U.S. FOOD & DRUG ADMINISTRATION

Harmonization of Bioequivalence
FDA Perspective

Robert Lionberger, Ph.D.
Director
Office of Research and Standards, Office of Generic Drugs

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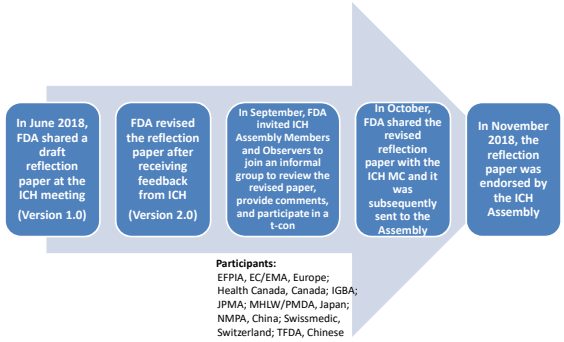
AAPS/EUFEPS Global Bioequivalence Harmonization Initiative (GBHI)

ICH Reflection Paper on Generic Drug Harmonization

- Outlines a strategic approach for developing and enhancing ICH guidelines to support the harmonization of scientific and technical standards for generic drugs
- Proposes steps and recommendations for global harmonization of standards for generic drugs
- The reflection paper (drafted by FDA) was discussed at the November 2018 ICH Assembly Meeting and endorsed

https://admin.ich.org/sites/default/files/2019-04/ICH_ReflectionPaper_GenericDrugs_Final_2019_0130.pdf

ICH Reflection Paper Timeline



Key Proposals from Reflection Paper

- Develop a series of ICH guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for
  - (1) non-complex dosage forms
  - (2) more complex dosage forms and products
- Establish a generic drug discussion group
  - To assist in assessing the feasibility of harmonization of standards for generic drugs
  - To prioritize work areas

Regulatory and Scientific Frameworks for "Generic" Drugs

- The reflection paper recognizes that different regions have different regulatory frameworks
  - Example: Tablet and Capsule
    - Not a "generic" in the US
    - Possible "generic" in the EU
- The reflection paper focuses on harmonizing scientific standards for bioequivalence that can be used within the existing regulatory frameworks

Reflection Paper Outcomes

- Formed an informal generic drug discussion group (IGDG) in April 2019*
  - To assist ICH in identifying recommended topic areas for harmonization
  - To survey existing ICH and WHO guidelines to assess gaps in guidances for generic drugs
  - To prioritize work areas and send proposals/make recommendations to ICH
- First ICH Topic on Bioequivalence Harmonization was endorsed by ICH Assembly in November 2019
  - Harmonization of BE standards for immediate-release oral dosage forms

 * https://database.ich.org/sites/default/files/IGDG_Remit.pdf

ICH: Future Steps

- Issues related to more complex products are on the horizon
  - Modified release products
  - Transdermal
  - Topical
  - Inhalation
  - Complex Injectables

What is the role of GBHI?

- "Soft" harmonization
- Through open discussion of complex scientific issues regulatory agencies evolve toward common approaches via their own internal processes
  - Example: Liposome topic at previous GBHI

What is the role of GBHI?

- Pre-ICH discussion
- Help identify which complex products should be next to enter an ICH harmonization process
  - Identify areas where scientific consensus exists and can be confirmed via ICH process
  - Help identify and understand the scientific basis of differences that should be discussed in a formal process
  - Example: Inhalation and long-acting injectable topics

What is the role of GBHI?

- ICH is an industry-regulator forum limited to ICH members
  - GBHI can include scientific experts outside this frame (academic or consultative perspective, non-ICH members)
  - GBHI focus should be on scientific discussion that can provide useful input into ICH discussions
  - Example: Fed BE studies for IR products discussion

Value of Scientific Harmonization

- Bioequivalence studies world-wide can be conducted according to common expectations
  - Increases efficiency of generic drug development
  - Increases quality of generic drug development
- It is the essential first step toward global development of generic products
  - Agreement on bioequivalence standards must come before any practical use of common global reference products

What are the Opportunities?

- Movement toward common standards and global development for generics can improve access to generic products
  - Products with small markets may not be economically viable unless markets can be aggregated across regions
  - Investment in development of complex generics can be supported by entrance into multiple markets

What are the Challenges?

- What are the scientific data and analytical tools that provide evidence that reference product sourced in region “A” and reference product sourced in region “B” are similar enough that BE comparisons will be the same? (GBHI role)
- A regulatory policy system in each region that will allow scientifically sound data to be used (beyond GBHI)