A Brief History of Pharmacopoeias: A Global Perspective

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In this series of articles, the authors provide an understanding about the need for pharmacopoeia compliance. The following articles can be found within this ebook and online at www.PharmTech.com/compendia:

- Why Pharmacopoeia Compliance is Necessary
- Why Pharmacopoeia Compliance is Difficult
- A Brief History of Pharmacopoeias: A Global Perspective
- Global Pharmacopoeia Standards: Why Harmonization is Needed
- Harmonization Efforts by Pharmacopoeias and Regulatory Agencies

Upcoming articles in this series will include the following:

- Revision Process for Global/National Pharmacopoeias
- Surveillance Process for Industry: Monitoring Pharmacopoeia Revisions
- Monograph Development: Why and When to Participate
- Monograph Development: How to Participate; How to Harmonize
- A Practical Approach to Pharmacopoeia Compliance
- A Case Study in Pharmacopoeia Compliance: Excipients and Raw Materials
- Pharmacopoeia Compliance: Putting it All Together; What is on the Horizon

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The global and historical perspective presented herein is critical to understanding the particular challenges that must be overcome to achieve harmonization among the pharmacopoeias, as well as providing a deeper appreciation of the important harmonization progress achieved to date. Also, by understanding the lack of harmonization, the reader will appreciate the complexity it adds to a company's processes for compendial monitoring and compliance.

Pharmacopoeias–A global perspective and brief history

According to the latest index compiled by the World Health Organization (WHO) (1), there are as many as 40 pharmacopoeias published around the world, with as many as 60 active pharmacopoeia commissions who carry out the work of developing and maintaining these pharmacopoeias (**Table I**). To better understand the situation today, it is instructive to consider the history of pharmacopoeias. A timeline is provided in **Figure 1** indicating the year when many of the pharmacopoeias were created. Although the earliest work presenting medical knowledge and herbal remedies may date back more than 3000 years to ancient Egypt (2), it was *De Materia Medica*, which appeared in the 1st century CE in Greece and Rome that perhaps represents the first example of a "pharmacopoeia" (3). (The word "pharmacopoeia" translates from the ancient Greek as "drug-making".) This treatise on medical matters compiled herbal remedies known at the time, along with their methods of preparation. Beginning in the 16th century, several pharmacopoeias containing medical prescriptions were prepared for apothecaries and physicians in important cities of Europe, including Nuremburg (4), London, Edinburgh, and Dublin (5).

BP and *USP*–early efforts to harmonize pharmacopoeias

In the 19th century, it was recognized that there were inconsistencies in the information contained in the various pharmacopoeias which then existed. As a result, there was an emerging focus on efforts to standardize and harmonize the content in the pharmacopoeias. An early example of the

The development of the *USP* and *BP* were intended to harmonize drug standards.

need for pharmacopoeial harmonization was the creation of the *British Pharmacopoeia* (*BP*) in 1858 to overcome the inconveniences and dangers resulting from the existence of three different pharmacopeias in the United Kingdom and Ireland, those of London, Edinburgh, and Dublin (5). Even earlier, in 1820, the *United States Pharmacopeia* (*USP*) was established by a group of 11 physicians who held the first United States Pharmacopeial Convention (USP) in the US Capitol building in Washington, because they recognized the need for consistent standards for the medicines that were being used in the separate states of the relatively young "united" country. Information contained in the preface to the first edition of the *USP* provides an early reference to the historical purpose, value, and usefulness of the pharmacopoeias, which also provides interesting perspectives for today (6). Modern pharmacopoeias strive to achieve similar value and usefulness, while shifting away from historical "recipes" that described methods of preparation for medicines, to instead focus on the attributes of drug products and ingredients that help ensure their identity, strength, quality, and purity. The preface to the first edition of the *USP* continues with the following remarkable comments that speak to the need and value of harmonization to achieve consistency in pharmacopoeial standards (6):

- "In the United States the evil of irregularity and uncertainty in the preparation of medicines has been felt with peculiar weight."
- "… (A) number of Pharmacopoeias … have been produced in different parts of the Union … and of course the character of medicinal preparations is liable to vary in every state and city of the Union."
- "… (A) National Pharmacopoeia … should be established and adopted … being evidently the only mode by which a uniform system could be introduced at once into all parts of the American territory."

