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Harmonization Efforts by Pharmacopoeias and Regulatory Agencies

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.

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The pharmacopoeias and regulatory agencies around the world, in collaboration with their stakeholders, have been actively and successfully working toward the goal of compendial harmonization for quite some time. The following takes a closer look at these ongoing efforts to harmonize compendial standards, with perspective that may be helpful in considering the future direction of pharmacopoeias.

PHARMACOPOEIAL DISCUSSION GROUP

One of the long-standing activities 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*

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Pharmacopeia (USP). Each of the participating pharmacopoeias has information on their website regarding PDG (see **Table I**), and the following summary highlights some key aspects of this work.

PDG was formed in 1989 with representatives from the European Directorate for the Quality of Medicines & HealthCare (EDQM/*Ph. Eur.*), the Ministry of Health, Labour, and Welfare (MHLW/*JP*), and the United States Pharmacopeial Convention (USP), with the World Health Organization (WHO) joining as an observer in 2001. During its 30-year history, PDG has met on a regular basis to advance harmonization work in Europe, Japan, and the United States, focusing on selected excipient monographs and general chapters in the pharmacopoeias. To date, harmonization work has been completed on 28 of the 31 general chapters and 46 of the 60 excipient monographs on the current PDG work program. These harmonized compendial standards are an important achievement and reflect the long-term commitment by the PDG partners to establish consistent standards for use in these three major regions of the world. But it can also be argued that the process has taken too long to reach the established goals. Indeed, retrospective harmonization of existing compendial standards is challenging and complex. Recognizing the concern over timely progress, PDG has recently streamlined their work structure, eliminating two stages of the harmonization process (**Figure 1**), with the objective of trying to achieve harmonized outcomes more quickly.

PDG has provided a practical definition of harmonization; a pharmacopoeial monograph or general chapter is harmonized when a pharmaceutical substance or product tested by the document's harmonized procedure yields the same results and the same accept/reject decision is reached. When full harmonization cannot be achieved through PDG discussions, an approach termed "harmonization by attribute" is pursued, in which some elements of the monograph or general chapter are harmonized,

Table I. Pharmacopoeial Discussion Group (PDG) members.

Pharmacopoeia	Website
US Pharmacopeial Convention (USP)	www.usp.org/harmonized-standards/pdg
European Directorate for the Quality of Medicines & HealthCare (EDQM)	www.edqm.eu/en/international-harmonisation-614.html
Pharmaceuticals and Medical Devices Agency (MHLW)	www.pmda.go.jp/english/rs-sb-std/standards-development/jp/0012.html

but others are not. This situation occurs when there is lack of full agreement between the PDG partners as to the specific tests, methods, or acceptance criteria needed in the monograph for a particular excipient or the specific details contained in a general chapter. With harmonization by attribute, interchangeability of the compendial requirements is achieved only with respect to the harmonized elements, while compliance with the individual non-harmonized pharmacopoeial requirements in each region is necessary. The PDG pharmacopoeias have agreed not to revise unilaterally any harmonized document after publication, while revisions for appropriate reason may be pursued through discussion among the members of PDG according to their established working procedures.

The accomplishments and commitment by PDG to achieve consistent pharmacopoeia standards in the *Ph. Eur.*, *JP*, and *USP* are to be recognized and commended. Any amount and degree of harmonization is good and moves in the desired direction of global pharmacopoeia standards. The challenge remains how to expand the harmonization outcomes, recognizing the scope of the PDG activities is somewhat limited. The focus of PDG harmonization is on excipient monographs and general chapters, but their current work program includes only a fraction of the total number of excipient monographs and general chapters in the pharmacopoeias. The PDG activities do not include harmonization of monographs for drug products or APIs. The pharmacopoeias participating in the PDG work represent three major regions of the world, and the standards are accepted in many countries outside the geographical boundaries of these countries and regions, but there are many other important pharmacopoeias and regions that are not part of this harmonization work, so global applicability has not been achieved. And the specific harmonization outcomes are not always fully aligned, as mentioned in the context of harmonization by attribute. All 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 (1). Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development. ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective, and quality medicines are developed and registered in the most resource-efficient manner. Harmonization is achieved through the development of ICH guidelines in four categories—quality, safety, efficacy, and multidisciplinary—through a process of scientific consensus with regulatory and industry experts working side-by-side. Initially, ICH included six members: representatives from the regulatory agencies and industry associations of Europe, Japan, and the US. In continuing to address the larger global situation for medicines, ICH has expanded to include seven additional regulatory members and three additional industry members, as well as more than 30 observers, including WHO.

