

Global Pharmacopoeia Standards: Why Harmonization is Needed

J. Mark Wiggins and Joseph A. Albanese



In this series of articles, the authors provide an understanding about the need for pharmacopoeia compliance and practical guidance to assist those who perform this work. 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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This series of articles continues to take a thorough look at compendial activities that impact the bio/pharmaceutical industry to help ensure compliance with requirements published by the pharmacopoeias. In these articles, the term “bio/pharmaceutical” should be considered in the broadest sense and includes innovator, generic, virtual, and start-up companies who discover, develop, manufacture, and/or distribute small-molecule drug products, biotherapeutic products, and vaccines, as well as the drug substances and excipients used in these products. One aspect of the history of the pharmacopoeias should be apparent; there is a long-standing tradition of evaluating existing, divergent drug standards and establishing instead a unified system that supports patient access to medicines with consistent quality. This is true whether the divergent standards existed at the city-level, as were addressed through the creation of the country-specific *British Pharmacopoeia (BP)*, or if the existing standards were at the state-level, as were addressed through the creation of the *United States Pharmacopoeia (USP)*. This is also true at a regional level, as in the creation of the *European Pharmacopoeia (Ph. Eur.)*, which established harmonized standards for medicines in Europe where individual country-specific standards had previously existed. And this is true in the initial intention of the *International Pharmacopoeia (Ph. Int.)* to develop a unified pharmacopoeia that could be used around the world.

In this context, it may be suggested that harmonization is embedded in the development and history of the pharmacopoeias. However, the pharmacopoeias are themselves embedded within the current regulatory and legal framework of the country or region in which they are applicable. The intersection of the pharmacopoeias and regulatory agencies impacts the direction and approaches taken to move toward harmonization at a global level. Pharmacopoeia harmonization provides better support for global regulatory agencies and addresses the global nature of bio/pharmaceutical manufacturing and supply, which ultimately benefits global patients who rely on these medicines to extend and improve their lives. This article provides some industry perspective on the need to harmonize compendial standards, which may be helpful in considering the future direction of pharmacopoeias. These

HARMONIZATION EFFORTS BY PHARMACOPOEIAS AND REGULATORY AGENCIES



There are many pathways to achieve compendial harmonization; several approaches are currently underway. The pharmacopoeias and regulatory agencies around the world, in collaboration with their stakeholders, have been actively and successfully working toward this goal for quite some time. In “Harmonization Efforts by Pharmacopoeias and Regulatory Agencies” in this series, the authors take a closer look at these ongoing efforts to harmonize compendial standards, with perspective that may be helpful in considering the future direction of pharmacopoeias. The following topics are discussed:

Pharmacopoeial Discussion Group. One long-standing activity focused on harmonization of compendial requirements is that of the Pharmacopoeial Discussion Group (PDG), which comprises the *European Pharmacopoeia (Ph. Eur.)*, *Japanese Pharmacopoeia (JP)*, and *United States Pharmacopoeia (USP)*. Information about the work of PDG is provided in this article, including their accomplishments to achieve consistent pharmacopoeia standards in the *Ph. Eur.*, *JP*, and *USP*. The challenge remains how to expand the harmonization outcomes, recognizing the scope of the PDG activities is somewhat limited. These limitations in the PDG work have led to additional harmonization activities to support and supplement the overall goal of global pharmacopoeia standards.

International Council for Harmonization. The International Council for Harmonization (ICH) brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. ICH's mission is to achieve greater harmonization worldwide to support safe, effective, and high-quality medicines. Representatives from *Ph. Eur.*, *JP*, and *USP* are either members or observers to the ICH process. However, the connection between harmonization activities carried out by PDG and ICH is not well understood, and further explanation is provided, with discussion of the ICH Q3 and Q4 guidelines and annexes.