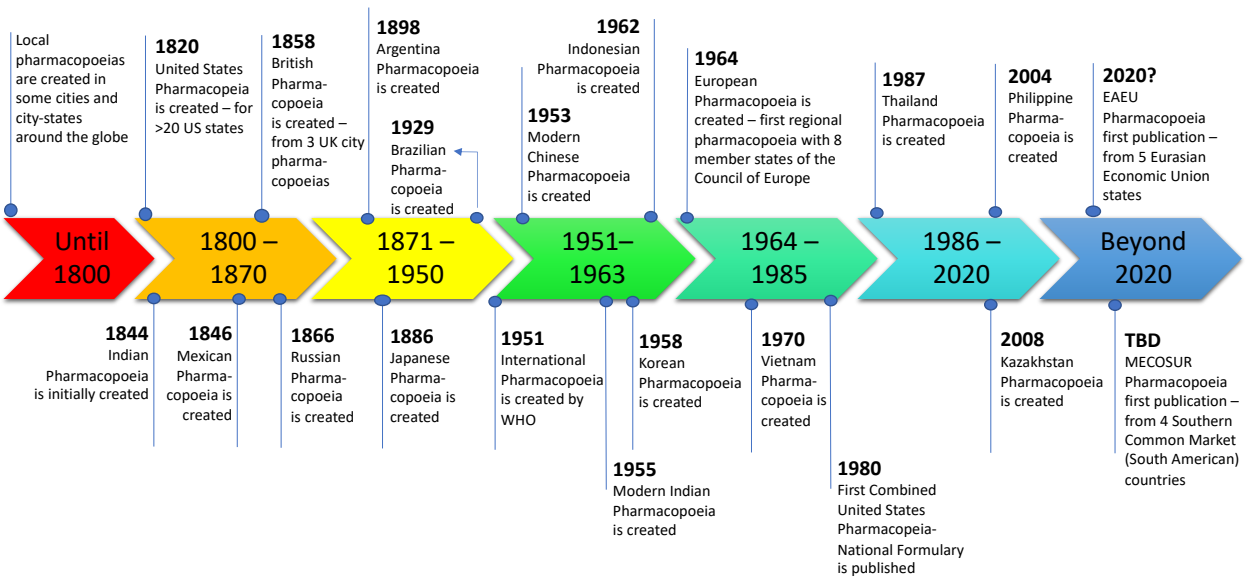
The work of the convention that introduced this uniform system of drug standards and led to the initial creation of the pharmacopoeia of the United States continues today, with the next meeting of stakeholders scheduled in May 2020, marking the 200th anniversary of the USP. However, the establishment of the USP in 1820 occurred long before modern bio/pharmaceutical manufacturing capabilities and regulatory systems that are in place today around the world to control the quality, safety, and efficacy of drug products. Although it was not known by its present name until 1930, FDA's modern regulatory functions began with the passage of the 1906 Pure Food and Drug Act (7), nearly a century after the first *USP* was published. The *USP* and *National Formulary* (*NF*) were subsequently recognized as official compendia in the 1938 Federal Food, Drug, and Cosmetic Act (FD&C Act). In 1975, USP acquired the previously separate compendium NF and the first combined edition

Table I. Pharmacopoeia commissions/published pharmacopoeias compiled from World Health Organization data (1).

