EFPIA Position Paper on the Impact of Non-harmonised Requirements in Local Pharmacopoeias and Opportunities to Promote Alignment of Public Standards

Executive Summary

This position paper describes the current pharmacopoeial landscape and issues faced by industry due to the lack of globally harmonised pharmacopoeial requirements, and the increasing importance of the local (usually national) pharmacopoeias from the new International Council for Harmonisation (ICH) members and emerging markets.

The scope of pharmacopoeial content and development of pharmacopoeial general chapters and monographs is discussed, together with the relationship between pharmacopoeial and regulatory requirements, and collaborative efforts between the pharmacopoeias.

Below are Efpia's key messages and recommendations to promote global harmonisation or convergence of public pharmacopoeial standards in the short to medium term.

Key Messages and Recommendations

Pharmacopoeial standards are an important part of the regulatory framework, facilitating the efficient review and approval of bio/pharmaceuticals, and providing official standards for quality control during the development, production and marketing of medicines. Globalisation of pharmaceutical supply chains drives the need for aligned standards between pharmacopoeias, to simplify the requirements for compliance and facilitate the availability of medicines to all patients worldwide.

Different pharmacopoeial quality standards, usually without any meaningful difference in the quality of the same medicine supplied to patients in different countries, can result in the need to source different grades of raw materials and duplication of testing of materials and medicinal products to fulfil local requirements. Thus these divergent standards increase complexity in manufacturing and supply chains which in turn can result in increased costs and, potentially, in shortages of medicines for patients.

To address these challenges EFPIA and its member companies and associations encourage:

- Harmonisation, convergence or alignment of pharmacopoeial and regulatory requirements wherever possible
- Mutual acceptance or reliance by regulatory agencies on established internationally-recognised pharmacopoeial standards (e.g. Ph.Eur., USP) based on the similarity of quality standards in different pharmacopoeias
- Adoption of international pharmacopoeial standards (preferably using internationally harmonised text, where available) in local pharmacopoeias rather than developing local standards, especially where the pharmacopoeia is updated infrequently
- Pharmacopoeial authorities and regulators to adopt the outputs of ICH guidelines and supporting the re-establishment/evolution of ICH Q4B
- Prospective harmonisation or alignment of requirements during development of new and revised content by collaboration between the pharmacopoeial authorities through initiatives such as WHO's Good Pharmacopoeial Practices and ICH (e.g. through re-establishing/refreshing Q4B)

- Development of 'General chapters' or revised standards that take into consideration emerging scientific, regulatory and pharmacopoeial developments, agreed methodologies and/or best practices that reflect the state of the industry, so that technological advances are incorporated when the technology is sufficiently mature
- Building flexibility into monographs and general chapters where appropriate (e.g. by allowing the use of alternative methods)
- Monograph requirements that are aligned with specifications registered by the regulatory agency, particularly with respect to the innovator product
- Good Manufacturing and Distribution Practices (GMDP) requirements remaining the remit of the regulatory authorities; Pharmacopoeias should not develop chapters and requirements pertaining to GMDP, unless specifically mandated by a regulatory agency.

Background

The latest World Health Organisation (WHO) Index of Pharmacopoeias (1) published in January 2018 notes 55 national pharmacopoeias/authorities and 3 regional/international pharmacopoeias. With the increasing prevalence of global supply chains (often a few manufacturing sites supply products to many markets around the world) the proliferation of national and regional/international pharmacopoeias creates a complex set of different requirements for compliance with pharmacopoeial standards. These differences in pharmacopoeial requirements - usually legal requirements in the local market - are rarely associated with meaningful differences in the quality of input materials and/or products, and consequently have little or no impact on the quality, safety and efficacy of medicines, while increasing the complexity of supply chain management.

Since the formation of the Pharmacopoeial Discussion group (PDG) in 1990, the harmonisation of pharmacopoeial standards between the founding ICH members (Europe, Japan and the USA) has made significant progress (2). However, the need for compliance with local/national pharmacopoeias of newer ICH members and emerging markets is an important consideration for global supply chains, but these local pharmacopoeias are currently outside the PDG process. Therefore, the landscape for pharmacopoeial compliance has become more complex and fragmented, and there is an even greater need for convergence of pharmacopoeial requirements and increased understanding of the pharmacopoeial processes being followed in these markets.

While a single set of international public standards, representing a global pharmacopoeia concept is the visionary solution that has been proposed in response to this need for harmonization (3), it is anticipated that it would take significant time and effort by stakeholders to overcome the many challenges to achieve this goal.

Industry support and engagement with the Pharmacopoeias is critical to make progress towards harmonisation and/or convergence of pharmacopoeial requirements, and this paper outlines EFPIA's key messages and recommendations to promote these efforts in the short to medium term.

