FDA Reflection on Further Opportunities for Regulatory Harmonization of Standards for Generic Drugs

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Disclaimer

- *This paper has not yet been endorsed by the ICH Management Committee but was shared with the ICH Assembly and IPRP Management Committee to assess interest in pursuing harmonization around scientific and technical criteria unique to the regulation of generic drugs*
- *FDA invites any comments on the paper and will discuss some possible next steps at this meeting*

Goals of the Reflection Paper

- To articulate the need for harmonization of scientific and technical aspects related to generic drugs
- To allow for a more focused discussion under ICH on initiating work in this area

Generic Drugs

- Generic drugs comprise a significant market share of all prescribed medicines in developed countries and constitute a critical part of the healthcare system in these regions
  - United States (89%)
  - Europe (56%)
  - Japan (60%)
- Percentage of generic drugs prescribed in developing countries is even higher

Why Harmonize Now?

- Absence of harmonized standards impedes generic drug global availability
  - Creates risk to quality of generic drugs
  - Contributes to challenges for generic drug importation
- Potential benefits of harmonization
  - Reduce the risk of inconsistent regulatory standards in different regions
  - Reduce manufacturer costs associated with meeting potentially duplicative regulatory requirements in different regions
  - Reduce the cost of regulatory oversight by providing regulators more opportunities for information sharing with their regulatory counterparts

Current Challenges for Harmonization

- FDA Observation:
  - Differences in regional statutes and regulations may present challenges in pursuing common definitions
- Earlier IGDRP work has provided the following definition:

A generic drug product *is generally defined as a drug product that in comparison with a reference product:*

- *is pharmaceutically equivalent to the reference product (i.e., the same amount of the same active substance in the same dosage form), and*
- *is equivalent to the reference product in terms of safety, efficacy, and quality.*

Considerations for Initiating Work Related to Requirements for Generic Drugs

- Acknowledge each region already has their own regulations on generic drugs and that these regulations are closely tied to regional definitions
- Recognize some work may also be applicable to new drugs

FDA Perspectives on Opportunities for Determining Pharmaceutical Equivalence and Bioequivalence

Harmonization of the following key criteria would allow for advancement in development and approval of generic drugs globally:

1) Elements of the formulation that are critical to pharmaceutical equivalence from which one can infer therapeutic equivalence in the context of use
2) Aspects of the pharmacokinetic profile that adequately define bioequivalence
3) Critical elements of similarity

Starting Point for Discussion

What are the Key Opportunities for Harmonization?

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Some near-term opportunities for harmonization under ICH include the following list of topics:

- Identifying and establishing critical scientific and clinical elements for determination of standards for pharmaceutical equivalence and bioequivalence
- Evaluation of formulation/process/equipment changes/differences and their expected risk level of changing a critical aspect of pharmaceutical equivalence
- Biowaivers for additional strengths (e.g., with respect to the strength for which *in vivo* bioequivalence has been shown) for solid oral dosage forms

What are the Key Opportunities for Harmonization?

Additional areas with potential for harmonization as a better understanding of regional frameworks develop include the following:

- Alternative approaches to *in vivo* pharmacokinetic or clinical endpoint bioequivalence studies in humans for BE assessment (e.g., *in vitro* characterization, quantitative methods and modelling, or innovative approaches to *in vivo* studies for locally acting drugs)
- Identification of critical aspects of a formulation and definition of significant differences from the reference product
- Scientific and technical factors to be considered in the selection of a reference product to facilitate global comparison of pharmaceutical equivalence and bioequivalence of a generic drug
- Evaluation of BE when there is no comparator (reference product) or comparator is no longer available
- Considerations for *in vitro* BE studies for certain classes of drug products (e.g., locally acting suspension products)

Proposed Next Steps

- Continued discussion by IPRP and ICH
- Possible IPRP discussion group to develop better understanding of regional regulatory frameworks and identify areas where harmonization is feasible:
  - Follow up discussion to review the issues and potential opportunities outlined in this paper
  - Further define and scope of scientific and technical issues and topics to make recommendation for a logical sequencing or priority ordering based on
    - Interest
    - Priority/Significance
    - Feasibility for harmonization
- Finalize the reflection paper and seek ICH endorsement

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Thank You!