Pharmacopoeia commission	Pharmacopoeia published	Pharmacopoeia commission	Pharmacopoeia published
Argentina#	√	Macedonia+	
Austria*	√	Malta*	
Belarus##	√	Mexico	√
Belgium*		Montenegro*	
Bosnia and Herzegovina*		Netherlands*	
Brazil#	√	Norway*	
Bulgaria*		Pakistan	√
Chilex	√	Philippines	√
China	√	Poland*	√
Croatia*	√	Portugal*	√
Cyprus*		Republic of Korea	√
Czech Republic*	√	Romania*	√
Denmark*		Russian Federation##	√
Egypt	√	Serbia*	
Estonia*		Slovak Republic*	√
Finland*		Slovenia*	
France*	√	Spain*	√
Germany*	√	Sweden*	
Greece*	√	Switzerland*	√
Hungary*	√	Thailand	√
Iceland*		Turkey*	
India	√	Ukraine*	√
Indonesia	√	United Kingdom*	√
Iran	√	United States	√
Ireland*		Vietnam	√
Italy*	√	**Regional/International**	
Japan	√	Africa	√
Kazakhstan##	√	Eurasian Economic Union##	√
Latvia*		Europe*	√
Lithuania*		MERCOSUR#	√
Luxembourg*		World Health Organization++	√

* Pharmacopoeia authorities are a party to the European Pharmacopoeia Convention.
\# Participating countries in the MERCOSUR Pharmacopoeia: Argentina, Brazil, Paraguay, Uruguay.
Participating countries in the Eurasian Economic Union (EAEU) Pharmacopoeia: Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russian Federation.
x Pharmacopoeia authority not active.
\+ Former Yugoslav Republic of Macedonia.
++ The World Health Organization (WHO) publishes the *International Pharmacopoeia* (*Ph. Int.*).

Figure 1: Timeline indicating the year when many of the pharmacopoeias were created.



of the *USP–NF*, as it is known today, was released in 1980. The *USP–NF* remains unique today among pharmacopoeias, because it is developed by a private, non-governmental standards-setting organization. Unlike most other pharmacopoeias, which are affiliated with, or formally part of the regulatory agency in that country or region, the *USP–NF* is not part of, nor is it affiliated with the US FDA. Still, USP and FDA have a long-standing collaboration and maintain official contact through a number of established channels to help ensure the standards that are published in *USP–NF* and enforced by FDA (among their many other responsibilities) contribute to the quality of medicines. The historical context and practical considerations in the development of the USP and FDA have led to instances where the pharmacopoeia and regulatory requirements in the US are not fully aligned, making it difficult to comply with both standards.

Historical perspective for other pharmacopoeias

A broader consideration of today's global community reveals a more complex situation with compliance challenges that result from the lack of broad harmonization across the various pharmacopoeias and regulatory agencies around the world. The publication of the *USP* in 1820 and the BP in 1858 aimed to bring consistency to drug standards for the benefit of pharmacy and medical practitioners and their patients. This objective has been pursued in other countries, continuing to modern times, with the initial development and subsequent updates to their pharmacopoeias. As noted earlier, there are currently as many as 40 pharmacopoeias published around the world, each with its own rich and unique history, while sharing a common goal of providing quality standards for medicines to benefit patients. Additional historical examples bring awareness of the overall timeline for development of the pharmacopoeias and provide the larger global context to aid in understanding the continuing efforts to achieve some degree of compendial harmonization.

Based on traditions for curing illnesses dating back to the 2nd millennium BCE, the classic *Shen-nung Pen-ts'ao Ching* represents the oldest known pharmaceutical work in China, a compilation of traditional Chinese materia medica (8). The current *Chinese Pharmacopoeia* (*ChP*) also has an interesting history for the establishment of quality standards for medicines, reflecting the great importance attached to medicine and healthcare by the Chinese government for the people of China (9). In 1949, the year the People's Republic of China was founded, the Ministry of Health convened a meeting of medical and pharmaceutical experts to compile a national pharmacopoeia for China. Over the following several years, a process for developing the pharmacopoeia was established, including a secretariat and experts charged with carrying out the practical and technical aspects of the work. The first edition of the *Chinese Pharmacopoeia* was published in 1953, containing 531 monographs for drug substances and products, including chemical medicines and traditional medicines of plant and animal origin. The first addendum to the 1953 edition was published in 1957. Since then, the content in the pharmacopoeia has continued to expand. The latest (10th) edition of the *Pharmacopoeia of the People's Republic of China*, referred to as the *ChP*, was published in 2015 and consists of four volumes covering traditional Chinese medicines, modern chemical medicines and antibiotics, biologics, excipients, and general chapters (10). *ChP* 2015 contains more than 5600 monographs, 10 times the number in the first edition, including more than

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1000 new monographs since the previous edition that was published in 2010, and more than 300 general chapters and requirements. The next edition of *ChP* is in development, with publication planned for 2020.

