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ICH Reflection Paper: Further Opportunities for Harmonization of Standards for Generic Drugs[1]

Executive Summary

This reflection paper outlines a strategic approach for developing and enhancing ICH guidelines to support the harmonization of scientific and technical standards for generic drugs. As part of this approach, this paper outlines recommendations to develop a series of ICH guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for (1) non-complex dosage forms and (2) more complex dosage forms and products. To accomplish this work, it is proposed to establish a generic drug discussion group to assist in assessing the feasibility of harmonization of standards for generic drugs and to prioritize work areas.

ICH is uniquely positioned to develop and implement these recommendations given its reforms in 2015 establishing it as the global venue for harmonization of standards for pharmaceutical products, including both new drugs and generic drugs. Although many ICH guidelines are applicable to generic drugs (e.g., ICH Quality Guidelines), historically ICH has focused on standards for new drugs. As a result, there are areas of great interest to generic drug regulators and developers where internationally harmonized guidance is lacking or where international harmonization could potentially lead to improved access to lower cost generic medicines. Generic drugs supply a significant portion (>50%) of the pharmaceutical market of the ICH Member and Observer regions and harmonization in this area presents opportunities for market competition, cost savings, and greater supply, thereby increasing patient access to pharmaceutical products globally. There would be a significant public health benefit in utilizing ICH's highly efficient and successful process to harmonize standards for generic drugs.

Below, we discuss the benefits of harmonization of standards for generic drugs and elaborate on our recommendations for proceeding with harmonization for generic drugs under ICH.

I. Proposed harmonization work should be targeted at scientific and technical standards for generic drugs

The mission of ICH is to achieve greater harmonization in the interpretation and application of technical guidelines for pharmaceuticals, and the harmonization of standards for generic drugs falls squarely within this mission. However, it is acknowledged that legal and regulatory requirements for generic drugs are not aligned across jurisdictions. For example:

- In the U.S., the Food and Drug Administration (FDA) does not allow a generic drug and its reference product to be different oral dosage forms (e.g., tablets and capsules). In contrast, in the European Union, the competent drug regulatory authorities allow a generic drug and its

[1] A generic drug product generally contains a small molecule active ingredient and an applicant obtains market access in different regions by demonstrating sameness or equivalence to an already marketed reference product, thus leveraging safety and efficacy data versus needing to provide independent data to demonstrate clinical safety and efficacy. Individual drug regulatory authorities may differ in the scope of this type of approval and may have different regulatory definitions of a generic drug.

reference product to be different oral dosage forms if the product meets bioequivalence criteria. Both regions may request a bioequivalence study as the scientific evidence needed to support marketing approval of different oral dosage forms but evaluate that study through different regulatory pathways.

- The U.S. FDA currently requires that the reference product used in testing to support approval (i.e., the "reference standard" for generic drug comparison as referred to in U.S. statutory text, not to be confused with a compendial reference standard) be registered in the United States. Not all ICH Members require that the reference product be marketed or registered in their country or region, as some permit the use of foreign sourced reference products.[2] For example, Health Canada outlines the criteria for the use of a foreign sourced reference product when demonstrating equivalence of the generic drug to the Canadian Reference Product (e.g., proof of similarity between domestic and foreign sourced reference products).[3]
- In Japan's Pharmaceuticals and Medical Devices Agency, the granting of biowaivers for specific classes of drugs and additional strengths may be limited due to the regulatory framework and scientific issues. Additionally, in Japan, biowaivers for additional strengths may be an issue related to Pharmacopeia standards.

Instead of harmonizing regional legal and regulatory requirements, it is proposed to develop and enhance ICH guidelines in scientific and technical areas that would be valuable and achievable across multiple regulatory pathways and where there is common interest in harmonization.