Representatives from the *Ph. Eur.*, *JP*, and *USP*—the pharmacopoeias that form the PDG—are either members or observers to the ICH process. However, the connection between harmonization activities carried out by PDG and ICH is perhaps not well understood and warrants further discussion. As detailed above, PDG develops harmonized compendial standards for some excipients and general chapters, engaging with their stakeholders, including industry, through established procedures of notification, review, and comment for each of the pharmacopoeias. The scope of harmonization by PDG is limited; the scope of pharmacopoeia harmonization by ICH is even more limited. For ICH, the areas of major focus are the processes for drug development and registration, with industry and regulators as the working partners. In the development of the ICH Q6A and Q6B guidelines for establishing specifications for new drug substances and new drug products, including both chemical and biological products, it was recognized that harmonization of 11 specific compen-

Figure 1. Pharmacopeial Discussion Group (PDG) revised working procedure: 5-stage approach for harmonization (2).

Stage 1: Preparation of first draft
Upon PDG approval to add the revision to the workplan, the coordinating pharmacopoeia (CP) prepares and forwards the Stage 1 draft and supporting data to PDG for pharmacopoeial expert committee review/comment. The CP reviews comments received and, if all three pharmacopoeias agree, the proposed harmonized draft document moves forward for public comment/inquiry.

Stage 2: Official inquiry
The Stage 2 draft and commentary are published in the respective forum of each pharmacopoeia. Each pharmacopoeia analyzes comments received during the public comment/inquiry stage and submits its consolidated comments to the CP for review. If appropriate, the CP prepares a draft harmonized document (Stage 3A) and commentary, which are sent to the other two PDG pharmacopoeias.

Stage 3: Consensus
The Stage 3A draft is reviewed and commented on by the other pharmacopoeias. Any remaining differences are resolved, or they are assigned as non-harmonized attributes or local requirements. When agreement is reached, a Stage 3B draft is sent by CP to the other pharmacopoeias for final confirmation and sign-off.

Stage 4: Regional adoption and implementation
Stage 4 takes place individually according to the procedures established by each pharmacopoeia. The harmonized document is submitted for adoption by the responsible pharmacopoeia organization. Each pharmacopoeia incorporates the harmonized content according to its own procedure and informs each other of the date of implementation, which may vary in the three PDG regions depending on their legal requirements, need of translation, and publication schedules. Each pharmacopoeia indicates the harmonization status according to their policy, with any residual differences indicated by specific symbols (black diamonds indicate non-harmonized attributes, white diamonds indicate local requirements).

Stage 5: Inter-regional acceptance
For chapters evaluated by ICH Q4B for regulatory interchangeability, a topic-specific annex is processed for publishing and implementation by each regional authority.

Revision
The PDG pharmacopoeias have agreed not to revise unilaterally any harmonized document after sign-off or after publication. Revisions with appropriate justification will follow the PDG working procedure described above, with revisions of a sign-off document indicated as Revision 1, 2, 3, etc. An expedited procedure may be applied in certain circumstances, resulting in a revision reverting to Stage 3A as opposed to Stage 1.

Correction
Any pharmacopoeia which has identified an error in a sign-off text may submit a request for correction to PDG together with appropriate justification.

FIGURE COURTESY OF THE AUTHORS

dial test chapters was essential to obtain full utility of the guidelines. In section 2.8 of the ICH Q6A guideline, there is specific reference to the pharmacopoeias and the work of the PDG; it is stated that pharmacopoeial procedures should be used wherever they are appropriate. This intersection of the ICH guidelines and the pharmacopoeia chapters, which were undergoing harmonization by PDG, created a formal connection between the two initiatives, resulting in the ICH Q4 topics (3). On the ICH website, there is a brief note regarding ICH Q4, which can be paraphrased as follows: ICH will trust the PDG process to achieve pharmacopoeia harmonization for the 11 compendial chapters. Perhaps due to the slow pace of the PDG harmonization work, ICH added a follow-on Q4A topic. On the ICH website, the brief note regarding Q4A goes a bit further that that provided for Q4, to state that ICH will receive progress reports from PDG on the pharmacopoeia harmonization work. Unlike other ICH topics, there are no specific guidelines associated with either ICH Q4 or Q4A.