Contributions of the World Health Organization. The *International Pharmacopoeia (Ph. Int.)* from the World Health Organization (WHO) supports the needs of developing countries by providing quality standards for medicines that are listed in the WHO Model List of Essential Medicines. As an observer to the harmonization work of both ICH and PDG, WHO is uniquely positioned to leverage the outcomes of that work and bring advantage by expanding its reach throughout the world. WHO has taken a leadership role through several initiatives, convening the International Meetings of World Pharmacopoeias (IMWP) to work toward harmonization of pharmaceutical standards to safeguard quality and improve access to medicines. WHO has also facilitated the development of the *Good Pharmacopoeial Practices (GPhP)* to encourage harmonization of compendial standards.

Prospective and informal harmonization. The initiatives described thus far have focused on harmonization of compendial standards already listed in the various pharmacopoeias—so-called “retrospective harmonization”. The *GPhP* guidance shifts the focus away from retrospective harmonization to facilitate “prospective harmonization”. This harmonization initiative has been undertaken through a collaboration between the bio/pharmaceutical industry and the pharmacopoeias, in particular *USP*, *Ph. Eur.*, and *BP*, with visibility provided to other pharmacopoeias. The “prospective harmonization” effort has evolved to an “informal harmonization” process between the participants and has resulted in the successful completion of several new, harmonized monographs for small-molecule drug substances and products.

Global pharmacopoeia standards would help to support the availability of medicines with consistent quality for patients around the world. Several approaches to achieve compendial harmonization are currently underway, including the important work by PDG and WHO. Compendial harmonization is also taking place at the intersection of the pharmacopoeias and ICH activities. The IMWP meetings have fostered greater collaboration among the pharmacopoeias of the world and resulted in the *GPhP* guidance documents to help in the development of new standards that are harmonized. Industry supports these ongoing harmonization activities.

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considerations are important because the sheer number of pharmacopoeias and the current lack of broad harmonization add complexity to a company's processes for compendial monitoring and compliance.

The ideal pharmacopoeia would provide a single compendial standard that could be used worldwide.

A word about "harmonization"

The history of pharmacopoeias since the earliest times has reflected the goal of creating consistent standards for medicines that are used by those who need them. The process of achieving these consistent standards may be described as standardization, harmonization, or any of a number of other words that have a similar meaning. Before delving into some of the ongoing activities to achieve consistent compendial standards in today's global environment for medicines, it is prudent to first address potential concerns with the term "harmonization" itself. Recent discussion has suggested that it may be preferable to shift from using the word "harmonization" to instead use "convergence" in the context of pharmacopoeias. There is perhaps some merit in this suggestion, as it might also be perceived as embodying a regulatory dimension of compendial interchangeability, which is essential to the ultimate goal of consistent requirements for medicines. However, it may also be suggested that the terms "harmonization" and "convergence" in fact have similar meanings. One definition of "harmonization" is the "process and/or results of adjusting differences or inconsistencies to bring significant features into agreement" (1). The term "convergence" means "moving toward union or uniformity" (2).

It should be noted in regard to pharmacopoeias that "harmonization" or "convergence" do not necessarily mean "unison" or "identical". Although the availability of completely "identical" compendial standards might be a desired goal to overcome the challenges of non-harmonized standards in the pharmacopoeias, it should be recognized that "identical" standards are probably not achievable for a number of practical reasons. Fundamentally, the standards published in the pharmacopoeias must be available in the languages needed by their users, regardless of the country. Compendial standards that are equivalent or interchangeable in a practical or functional way should be the goal. Any level of harmonization is beneficial and moves in the right direction to help provide medicines with consistent quality to patients around the world.

To further enable the development of consistent standards for medicines, it is proposed to shift the focus away from the process (i.e., harmonization or convergence) and instead

emphasize the intended outcome: global pharmacopoeia standards. Details about ongoing activities to achieve global pharmacopoeia standards will be provided later, but first, it is appropriate to ask why this goal is important.

The challenge of compliance with the separate compendial requirements around the world provides a strong argument for global pharmacopoeia standards.