The history of the *Indian Pharmacopoeia* (*IP*) (11) began in 1833, when a committee recommended publication of a pharmacopoeia, which was first completed in 1844 and mainly consisted of commonly used indigenous remedies. A subsequent publication in 1868 included not only the indigenous drugs used in India, but also the drugs of the *British Pharmacopoeia*. Then in 1885, the *BP* was made official in India. After independence from Britain, the Indian Pharmacopoeia Commission was established in 1948, with its main function being the publication of *IP* as the national pharmacopoeia. The first edition of the modern *IP* was published in 1955, and the current 8th edition was published in 2018.

Elsewhere, the first edition of the *Russian Pharmacopoeia* (now the *State Pharmacopoeia of the Russian Federation* or *SP RF*) dates back to 1866 (12); it is now in its 14th edition, which was published (in Russian and on-line only) by the Russian Ministry of Health in December 2018, with implementation required by January 2022. The *Japanese Pharmacopoeia* (*JP*) was first published in 1886 (13) and is now in its 17th edition including two supplements, with the 18th edition planned for publication in 2021. The pharmacopoeias in Mexico and Argentina were first published in 1846 and 1898, respectively (1). The first edition of the *Brazilian Pharmacopoeia* was published in 1929 (1) and is currently in its 5th edition including two supplements, with an updated 6th edition nearing completion. The *Korean Pharmacopoeia* was first published in 1958 (1); the *Indonesian Pharmacopoeia* in 1962 (12). Other recent examples include the pharmacopoeias in Vietnam, Thailand, the Philippines, and Kazakhstan, first published in 1970, 1987, 2004, and 2008, respectively (1).

Each pharmacopoeia was initially established to standardize medicines and serve the needs of patients within their respective country. Today, a global view is necessary in order to meet the needs of global patients. Within this perspective, there is a special place held by the *European Pharmacopoeia* (*Ph. Eur.*) and the *International Pharmacopoeia* (*Ph. Int.*), each of which deserves further consideration.

Ph. Eur.–Creation of a modern, harmonized pharmacopoeia

In their historical context, the development of the *USP* and *BP* were intended to harmonize drug standards. But unlike the *USP*, *BP*, and many other pharmacopoeias, the more recent creation of the *Ph. Eur.* occurred within the context of modern manufacturing and regulatory systems in Europe and around the world, providing a recent and successful example of harmonization. In 1964, the Convention on the Elaboration of a European Pharmacopoeia, set forth by eight member states of the Council of Europe, established harmonized standards for medicines in Europe (5). The convention facilitated the free movement of medicines throughout member states and ensured access to medicines by European citizens. Today, this convention has 39 signatory parties from Europe, including the European Union, in which there is mandatory compliance with the requirements of the *Ph. Eur.* These member states participate and vote in the European Pharmacopoeia Commission sessions, where the standards published in the *Ph. Eur.* are adopted (14). Currently, there are also 30 observers from all over the world, including the US, China, and WHO, that are able to participate in the scientific work of the Commission and benefit from the European experience in this area. Observers also gain access to the work on the quality control of medicines and the methods of analysis in the *Ph. Eur.*, which could further support compendial harmonization through adoption or adaptation of the *Ph. Eur.* standards.