Pharmacopoeial Requirements

It is generally recognized that divergent pharmacopoeial requirements can result in the need to source different grades of raw materials, and for QC labs to perform duplicative, redundant testing of materials or products using different methods, in order to satisfy different but similar requirements. Additional time and resources must be expended to meet these different requirements without providing improvements to the quality, safety or efficacy of the product.

Some pharmacopoeias may have established practices and policies that can present challenges when developing harmonised text for monographs or general chapters. It should also be recognised that fully harmonised content across the pharmacopoeias may reduce the need for users to purchase a particular pharmacopoeia, potentially adversely impacting the ability of pharmacopoeial authorities to sustain their activities in developing and maintaining standards to protect public health. While harmonised text is the ideal, alignment of analytical procedures/ methodology and the acceptance criteria (where this is possible) may be sufficient to avoid the need for multiple testing of the same drug substance, drug product, or excipient etc. to meet different pharmacopoeial requirements. Over time, the revision of monographs etc. can provide opportunities for convergence of standards: a pharmacopoeial authority could choose to adopt an analytical procedure and/or acceptance criteria from another internationally-recognised pharmacopoeia, rather than continuing with dis-harmonised procedures and requirements. Pharmacopoeias often allow the manufacturer to use alternative, equivalent analytical methods to test the product, and this flexibility may allow the manufacturer to demonstrate compliance with multiple, different pharmacopoeial requirements for a quality attribute with a single test.

Where harmonised international standards have been developed (e.g. through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)) it is important that pharmacopoeias adopt these standards rather than developing their own, or seeking to expand or add to the requirements in these standards

General chapters

'General chapters' in pharmacopoeias are usually applicable to a range of materials or products and therefore it is critical that they reflect the state of the industry. Any technology cited should, as far as possible, be well-established i.e. reflecting common manufacturing laboratory equipment, with agreed methodology and/or best practices. Careful consideration needs to be given with the introduction of new technology or requirements to allow sufficient time for implementation by industry around the world. Unlike individual monographs, which may be relevant to only a few companies, the need for agreement on the general chapters across the industry is very important and trade associations, such as Efpia, can enable industry to develop consensus positions and ensure that the most appropriate science is applied.

Monographs for Pharmaceutical Substances and Formulated Preparations

When monographs on materials or products are developed by the pharmacopoeias it is important that registered specifications and industry experience are considered to ensure that the monograph is of high quality. To be useful as a 'public standard', monographs for 'new' active pharmaceutical substances and/or drug products (Formulated Preparations) that will come into effect soon after loss of patent exclusivity should be developed by the pharmacopoeial authority with input from the innovator company. Monographs should not create or preserve a monopoly for supply of a material or product (i.e. the monograph requirements are anti-competitive) and therefore the development of monographs for inactive substances/materials and existing generic products should take into account the specifications from multiple suppliers wherever possible. The content of pharmacopoeial monographs may change over time as a result of market developments, new safety information, technological developments etc.. However, it is important to avoid potentially affecting product availability, for example through the imposition of tighter acceptance criteria than those of the innovator product, unless this is linked to a need to protect public health.

It is important to build flexibility into the pharmacopoeias where appropriate, and many pharmacopoeias allow the use of alternative methods. Where allowed by regulations, some manufacturers make use of this to apply one suitably qualified methodology across multiple pharmacopoeias, thereby avoiding the need for multiple different tests for the same quality attribute.

Pharmacopoeial standards should not remain static and unchanging, but should evolve to take account of scientific advances and increased understanding. When developing new or revised standards the pharmacopoeial commissions should consider emerging scientific and regulatory developments and incorporate technological advances when the technology is sufficiently mature. Consultation and collaboration with industry is essential for this to be done effectively, and any existing pharmacopoeial and regulatory requirements should be considered

The scope of standards included in the pharmacopoeias also needs consideration. For example, there has been an increase in the development and inclusion of GMP-related requirements in some Pharmacopoeias, which can lead to redundant/duplicative/conflicting pharmacopoeial and regulatory expectations. In general, the competent authorities for GMP regulations are government regulatory agencies rather than the pharmacopoeias. EFPIA believes that GMDP requirements should remain the remit of the regulatory bodies, and that the pharmacopoeias should refrain from developing chapters and requirements pertaining to GMP unless specifically mandated by a regulatory agency.