The need for global pharmacopoeia standards: Making the case

The challenge of compliance with the separate, often divergent compendial requirements contained in the various pharmacopoeias around the world provides a strong argument to support the need for global pharmacopoeia standards. The benefits seem obvious in having global pharmacopoeia standards to ensure consistent quality of medicines. Manufacturing and supply-chains for the bio/pharmaceutical industry today are global. There is benefit to the industry in having consistent standards with which to comply. There is benefit to regulators who can review drug applications and inspect pharmaceutical facilities anywhere, without the complication of divergent pharmacopoeia standards. Most importantly, the patient population today is global. Ultimately, there is benefit to patients located around the world who can receive medicines with the same quality, evaluated against consistent specifications included in all the pharmacopoeias, regardless of where the product or its ingredients were manufactured.

Compliance with differing quality standards across the many pharmacopoeias has long been a challenge to be addressed by the bio/pharmaceutical industry. The value and benefits of global pharmacopoeia standards to industry and patients have been noted by the different pharmacopoeia organizations. USP has written, "Harmonization reduces manufacturers' burden of having to perform analytical procedures in different ways, using different acceptance criteria, in order to satisfy pharmacopoeial requirements that vary across regions" (3). The *Ph. Eur.* notes the practical consideration of international trade as it relates to the availability of medicines. "Globalisation and expansion in international trade present a growing need to develop global quality standards for medicines" (4). For medicines, the standardized test methods and specifications in the pharmacopoeias must "ensure consistent product quality, regardless of its source ... especially in view of the shift of API production from Europe and the [United States] US to India and China"

(5). It is also noted that a “harmonized regulatory system, with mutual recognition of assessment/decision-making by licensing authorities and inspectors, including globally harmonized pharmacopoeias, would be beneficial in several ways” (5). Pharmacopoeias can “also play an important role in protecting patients from some of the downsides of globalization, namely adulteration and counterfeiting of medicines,” however the “prevention of drug adulteration or counterfeiting is not achievable by a pharmacopoeia or any other stakeholder alone” (5). Still, it seems evident that global pharmacopoeia standards could help in this objective, providing consistent standards of quality for medicines to support patients around the world, whereas divergent compendial standards only serve to complicate the situation.

Appropriate standardization means the pharmacopoeia would focus on the specific content that provides the greatest value to the bio/pharmaceutical industry for the quality control of drugs.

Ideal pharmacopoeia and compendial globalization—an industry perspective

The bio/pharmaceutical industry has itself been discussing the benefits of “harmonization” in today’s global pharmacopoeia environment. The purpose and role of the pharmacopoeias and the global picture were described in previous articles in this series. There are as many as 40 pharmacopoeias published by authorities around the world. The pharmacopoeias were established and evolved to ensure the quality of medicines and their ingredients for patients in a country or region. Today’s global patient population was not necessarily part of the overall consideration for the pharmacopoeias, especially early in their development. As a result, the standards contained in the various pharmacopoeias were not generally aligned, creating a challenge for the industry to comply with all the applicable requirements. Having struggled with the challenge of differing compendial standards for many years, discussion was initiated between pharmaceutical industry representatives from the Pharmaceutical Research and Manufacturers of America (PhRMA) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) to explore what might be described as the “ideal” pharmacopoeia. The result of these discussions was a position paper, published in 2008, that presents this industry perspective (6). The paper stated that the ideal pharmacopoeia would provide

appropriate standardization to facilitate drug registration and support regulatory agencies through a single, global compendial standard.

Considering each of these points in turn, appropriate standardization means the pharmacopoeia would focus on the specific content that provides the greatest value to the bio/pharmaceutical industry for the quality control of drugs. Facilitating drug registration would be achieved by simplifying the preparation (by industry) and assessment (by regulators) of drug applications using reference to a common standard for generally accepted quality parameters for pharmaceutical products and ingredients. Alignment between the pharmacopoeias and regulators is essential, so the ideal pharmacopoeia would include standards that are consistent with the needs and expectations of regulatory authorities. Most importantly, the ideal pharmacopoeia would provide a single compendial standard that could be used worldwide. The industry perspective on the ideal pharmacopoeia provides a model for the future: a long-term goal that could achieve harmonization of compendial standards, further enhancing the role of the pharmacopoeias to support and promote global public health through safe and effective medicines with appropriate quality to benefit patients around the world.