Q4B WORKING GROUP EXAMINES INTERCHANGEABILITY

Recognizing the imperfect outcomes reflected in PDG's harmonization by attribute, in 2003, industry requested that ICH establish the Q4B Expert Working Group (EWG) to address how regulatory authorities in the ICH regions would recognize the interchangeability of the PDG harmonized pharmacopoeial chapters in the *Ph. Eur.*, *JP*, and *USP* (4). The resulting ICH Q4B guideline, titled "Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions", was finalized in 2007 and describes a process for the EWG to develop topic-specific annexes with information about the PDG harmonized chapters and their implementation (the Q4B Outcomes) to avoid redundant testing by industry (5). The initial scope for the Q4B EWG was the 11 specific compendial chapters needed to facilitate use of the Q6A and Q6B guidelines, but this was expanded to result in 16 topic-specific annexes. These annexes cover a wide range of pharmacopoeia general chapters, including Residue on Ignition/Sulphated Ash, Disintegration, Dissolution, Uniformity of Dosage Units, Extractable Volume of Parenteral Preparations, Microbiological Examination of Non-Sterile Products, Sterility, and Capillary

Electrophoresis. Each of the annexes provides the Q4B Outcome regarding interchangeability of the harmonized compendial test chapters, along with the conditions, considerations, and timelines to assist in the implementation and use of the referenced pharmacopoeial text by stakeholders.

The conditions included in the Q4B annexes address point-by-point the residual differences between the *Ph. Eur.*, *JP*, and *USP* texts following the completion of the PDG harmonization activities, thereby enabling the use of any of the referenced pharmacopoeia chapters as interchangeable in the ICH regions. The need to include conditions is based on the degree to which the harmonized chapters in each of the three pharmacopoeias differ from one another. For example, in the Q4B annex for the Dissolution test chapters, which contain several non-harmonized attributes, the ICH topic-specific annex contains eight conditions that must be addressed in a product registration in order for the compendial chapters to be considered interchangeable. By contrast, the ICH Q4B annex on Capillary Electrophoresis declares that each of the referenced compendial chapters in *Ph. Eur.*, *JP*, and *USP* are interchangeable without any conditions, a situation made possible because the compendial chapter on Capillary Electrophoresis was developed through "prospective harmonization" of the PDG pharmacopoeias. "Interchangeable" is defined in the Q4B guideline to mean that any of the official texts from *Ph. Eur.*, *JP*, or *USP* can be substituted one for the other (appropriately referenced) for purposes of the pharmaceutical registration/approval process with the understanding that an analyst using any of the interchangeable methods will reach the same accept/reject decision irrespective of which PDG pharmacopoeia is used.

The *Ph. Eur.* in particular has taken a pro-active approach in adopting the concepts of the ICH Q3A/B guidelines.

In 2010, after finalizing the 16 annexes, ICH disbanded the Q4B EWG as it was concluded that essentially all chapters within its scope were completed. In the Q4B guideline (6), it was recognized that subsequent changes to the harmonized compendial chapters might occur, which could impact the annexes. The guideline states that ICH should be notified of any future revisions to chapters that had been assessed by the Q4B EWG. In 2018, PDG proposed that they assume responsibility for carrying out any necessary assessment and revision of Q4B annexes as a result of changes made to the harmonized chapters (6). This proposal was accepted by ICH, continuing the important collaboration and intersection between the ICH and PDG harmonization initiatives and among the representatives of the regulatory agencies, industry, and pharmacopoeias.

Q3 GUIDELINES

The ICH Q4/4A/4B topics are not the only connection between ICH and the pharmacopoeias; the Q3 topics on impurities represent another area where the harmonization activities overlap. Most recently, the development of the ICH Q3D guideline on control of elemental impurities in drug products was completed. This guideline addressed a long-standing issue associated with the pharmacopoeia test for heavy metals in pharmaceutical products and ingredients, while expanding on regulatory guidance from Europe that established limits for the residues of metal catalysts or metal reagents that may be present in pharmaceutical substances or drug products. With the publication of the Q3D guideline, the PDG began the process of adopting the new requirements, while moving to eliminate the historical chapters on heavy metals, which employed wet-chemical techniques that were non-specific limit tests to control some metal impurities. While the transition from heavy metals to elemental impurities through the pharmacopoeias and ICH Q3D improves the control of inorganic impurities in drug products, the situation has posed a challenge for industry. How can non-ICH countries be moved toward adopting the ICH guideline, given that the old heavy metals test is being eliminated from several pharmacopoeias? The picture is complicated by the uncertain acceptance of the harmonized requirements by other regulatory agencies and pharmacopoeias around the world; not everyone is moving at the same pace for implementation.