Regulatory Requirements

Pharmacopoeial requirements frequently serve as market standards, enabling an independent check of the quality of a commercial product, and local regulations often specify compliance with a particular local or regional pharmacopoeia (for example, compliance with Ph.Eur. is a legal requirement defined in Directive 2001/83EC; USP in the US Food Drug & Cosmetic Act 1938). Therefore, the introduction of a single, global pharmacopoeia could require a revision to the regulations in multiple countries, and so this is not a practical proposition in the near future. Instead, convergence of national and regional pharmacopoeial and regulatory requirements, to avoid multiple testing of the same material or product to meet different pharmacopoeial requirements, should be supported and could be implemented through:

- Mutual acceptance or reliance by regulatory agencies and pharmacopoeial authorities - Regulatory authorities working with their local legislature to permit mutual acceptance of quality standards developed by internationally-recognised pharmacopoeias
- Regulatory authority acceptance of the equivalence of quality standards in different pharmacopoeias. In practice, differences in monographs, test methods, general chapters etc. between pharmacopoeias have little or no impact on the quality, safety and efficacy of products and therefore on patients. Australia's TGA is an example of an agency that will accept regulatory filings with different pharmacopoeial standards (e.g. USP, Ph.Eur, JP) specified in the dossier.

Collaboration between Pharmacopoeias

The need for alignment of pharmacopoeial requirements has been acknowledged by many stakeholders, including the leading international pharmacopoeias (2), and progress in this area has been made in several forums. Nevertheless national pharmacopoeias continue to independently develop non-harmonised content and increase the complexity for compliance with these different

requirements. Furthermore, some national pharmacopoeias may be updated infrequently; in such cases adoption of an internationally recognised pharmacopoeia (e.g. the European Pharmacopoeia) could be of greater benefit to patients than maintaining a local pharmacopoeia. Although there is evidence of regional developments in, for example, South America and Eastern Europe that may result in regionally aligned expectations, it is reasonable to consider if these efforts would be more efficient if they could utilise content from other leading, internationally-recognised pharmacopoeias.

ICH promotes global requirements for the quality, safety and efficacy of medicines, which includes harmonisation of pharmacopoeial standards through ICH Q4B (4). However, ICH Q4B has terminated its activities, and the need for alignment of requirements of other pharmacopoeial standards not included in ICH Q4B annexes still remains. The Pharmacopoeia Discussion Group (PDG) has diligently worked to create international standard agreement between pharmacopoeial authorities of the EU, Japan, and the USA. In addition, the expanding membership of ICH creates further opportunities to establish globally-aligned standards. However, agreeing harmonised text has proved to be a slow, resource-intensive process, and does not always come to a fully harmonised text. While other markets can choose to adopt the PDG-harmonised standards, there is no current mechanism for other pharmacopoeial commissions to formally contribute to the work of the PDG. If PDG were to expand its membership in the future to accommodate new ICH members such as China, Brazil and South Korea, this will likely slow the current process further, and thus there is a need to consider mechanisms to enable multiple pharmacopoeial authorities to efficiently develop harmonised standards.

Development of regionally harmonised standards is exemplified by the work of the European Directorate for the Quality of Medicines (EDQM) in developing the European Pharmacopoeia (Ph.Eur) through a collaboration of nearly 40 European countries and the European Union (EU). The Ph.Eur. provides harmonised standards for EU member states and extends the influence of these regional activities to a growing number of observer countries. The European Pharmacopoeia is published in English and French, the two official languages of the Council of Europe and two of the three procedural languages of the European Commission (there are 24 official languages of the European Parliament). Publication in English and French facilitates the adoption and use of the European Pharmacopoeia internationally, and the publication of other pharmacopoeias in English would also facilitate their adoption as internationally recognised standards. Publication by pharmacopoeial authorities of proposals for new pharmacopoeial monographs and general chapters in English, together with reasonable timescales for review and comment, greatly assists industry to provide feedback to the pharmacopoeial authorities to help them in developing high quality monographs etc.

Development of the WHO Good Pharmacopoeial Practices (5) (GPhP) showed a common understanding and recognition of the value for harmonized international standards. The importance of existing PDG work was acknowledged as part of the output from the GPhP discussion. Although there were no obligations for the participating Pharmacopoeias to adopt the established harmonized content, further insight into the extent to which pharmacopoeias may have changed their practices as a result of the GPhP document would be welcomed. Nevertheless, the document, and the process to develop it, represents an important first step towards global alignment of pharmacopoeial practices and content.

EFPIA supports the collaboration between pharmacopoeias through initiatives, such as WHO's Good Pharmacopoeial Practices and ICH, and the further development of mechanisms to enable industry to provide input into the development of general chapters, monographs and other pharmacopoeial content that is relevant to the manufacture and supply of medicines in the 21st century. This could include:

- Encouraging prospective harmonisation/convergence by using a 'lead' pharmacopoeia approach for development of new and revised content (perhaps modelled on the PDG approach to harmonisation)
- Encouraging the pharmacopoeial authorities and regulators to embrace and adopt the outputs of ICH guidelines and consider re-establishing or evolving ICH Q4B

References

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