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

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Disclaimer

- *This paper has not been endorsed by the ICH Management Committee but was shared with the ICH Assembly and IPRP Management Committee to obtain feedback and assess interest in pursuing harmonization of scientific and technical requirements particularly relevant to marketing authorization for generic drugs*

Goals of the Reflection Paper

- To articulate the need for greater harmonization of scientific and technical requirements related to generic drugs
- To initiate further and more focused discussion of potential new guideline topics that could be pursued in ICH

High volume of Dispensed 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

Some Potential Near-Term Opportunities for Harmonization

- 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

Areas with Potential that Need Further Discussion (e.g., in IPRP)

- 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)

Feedback Received from IPRP MC and ICH MC

- Overall support for harmonization where feasible and appropriate
- Need to recognize differences in laws and regulation across regions – where harmonization not feasible
- More detail is needed to understand what FDA is actually proposing for near-term opportunities (e.g., Slides 8-9)
- Areas not ready for harmonization might be further discussed outside ICH
  - Discussion might be taken up in IPRP's Quality and Bioequivalence Working Groups (WGs) for Generics
  - However, these IPRP WGs current workplans do not include this sort of follow up discussion with goal of identifying topics for regulatory harmonization in ICH and such follow up would be weighed against other WG priorities

FDA Planned Next Steps

- Revision of FDA's reflection paper to focus only on scientific and technical work that would be feasible to pursue in ICH in relatively near term
- Further detail scope of work that might be pursued under the high-level bullets identified in the current reflection paper (shown on Slides 8 and 9) that could be translated into one or more future proposed topics for new ICH guidelines
- Form an *informal-informal working group* of expert contacts from interested ICH Members
  - This group of contacts could be an informal sounding board and could review the scoped out work (previous bullet) to provide quick-turnaround feedback
- Aspire to submit a new topic proposal addressing a candidate area identified within the above work—in time for the next round of new topic proposal submissions in December 2018

Thank You!