The Q3C topic on residual solvents represents a similar connection between ICH guidelines and the related pharmacopoeia general chapters for control of these impurities. The Q3A and Q3B guidelines, which establish threshold limits for organic impurities in new drug substances and

products also represent an area of overlap with the pharmacopoeias, which control impurities through specific requirements in monographs for drug products and ingredients. The *Ph. Eur.* in particular has taken a pro-active approach in adopting the concepts of the ICH Q3A/B guidelines, with general chapters and monographs that help ensure control of identified and unidentified impurities and set limits for both specified and unspecified impurities. Each of the ICH Q3A/B/C/D guidelines has strengthened the connection between the regulatory agencies and pharmacopoeias in the ICH regions, to the benefit of industry through consistent quality standards, and ultimately to patients through consistent quality products.

ICH AND PDG

With the successful interaction between ICH and PDG, it may be asked whether ICH could be leveraged to expand compendial harmonization to achieve global pharmacopoeia standards and regulatory acceptance, further facilitating the development and registration of drug products around the world. It does not appear, however, that the current ICH work program could pursue this opportunity, being filled with other important and beneficial topics to support the overall goal of medicine availability for patients around the world. In terms of scope, the current connection between ICH and PDG through Q4B only addresses 16 chapters out of 300 or more chapters contained in the pharmacopoeias and none of the monographs for excipients, drug substances or products. While there are 40 published pharmacopoeias, PDG consists only of the *Ph. Eur.*, *JP*, and *USP*. Efforts to expand the participating pharmacopoeias in PDG have been discussed but not pursued because it is recognized that retrospective harmonization between the current three pharmacopeias is already difficult.

WHO is uniquely positioned to leverage the outcomes of the ICH and PDG harmonization work and bring advantage by expanding its reach throughout the world.

While ICH has continued to expand its membership in the past several years, there are still questions about how the newly joined countries will adopt the ICH guidelines, including the Q4B annexes. At a workshop held in Beijing in the fall of 2018, this specific challenge for China was discussed among key stakeholders: regulators, industry, and the pharmacopoeia (7). The unique challenges for the Q4B topic, with its guideline detailing the process for determining compendial chapter interchangeability and the 16 associated topic-specific annexes, were detailed, and the question posed: how should the regulators and pharmacopoeia in China adopt compendial standards that were harmonized without any input from China? Several examples were presented with assessment of differences and scientific rationale that challenged some of the content contained in the PDG harmonized chapters, including particulate contamination, dissolution, microbiological, and sterility testing. The meeting in China serves as a reminder of the difficulties in achieving harmonized compendial standards and expanding their adoption once available. Still, there are additional activities being pursued, aimed at facilitating the development and use of global pharmacopoeia standards.

CONTRIBUTIONS OF WHO

WHO's *International Pharmacopoeia* (*Ph. Int.*) supports the needs of developing countries by providing quality standards for medicines that are listed in the WHO Model List of Essential Medicines. What else is WHO doing to enable compendial harmonization? 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. Over the past several years, WHO has adapted the test chapters that were harmonized by PDG and evaluated by the ICH Q4B EWG and included them in *Ph. Int.*, providing broader visibility to these harmonized standards in developing countries.

The WHO has taken a leadership role through additional initiatives, continuing the collaboration with and among national and regional pharmacopoeia commissions, which was essential to the development of the first edition of *Ph. Int.* Beginning in 2012, WHO convened the International Meetings of World Pharmacopoeias (IMWP), recognizing that in an increasingly globalized world, international pharmaceutical standards are increasingly important to safeguard quality and improve access

to medicines (8). Representatives from pharmacopoeias from 23 countries came together at the first IMWP and committed to working further toward harmonization and strengthening WHO's role in developing global standards for the production and testing of medicines. This unprecedented commitment by WHO and the pharmacopoeias to work together to strengthen international standards has continued through additional IMWP meetings, which have occurred on a regular basis since 2012. The most recent IMWP, the 10th such meeting, was hosted by WHO in Geneva in March 2019, with representation of national and regional pharmacopoeial authorities, including those in Brazil, China, Europe, India, Indonesia, Japan, Russia, and the US. One concrete step toward strengthened cooperation has been the development of a rapid alert system to exchange information and take urgent action during health emergencies. The connection between ICH and PDG also continues to strengthen. At the March 2019 PDG videoconference, a discussion took place on how information on the progress made by PDG should be shared amongst the PDG member pharmacopoeias and other pharmacopoeias participating in the IMWP. These discussions will continue at the next face-to-face PDG meeting, hosted by JP in October 2019 in Tokyo, which will also celebrate the 30th anniversary of PDG (9).