Another article from industry describes compendial globalization and achieving harmonization through standardized practices and collaboration among the pharmacopoeias and health authorities (7). This article discusses the need for “consistent and appropriate quality requirements for medicines because disharmonized standards do not provide additional value or benefit, but rather increase the cost and complexity of bringing medicines to patients worldwide.” The approach to harmonization described as compendial globalization “provides a basis for the pharmacopoeias to work together in new ways with consistent processes coupled with sharing of information and work.” The three principles that support compendial globalization are:

- Standardized pharmacopoeial practices, which establish a consistent approach for the pharmacopoeias to elaborate compendial standards
- Pharmacopoeial collaboration, which enhances the cooperation among the pharmacopoeias to enable the development, sharing, and adoption of harmonized compendial standards
- Regulatory acceptance, which ensures the participation and agreement by regulatory authorities with the harmonized processes and outcomes in those countries where the pharmacopoeia standards apply.

The pharmacopoeias and regulators around the world, in collaboration with their stakeholders, have been actively and successfully working toward the goal of harmonization for quite some time. These ongoing harmonization efforts are supported and encouraged by the bio/pharmaceutical industry.

A world without translation

The principles of the ideal pharmacopoeia and compendial globalization reflect industry's support for and alignment with pharmacopoeia initiatives that move toward harmonization. Industry's view of an aspirational goal for harmonization to achieve global pharmacopoeia standards was presented at a joint workshop held between the European Directorate for the Quality of Medicines and HealthCare (EDQM/*Ph. Eur.*) and the *Chinese Pharmacopoeia (ChP)* in 2016. Invited remarks were provided on behalf of EFPIA, the trade association representing the research-based pharmaceutical industry in Europe, and whose members supply many important medicines that contribute to the health of patients in Europe, China, and around the world. In these remarks (8), it was noted that the pharmacopoeias and industry share a common goal, which is to ensure the availability of medicines for people around the world. The pharmacopoeia's core mission is protecting public health by creating public standards to help ensure the quality of medicines. The bio/pharmaceutical industry's mission is to provide medicines that extend and improve the lives of patients around the world, medicines with consistent quality, complying with the applicable regulatory and pharmacopoeia requirements.

When the standards published by the pharmacopoeias are not aligned, the differences increase the cost and complexity of compliance.

When the standards published by the pharmacopoeias are not aligned, the differences increase the cost and complexity of compliance, potentially hindering the export and import of products between countries and creating uncertainty in the supply of medicines to the patients who need them. There are important initiatives underway to bring more consistency between pharmacopoeia standards, including retrospective and prospective harmonization, the World Health Organization's (WHO's) *Good Pharmacopoeial Practices* (9), and greater collaboration among the pharmacopoeias. Attendees at the joint workshop were asked to imagine consistent standards published by the pharmacopoeias in the languages needed by their stakeholders ... to imagine a global pharmaceutical industry that can ensure compliance with these standards, because they contain consistent requirements ... and to imagine regulators who can use these globally consistent pharmacopoeia standards to help ensure the quality of medicines.

Ultimately, attendees were asked to imagine the patients around the world who would be able to receive medicines with consistent quality, wherever the medicines are manufactured. To imagine this world, where there is no need for translation, because the pharmacopoeias are saying the same thing. How do we get there? Pharmacopoeias and stakeholders get there through retrospective, prospective, and informal harmonization to achieve global pharmacopoeia standards, through implementation of WHO's *Good Pharmacopoeial Practices*, and through ongoing collaboration. Continued progress toward this goal is in the interest of global patients and society as a whole.

Conclusion

Global pharmacopoeia standards would help to support the availability of medicines with consistent quality for patients around the world. There are many pathways to achieve compendial harmonization, and several approaches are currently underway. Industry's perspective on the ideal pharmacopoeia and approaches to achieve compendial globalization support these ongoing harmonization activities. Subsequent articles in this series will describe how the industry still faces challenges in complying with compendial standards, whether those standards are harmonized or not

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