The *Ph. Eur.* marks the creation of a single, unified regional pharmacopoeia—it may be argued even an international pharmacopoeia—providing legally binding standards for the quality of medicines and their ingredients in Europe for the signatories to the convention, where previously there had been separate pharmacopoeias in each member country. This represents an important advance in the historical evolution of pharmacopoeias to move toward global standards. With this achievement, why are there still pharmacopoeias in some individual countries in Europe? Maintaining a national pharmacopoeia in these countries provides text that is either of interest to one member state only, or out of scope of the *Ph. Eur.* (e.g., national formularies) (15). Three main approaches were taken in Europe following the creation of the *Ph. Eur.*, with the decision being country specific:

- Discontinuation of the national pharmacopoeia (e.g., Sweden, Finland, Netherlands); *Ph. Eur.* established as the only pharmacopoeia, potentially translated into the national language
- Inclusion of the *Ph. Eur.* content in the national pharmacopoeia (e.g., United Kingdom [*BP*], Spain)
- Publication of the national pharmacopoeia in addition to the *Ph. Eur.* (e.g., France, Germany, Switzerland, Austria).

Regardless of the approach taken, the standards contained in the *Ph. Eur.* remain mandatory in these countries, even as their national pharmacopoeia serves to complement the content of the *Ph. Eur.* by including standards for drug products and ingredients that are applicable in that individual country.

An article written by the Director of the European Directorate for the Quality of Medicines and HealthCare (EDQM) provides perspective on the continuing role of the pharmacopoeia in the 21st century (3). The article describes how pharmacopoeias continue to modernize in changing times to support the availability of affordable medicines without compromising their quality, safety, and efficacy. The 9th edition of the *Ph. Eur.*, which became official in January 2017, has continued to add new and revised general chapters and monographs, including the publication of the first

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monograph for a finished product containing a chemically defined active substance. The *Ph. Eur.* has moved to allow the use of reverse osmosis for the production of water for injections (WFI) and has increased focus on impurities, quality by design (QbD), process analytical technology (PAT), and biotherapeutic products, including monoclonal antibodies (mAbs). EDQM, which publishes the *Ph. Eur.*, has also recognized that a high percentage of APIs come from outside Europe, Japan, and the US, leading to even further need to strengthen the collaboration among pharmacopoeias. To mark the publication of the 10th edition of the *Ph. Eur.*, which is official in January 2020, EDQM organized an international conference in Strasbourg in June 2019, bringing together leading scientists and experts to exchange views and share experiences on all aspects of the quality of medicines. The conference, titled "EDQM and European Pharmacopoeia: State-of-the-Art Science for Tomorrow's Medicines," highlighted developments in the Ph. Eur. to help ensure that modern pharmacopoeias continue to make a vital contribution to the protection of public health.

Other regional pharmacopoeia initiatives

There have been other efforts to support the harmonization of pharmacopoeia standards between several countries in a particular region, drawing on the successful experience of the Ph. Eur. The MERCOSUR pharmacopoeia is being developed to provide harmonized compendial standards for four Southern Common Market (South American) countries: Brazil, Argentina, Paraguay, and Uruguay. The Eurasian Economic Union (EAEU) pharmacopoeia, currently under development, is intended to provide a core set of requirements for the quality of medicinal products in the countries of the Eurasian Economic Union, which includes the Russian Federation, Armenia, Belarus, Kazakhstan, and Kyrgyzstan. It will be interesting to monitor the continued development of these pharmacopoeias, including how the published compendial standards are received and accepted by the health authorities in these countries and around the world. It remains to be seen if the existing national pharmacopoeias will continue to exist, or if they will be discontinued or absorbed in the new regional publication.

Ph. Int.–Toward global pharmacopoeia standards

With the inclusion of "international" in its title and considering the numerous other pharmacopoeias also in existence today, it is useful to understand the history and specific role played by the *Ph. Int.* in the global pharmacopoeia landscape.

Among its many responsibilities, WHO provides important support to global healthcare through the publication of the *International Pharmacopoeia*. The work on the *Ph. Int.* is carried out in collaboration with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Also involved in this work are specialists from regulatory authorities, from industry and from other institutions, including national drug quality control laboratories, WHO collaborating centers, and other standards-setting organizations (16). The eighth edition of Ph. Int. was published in 2018 and constitutes a collection of recommended procedures for analysis and specifications for the determination of pharmaceutical substances and dosage forms. These are intended to serve as source material for reference or adaptation by any WHO Member State (194 countries) wishing to establish pharmaceutical requirements (17). From a compliance perspective, it is important to understand that the *Ph. Int.* only has legal status whenever a national or regional authority expressly introduces it into appropriate legislation.