There are additional contributions from WHO. The initiative to reopen discussion on international harmonization of quality control specifications on a global scale began back in 2002, during meetings held at the 10th International Conference of Drug Regulatory Authorities (ICDRA), "Pharmacopoeial Specifications–Need for a Worldwide Approach?", in Hong Kong. This led to further discussions among regulators at subsequent ICDRA meetings and at other international events during the following years, including discussions with and among the pharmacopoeias on this topic.

Global pharmacopoeia standards would help to support the availability of medicines with consistent quality for patients around the world.

The main suggestion emerging from all these events was the development of good pharmacopoeial practices (GPhP) to encourage harmonization, facilitated by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, and benefiting from its well-established international standard-setting processes and procedures. The important work of preparing the *GPhPs* began with the first IMWP meeting and continued through later meetings, with formation of an initial drafting group comprising pharmacopoeia representatives from Argentina, Brazil, Europe, India, Japan, Mexico, the Russian Federation, Ukraine, the UK, and US (10). As a truly global initiative, the entire process was open to all pharmacopeias. With focus and persistence by WHO and the participating pharmacopoeias, and with input provided by stakeholders who reviewed early drafts, the *Good Pharmacopoeial Practices* document was finalized in 2016 (11).

The *GPhPs* define approaches and policies, along with technical guidance for the development of monographs for APIs and finished pharmaceutical preparations. The guidance is intended to facilitate collaboration and possible work-sharing among the pharmacopoeias, with the ultimate goal of harmonization of compendial standards. Additional GPhP chapters were completed in 2018 to address the development of monographs for compounded preparations and herbal medicines (12, 13). An essential element contributing to the completion of the GPhP guidance documents was the collaborative environment that was engendered among the pharmacopoeias and WHO through the IMWP meetings. This engagement has also contributed to other compendial harmonization initiatives, including bilateral and multilateral agreements, memoranda of understanding (MoUs), regional activities between the various pharmacopoeias, and collaboration to support the development of global pharmacopoeia standards.

PROSPECTIVE AND INFORMAL HARMONIZATION

Most of the initiatives described thus far have focused on harmonization of compendial standards already listed in the various pharmacopoeias, to resolve differences between the existing standards—so-called "retrospective harmonization". This is difficult, as evidenced by the efforts of the PDG pharmacopoeias to harmonize existing general chapters and excipient monographs resulting in harmonization by attribute.

It is also reflected in the discussion on how China might adopt the topic-specific ICH Q4B outcomes, an issue that other countries will also face as they join in the membership of ICH. The underlying question for retrospective harmonization is why a pharmacopoeia should change from a standard that has been developed and used to control the quality of medicines in that particular country, and to adopt a different compendial standard that was "not invented here." Even with the effective collaboration achieved through the IMWP meetings, much time has been devoted to discussing harmonization of existing standards in the various pharmacopoeias.

The *GPhP* guidance documents shift the focus away from retrospective harmonization to facilitate an approach for the development of new monographs that do not yet exist, which may be widely adopted by the pharmacopoeias. The benefit of this approach—so-called "prospective harmonization"—was mentioned for the PDG harmonized chapter that was developed for Capillary Electrophoresis, which did not require any conditions regarding interchangeability in the ICH Q4B annex because there were no residual differences for this standard in the *Ph. Eur.*, *JP*, and *USP*. This chapter, along with several others used to characterize biotechnology-derived articles, was harmonized from the beginning through the PDG partnership.

Another example of prospective harmonization has been the development of new monographs for drug products and drug substances. This 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, including those in Japan, China, Korea, and India. This effort, which has resulted in the successful completion of several new, prospectively harmonized monographs for small-molecule drug substances and products, has evolved to an "informal harmonization" process between the participants

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, 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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