Bioequivalence Requirements: USA and EU

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Bioequivalence Concept

- Regulations exist worldwide to assure Quality, Safety, and Efficacy of Medicines
- The Bioequivalence (BE) concept addresses the Safety and Efficacy issue for Generic Drug Registration
- BE provides the bridge from the generic product to the innovator’s clinical and non-clinical studies and labeling
- As noted in our 2012 Kyoto statement IGPA promotes global harmonization and strict adherence to regulatory bioequivalence standards
Regulatory Convergence may be defined as a process whereby regulatory requirements across nations become more aligned over time as a result of the adoption of internationally recognized technical guidances, standards, and best practices.
Regulatory Convergence is a desirable and feasible process for Bioequivalence Concepts.

Regarding the USA, EU, and Japan there is regrettably no ICH technical guideline on Bioequivalence.

The necessary conditions are present for convergence:
- The underlying science and experts on BE are global
- Important Scientific Meetings are global in scope and participation
- Individual National Regulators are communicating with each other and industry on developing technical guidances

Ultimately, Regulatory Harmonization (identical standards and requirements) on BE is achievable and should be our goal as an industry.
Key BE Guidelines

- Guideline on the Investigation of Bioequivalence (January 2012)
- Modified Release Oral and Transdermal Dosage Forms: Sections I and II (CPMP/QWP/604/96, CPMP/EWP/280/96)
- Clinical Requirements for Locally Applied, Locally Acting Products containing Known Constituents (CPMP/EWP/239/95)
- Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD)(CPMP/EWP/4151/00 rev 1)
USA

- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations (March 2003)
- Food Effect Bioavailability and Fed Bioequivalence Studies (December 2002)
- Statistical Approaches to Establishing Bioequivalence (January 2001)
- Waiver of In-Vivo Bioavailability and Bioequivalence Studies for immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (August 2000)
- Bioequivalence Recommendations for Specific Products – Draft – (June 2010)
Oral Immediate Release Dosage Forms

- Audience is referred to the specific guidelines available on the FDA and EMA websites for details.
- In addition to the EU guideline itself an overview (248 pages) of the comments received on the draft guideline is published on the EMA website. This overview provides valuable insight into the EMA thinking on BE issues.
- Although this general case is covered in in the current FDA and EU guidelines, requirements are not harmonized.
- Some examples:
  - Add-on studies
  - Submission of all BE studies performed
  - Dissolution requirements
Generic Industry Concerns with the 2011 EU Guideline

- Implementation policy regarding “legacy” applications and studies and if submission of approved dossiers to new countries will require new review of BE study
- Existing Guideline on Modified Release Products is now obsolete and conflicts with the new guideline
- Concern is that although the new guideline is not mandatory, it will be applied literally and justifications required will be variable and difficult to predict
- Industry requests flexibility and common sense from regulators in applying the new guideline
Modified release (MR)
Dosage Forms

- In USA MR dosage forms are covered in the General Considerations guidance.
- In EU there are separate guidelines for MR products. The EU guidelines are out of date. Revision of these guidelines is in progress and expected imminently.
- Generally speaking, MR guidances are more difficult to develop and harmonize as underlying science is more complex and expert scientific opinion is mixed.
Clinical Endpoint BE Studies

- A new department has been established in US FDA Office of Generic Drugs – **Division of Clinical Review**

- Responsibilities of Clinical Review Division include:
  - Safety issues related to generic drug BE studies
  - Clinical endpoint BE studies for locally acting drug products
  - Protocol development and review for all clinical endpoint BE studies
  - Review of Bio-INDs (INDs are generally not required for BE studies)
  - Guidance development for specific drugs
    - E.g. mesalamine, methylphenidate, paclitaxel
Biowaivers

- A type of in vitro BE study
- US FDA 2000 Guidance
  - The world’s first guidance using BCS
  - Only allows for BCS Class 1 drugs
  - Initial uptake slow – still not widely used
- EU
  - Concept finally covered in 2010 General guideline
  - Allows Class 1 plus limited Class 3 drugs
  - Generic industry thus far is reluctant to use this approach in EU due to uncertainty with review
Biowaivers

US FDA Experience – most common deficiencies include:

- Lack of multi-pH solubility profiles
- Inappropriate method of solubility determination
- Lack of dissolution data for all strengths
- Missing SOPS for analytical methods
- Missing data supporting GI stability
- Lack of bi-directional in vitro permeability data on model compounds
Both USA and EU require the reference product for BE studies for generic applications to be one that is sourced from the home market.

Requires multiple BE studies for potentially an identical reference product.

What is the benefit to the patient and national healthcare systems?

If a non-local comparator is allowed in the EU and apparently USA for the much more complicated case of biologics and biosimilars, why can a similar scientific approach not be taken for small molecule immediate release product formulations?

Perceived legal barrier seems to have been overcome in the case of biosimilars.

An ancillary reference product issue for US generic applicants is the non-availability of the reference product to generic companies due to restricted access programs.
US FDA has become very concerned with quality of In Vivo BE studies and data

A total of 91 “For Cause” inspections were conducted by US FDA from 2003 – 2011

60% of these inspections were conducted for data integrity concerns

Other issues triggering “For Cause” inspections were adverse inspection history, high number of repeat assays, inadequate documentation, and improper study conduct
Confidence in Generic Drugs

- US FDA strategic approach:
  - Strengthen review requirements (QbD, NTI drugs)
  - Post-marketing surveillance
  - Scientific Studies
    - Lamotrigine
    - Tacrolimus
    - Pharmaceutical Quality Surveys (NTI drugs)
  - Communication and Action (FDA sponsored meetings with medical associations)
Bioanalytical Methods

- A guidance on Bioanalytical Method Validation was published by US FDA in May 2001
- Although covered briefly in the new EMA BE guideline, a draft guideline on Bioanalytical method validation is being prepared by EMA
- Hopefully, the new EMA can/will be prospectively harmonized with FDA guidance
Conclusions

- USA and EU technical guidelines on BE are converging.
- However, they are not harmonized as differences in detailed regulatory requirements still exist between the two regions.
- Generic industry needs to step up and become a partner with national regulatory authorities in formulation of effective and harmonized guidances.
- IGPA can serve a very important role in assuring that new guidances are prospectively harmonized on an international basis and existing guidances continue to converge.