The ultimate goal of the *Ph. Int.* is to provide quality control specifications to help enable access to quality medicines worldwide.

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The ultimate goal of the *Ph. Int.* is to provide quality control specifications to help enable access to quality medicines worldwide. The *Ph. Int.* is published by WHO with the aim to achieve wide global harmonization of quality specifications for selected pharmaceutical products, excipients, and dosage forms. Compared to other pharmacopoeias, priority is given to medicines that are included in the WHO Model List of Essential Medicines and to medicines that are important for WHO health programs; the needs of developing countries are taken into account (17). However, this focus on essential medicines and developing countries is a fairly recent development and was not always the primary intention of the Ph. Int. Indeed, the goal of achieving harmonized pharmacopoeia standards for drug quality is deeply rooted in the history of Ph. Int., which dates back to 1874 when the need to standardize terminology and to specify dosages and composition of drugs led to attempts to produce an international pharmacopoeia (18). In 1937, the League of Nations set up an expert committee in response to repeated calls from pharmaceutical experts in various countries to coordinate the work of national pharmacopoeia commissions and develop a unified pharmacopoeia. The first committee comprised seven experts from Belgium, Denmark, France, the Netherlands, Switzerland, the United Kingdom, and the United States.

In 1947, WHO took over the work begun under the League of Nations for the unification of pharmacopoeias. The first edition of the Ph. Int. was published in two volumes (1951 and 1955) and a supplement (1959) in English, French, and Spanish, and also translated into German and

Japanese. The *Ph. Int.* was originally published with the aim of creating a worldwide, unified pharmacopoeia and relied on collaboration with national pharmacopoeia commissions for its preparation. However. it was recommended that *Ph. Int.* was not intended to be a legal pharmacopoeia in any country unless adopted by the pharmacopoeial authority of that country. In 1975, the purpose of the *Ph. Int.* was reconsidered. It was decided that the publication should focus more on the needs of developing countries, applying simple, classical chemical techniques for the testing of medicines. Priority would be given to drugs that were widely used throughout the world, with emphasis on the therapeutic value of these drugs. High priority would be accorded to drugs important to WHO health programs, and to those likely to contain impurities arising from degradation or due to difficulties in their manufacture. Since 1979, monographs in *Ph. Int.* have provided specifications for the identification, purity and content for drugs in the WHO Model List of Essential Medicines.

As with all pharmacopoeias, the activities related to *Ph. Int.* provide an important element in the overall quality assessment of bio/pharmaceuticals, thereby contributing to the safety and efficacy of medicines. Currently, the focus for *Ph. Int.* is on essential medicines, and more recently on priority medicines of major public health importance, for instance, medicines to treat malaria, tuberculosis, and HIV/AIDS, as well as medicines for children. However, from the earliest times, dating back to 1874, the objective had actually been to create a unified pharmacopoeia that could be used around the world—truly an international pharmacopoeia.

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Conclusion

The history of the pharmacopoeias around the world reveals a common purpose to support the health of the population through consistent standards for medicines. Early examples, like the creation of the *USP* and *BP* at a national level, as well as later examples, such as the *Ph. Eur.* on a regional level, also show an emphasis on trying to harmonize the quality standards contained in the pharmacopoeias. The history of the *Ph. Int.* demonstrates that the vision of creating a unified, international pharmacopoeia is not new; the goal of such a pharmacopoeia, which could support public health at a global level goes back nearly 150 years.

The next articles in this series will use the historical context presented in Part 3 to further explore the need for harmonization of compendial standards, with discussion about some of the approaches that are underway to reach this important goal. Later articles will build on this information to propose a practical basis for classifying pharmacopoeias as "global" or "national", which enables a thorough consideration of the variety of approaches that may be taken by bio/pharmaceutical companies to meet health authority expectations around the world in regard to pharmacopoeia compliance.

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