria that are now included in "official monographs" that supplement the USP. Concerns were also raised regarding allowing physicians to prescribe drugs that would otherwise be compounded by pharmacists rather than being sold in pre-packaged form. The USP did not cover many of the readily available medications. As a result, there is a need for a formally compiled set of "unofficial preparations." Charles Rice and Joseph Remington took the lead of this initiative. In July 1888, the first edition of the National Formulary was released. The APhA issued a book with the official title "National Formulary of Unofficial Preparations." There were just preparation recipes (435 total) in NF I, although they covered every known oral dose form at the time. The idea of NF I was that it would not only serve as a repository for USP discards or a testing ground for novelties, but also as a source of reliable preparations. As two separate compendia of pharmaceuticals, the

USP and NF eventually converged on a format and set of contents that were quite similar. In 1936, the APhA set up a lab to test drugs and make sure they met certain standards[7]. Prior to that time, APhA only partially subsidized or encouraged independent laboratories to conduct testing that was incidental to the creation of NF standards. In the past, the USP had to send its samples to independent labs for analysis. The Drug Standards Laboratory, which serves the USP, NF, and AMA, was established in 1962. The lab's primary function was to create and analyze standards[8]. The laboratory's work progressed to include analyses of methods. After the USP acquired the NF in 1975, the two compendium were merged into a single one, with two distinct entry areas for monographs. Before 1978, it was known as the Drug Standards Laboratory. The dissolution testing criteria and qualification of reference standards were the laboratory's primary focuses. At the moment, USP runs and takes care of two laboratories.

One lab does research and development on high-quality reference standards and tests the quality of drugs. The second lab makes and packages these reference standards so that they can be shipped all over the world. Validation of testing procedures developed to support qualification and release of material to serve as USP reference standards falls on the laboratories. Right now, the USP testing laboratory, along with at least two other laboratories around the world, examine a batch of material intended to serve as a reference standard article. The USP Board of Trustees authorizes the release of reference standards when the USP Reference Standards Expert Committee recommends a particular lot of reference standard based on the results of the testing laboratories' evaluations of the reference standard's quality and purity[9]. The USP laboratories also help the Expert Committees evaluate analytical tests and methods that could be added to the USP by giving them scientific support.

Impact of USP on Drug Approval

Until 1906, neither federal nor state legislation in the United States mandated that medicinal items manufactured or marketed in the country follow to the standards set forth in the United States Pharmacopeia (USP) or the National Formulary (NF). The Federal

Food and Drugs Act of 1906 made it very apparent that any drug sold in interstate commerce by a brand name that is listed in the USP or NF monographs must meet the standards for strength, quality and purity set forth in those monographs[4]. To the contrary, the Bureau of Chemistry will take legal action against companies selling noncompliant products on the grounds that they are misbranded. Products sold under the compendial monograph that aren't the same quality as those listed in the USP or NF monographs must list the strength, purity, and quality of the article on the label[4]. The Bureau of Chemistry was split into two separate groups in 1927. One of these groups was the Food, Drug, and Insecticide Administration. The agency was renamed as the Food and Drug Administration in 1930. In 1940, the FDA was transferred from the Department of Agriculture to the Federal Security Agency for administrative purposes. The Federal Security Agency changed its name to the Department of Health, Education, and Welfare in 1953[2]. Efforts are made to modify the 1906 Food and Drugs Act as a result of lingering concerns over the Act's inadequacies in addressing false therapeutic claims for patent medicines and food adulteration. More than a hundred people died in 1937 after taking Massengill's Elixir of Sulfanilamide, which contained diethylene glycol and accelerated the revision process. The "Federal Food, Drug, and Cosmetic Act" was passed by Congress in June of 1938, mandating that all pharmaceutical companies submit an application to the FDA detailing the steps they have taken to ensure the safety of their products. Manufacturers were not mandated to submit evidence regarding the effectiveness of new drugs or new formulations of existing drugs on the market. The continuation of the USP and NF as official public standards for pharmaceuticals, including packaging and labeling requirements, was a fundamental component of the Act[10]. The new law also expanded FDA jurisdiction to cover cosmetic and medical equipment.

U.S. law was passed in 1962 by the Kefauver-Harris amendments to the 1938 Food, Drug, and Cosmetic Act (Drug Amendments) to further strengthen the role of the FDA in controlling prescription pharmaceuticals, novel drugs, and investigational drugs. Except for the formation of the antibiotic certification program, the role of the USP and NF as public standard-setters was not dramatically impacted by the Act. There was no change to the compendia's responsibility for naming new medications[10]. It is interesting to note

that in order to be covered by Medicare, drugs and biologics must be included in or approved for inclusion in the USP or NF (or in hospital formularies for administration in hospitals) as stated in the 1965 Medicare amendments to the Social Security Act[11]. As part of the Food, Drug, and Cosmetic Act modifications that took effect in 1994, the USP, NF, and Homeopathic Pharmacopeia were designated as the official compendia for dietary supplements. If there is a USP/NF monograph for a dietary supplement and the product on the market claims to satisfy "USP standards," but does not, it is deemed misbranded. A dietary supplement that does not claim to adhere to USP standards cannot be held to the monograph's requirements because the program is entirely voluntary[11].

USP Information vs. FDA Requirements

In its general chapters and general information, the USP talks about things that have an effect on compendial testing. A lot of the time, FDA guidance and ICH guidelines talk about the same things. Updates happen, so it's important to always compare the information in the USP to the most recent FDA guidance or ICH guidelines. Any inconsistencies or problems must be brought to the attention of the USP right away. It is important for people who have a stake in USP products and services to know how the USP change control processes work. Participating in and being aware of USP conferences and workshops can be a very important way to find out about changes that USP might be thinking about that could affect a company's understanding of USP-defined procedures and practices. Keeping internal controls, procedures, and drug product applications up-to-date based on changes to the USP is a never-ending task that can't be put off.

Conclusions

The USP/NF continues to help people stay healthy by setting standards for drugs and dietary supplements. By working together with the EP and JP on harmonization, the USP makes sure that monographs and general chapters are known around the world. Also, as

long as the analytical technologies in the USP are kept up-to-date, the FDA will almost certainly continue to use the USP as a good benchmark for judging the quality of key product attributes for regulatory submissions.

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