II. Harmonization of scientific and technical standards for generic drugs could improve public health and health systems domestically and internationally

Generic drugs are often the product of a global supply chain and produced with the intent to market in multiple jurisdictions. They comprise a significant portion of the pharmaceutical market in developed countries, including 89 percent of dispensed medicines in the United States,[4] 56 percent of prescribed medicines in Europe,[5] and 60 percent of the market share in Japan,[6] and as such, constitute a critical part of the healthcare system in these and other regions globally. Generic drugs' portion of the pharmaceutical market in developing countries is even higher.

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[2] IGDRP generic drug product regulatory gap analysis - Regulatory collaboration (WHO Drug Information Vol. 30, No. 3, 2016), available at http://apps.who.int/medicinedocs/en/m/abstract/Js23011en/

[3] HC Guidance Document - Use of a Foreign-sourced Reference Product as a Canadian Reference Producthttps://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/canadian-reference-product-guidance.html

[4] 2016 Generic Drug Savings & Access in the United States Report, Generic Pharmaceutical Association, available at http://www.gphaonline.org/media/generic-drug-savings-2016/index.html

[5] Factsheet On Generic Medicines, medicines for Europe, available at http://www.medicinesforeurope.com/wp-content/uploads/2016/05/4.-Generic-Medicines_On-Generic-Medicines.pdf

[6] Overview of Japanese Generic Drug Market 2016: Market Size, Primary Makers, Market Trends, and Updated Situation on Biosimilars and Authorized Generics – Research and Markets, Cision PR Newswire, Oct 20, 2016, available at https://www.prnewswire.com/news-releases/overview-of-japanese-generic-drug-market-2016-market-size-primary-makers-market-trends-and-updated-situation-on-biosimilars-and-authorized-generics---research-and-markets-300348466.html

At present, a lack of harmonized standards reduces the number of potential markets in which data and information submitted in support of a generic drug marketing application can be used by a developer to support marketing authorization in another jurisdiction. This can lead to monopolies or limited sources of drugs in those markets in which approval is not sought due to the additional development burdens. By contrast, harmonization may allow developers to use the data submitted in support of a generic drug marketing application to meet multiple jurisdictions' regulatory requirements for marketing authorization. In addition, harmonization may increase the size of generic drug markets and thereby attract more competition from developers, lower costs by increasing the number of market entrants, and expand patient access in jurisdictions in which developers otherwise may have decided not to pursue marketing authorization due to differences in scientific and technical standards that require additional expensive studies in each jurisdiction.

In addition, harmonization may streamline generic drug development and make it more cost effective, including by potentially reducing the number of duplicative studies (e.g., bioequivalence studies) that are required to meet the standards for more than one jurisdiction. This also may lead to a reduced number of human subjects that are required for these studies. Duplicative bioequivalence studies may place participants at additional risk and delay patient access to more affordable medicines. For some studies requiring patients with certain specific diagnoses, duplicative studies can exhaust the available human subjects or may require extended recruitment periods which leads to delays in completion of studies. These challenges may also limit the number of manufacturers that enter the market thereby delaying patient access to more affordable medicines. This is already the case for generic versions of certain oncology drugs targeting relatively rare types of cancer.

Finally, harmonization may increase the quality of generic medicines by establishing a globally consistent culture of quality and moving compliance with quality standards in a common direction. For example, a pharmaceutical company may have two or more manufacturing lines – one that is subject to domestic regulatory standards and others that are subject to different foreign regulatory standards. This potentially results in greater cost, an increase in the likelihood of error in applying the correct regulatory and scientific standards, and in the complexity of recordkeeping.

III. Recommendations

The development of the ICH M9 and M10 Guidelines on *Biopharmaceutics Classification System-based Biowaivers* and *Bioanalytical Method Validation* represent the first step towards harmonization of standards for generic drugs. Subsequent work can build on these guidelines and further expand to additional topic areas including standards for demonstrating equivalence.

a. Develop a series of ICH guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for non-complex dosage forms

It is proposed to begin with development of guideline(s) on bioequivalence studies for immediate-release oral dosage forms, as these products constitute a significant portion of submissions to regulatory authorities. This work would include development of guidance on bioequivalence study design (e.g., crossover vs. parallel, subject, sample size, fasting vs. fed, replicate design) and data analysis (e.g., statistical methods for BE assessment, handling outlier data, average bioequivalence vs. scaled bioequivalence, parent vs. metabolite). As part of this work, a working group could consider the feasibility of harmonizing bioequivalence standards and work to align them to the extent possible.

Special considerations for narrow therapeutic index drugs and highly variable drugs including drugs with non-linear kinetics might also be included.

It is noted that such a harmonized bioequivalence study design could be expanded to include additional study arms to accommodate more than one reference product for bridging purposes. For example, a three-way crossover study may allow generic drug manufacturers to submit data from the same study using one test product in support of marketing approval in more than one region.

It is also acknowledged that the requirements to support waivers of bioequivalence studies for non-biostudy strengths are not harmonized. The work under this series of guidelines could include developing harmonized requirements for biowaivers for additional strengths within a product line.

Another work stream under this topic may also include harmonization of biowaivers for solutions such as oral and injectable solutions.

b. Develop a series of ICH guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for more complex dosage forms or products

Following the development of ICH guideline(s) on non-complex dosage forms, it is proposed to develop guidelines on more complex dosage forms or products. One such guideline may address bioequivalence studies for modified-release oral dosage forms, which could address scientific considerations such as "waivers" for additional strengths for modified-release products and when partial Area Under the Curve (pAUC) measurements may be important. In addition, other guidelines could address pharmaceutical equivalence and bioequivalence standards for products with complex active pharmaceutical ingredients (e.g., peptides, oligonucleotides), products with complex formulations (e.g., liposomal products), locally acting products (e.g., topical dermatological and orally inhaled products), and drug-device combination products. Such harmonization might reduce the need for comparative clinical endpoint bioequivalence studies and improve the sensitivity and reproducibility of bioequivalence determinations.

IV. Establish a generic drug discussion group and linkages with other international initiatives on generics

As a near-term next step, it is proposed that ICH establish a discussion group to further consider the specific areas and opportunities for harmonized guidelines as outlined in the recommendations under section III. Additionally, the discussion group could conduct a review of existing ICH Guidelines to assess whether there are any gaps in existing guidance for generic drugs and make proposals for revision of ICH Guidelines as necessary (see Annex I).[7] Given that the harmonization process is resource intensive and time consuming, the discussion group could serve to prioritize work areas and ensure that priorities are set carefully.

The discussion group could primarily interact through email correspondences and teleconferences, or via face-to-face meetings, as appropriate. The discussion group's responsibilities would include:

[7] It is noted that a quality discussion group will be stood up under ICH to assess the need for modernization or revision of any existing ICH Quality Guidelines. This discussion group could also assess whether there is a need to make any revisions for quality aspects for generic drugs that may be unique from new drugs (e.g., sameness of active substance).

- Revising this reflection paper based on regional input
- Establishing an overarching vision for the harmonization of generic drug standards under ICH
- Identifying new topics for harmonization of generic drug standards (considering the areas identified in sections III.a and III.b of this paper)
- Surveying existing ICH guidelines as well as relevant WHO guidelines related to generic drug standards to identify any gaps in guidance for generic drugs
- Working with the ICH implementation subcommittee to assess consistency in the regional implementation of ICH guidelines for generic drugs
- Prioritizing areas for harmonization and making recommendations to the ICH Management Committee

Additionally, it is acknowledged that international collaborative initiatives are ongoing on issues relating to generic medicines. For example, the International Generic Drug Regulators Programme (IGDRP), now within the International Pharmaceutical Regulators Programme (IPRP), has published or provided input into several informative papers on international guidelines and expectations for generic products, including:

- *IGDRP Generic Drug Product Regulatory Gap Analysis*[8]*;*
- *International Guidelines for Bioequivalence of Systemically Available Orally Administered Generic Drug Products: A Survey of Similarities and Differences*[9]*;*
- *A Survey of the Regulatory Requirements for BCS-Based Biowaivers for Solid Oral Dosage Forms by Participating Regulators and Organisations of the International Generic Drug Regulators Programme*[10]*.*

Additionally, WHO's Prequalification of Medicines Programme helps ensure that medicines purchased by or through international procurement agencies for resource-limited countries meet acceptable standards of quality, safety, and efficacy. Through this program, several guidelines have been developed and should be considered by the ICH discussion group to avoid any inconsistencies, as appropriate.

This discussion group should leverage prior work that has been done to date and take measures to avoid duplication of work that continues in other international fora.

Establishment of this discussion group will allow for the necessary scientific and technical engagement and communication between experts to advance harmonization of guidance for generic drugs.

V. Conclusion

Harmonization of technical and scientific standards for generic drugs presents an opportunity for significant public health benefits by streamlining drug development across regulatory jurisdictions and increasing patient access globally to high quality affordable pharmaceuticals. It is recommended that

[8] WHO Drug Information Vol. 30, No. 3, 2016

[9] AAPS Journal, Vol. 15, No. 4, October 2013

[10] J Pharm Pharm Sci , 21, 27 - 37, 2018

ICH initiate topics where a need for harmonization seems most feasible and where agreement exists among ICH parties. As experience is gained, ICH may refocus its harmonization efforts to more complex topic areas where harmonization may not seem feasible at present. To assist in this effort, it is recommended that as a next step, ICH establish a discussion group to assess the feasibility of harmonization of various topic areas specific to standards for generic drugs and to assist in prioritizing work areas to ensure appropriate use of resources.

Annex I

Table I below identifies existing ICH Guidelines that might be revised to include recommendations for generic drugs (*left column*) as well as guidelines that likely would not have to be revised (*right column*) because they are not relevant to generic drugs. For example, the following Efficacy guidelines might be revised to include recommendations on:

- The conduct of comparative clinical endpoint bioequivalence studies: E3, E6, E8, E9, E10, E17
- Pharmacovigilance for generic drugs: E2
- Identification of products with a narrow therapeutic index: E4
- Statistical considerations for bioequivalence: E9

However, as indicated in Table 1, guidelines related to the generation of new safety or efficacy data (E2A, E14, and E19) would generally not be applicable to the generic drug development process.

Table 1: Efficacy Guidelines

Efficacy guidelines that have an impact on the generic drug industry and may potentially need to be revised	Efficacy guidelines that do not have an impact on the generic drug industry and likely do not need to be revised
• E2C(R2) Periodic Benefit-Risk Evaluation Report • E2C(R2) Q&As Questions & Answers: Periodic Benefit-Risk Evaluation Report • E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting • E2E Pharmacovigilance Planning • E2F Development Safety Update Report • E3 Clinical Study Reports • E4 Dose-Response Studies • E6 Good Clinical Practice • E8 General Considerations for Clinical Trials • E9 Statistical Principles for Clinical Trials • E10 Choice of Control Group in Clinical Trials • E17 Multi-Regional Clinical Trials	• E1 Clinical Safety for Drugs used in Long-Term Treatment • E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting • E2B(R3) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports • E2B(R3) IWG Implementation: Electronic Transmission of Individual Case Safety Reports • E5 Ethnic Factors • E7 Clinical Trials in Geriatric Population • E11 - E11A Clinical Trials in Pediatric Population • E12 Clinical Evaluation by Therapeutic Category • E14 Clinical Evaluation of QT • E15 Definitions in Pharmacogenetics/Pharmacogenomics • E16 Qualification of Genomic Biomarkers • E18 Genomic Sampling • E19 Safety Data Collection