Best Practices for Conducting Bioequivalence Studies

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Outline

- Generic Drugs and Bioequivalence
- Certain regulations governing bioequivalence (BE) studies
- Different types of BE studies that may be submitted in support of Abbreviated New Drug Applications (ANDAs)
- Product-Specific Guidances and their development
- Biopharmaceutics Classification System (BCS)-based waivers
- Tips from the Office of Bioequivalence

Generic Drugs and Bioequivalence (BE)

- Generally, a generic drug must be pharmaceutically equivalent and bioequivalent (and thus therapeutically equivalent) to the Reference Listed Drug product in order to be approved. (21 CFR Part 314).

- **Pharmaceutical Equivalents:** "are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient . . . ." (21 CFR 314.3).

- **Bioequivalence**: "is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. . . ." (21 CFR 314.3).

Overview of Certain Regulations Governing BE Studies

- **21 CFR 314.94(a)(7)-***requires BE documentation in support of an ANDA.*
- **21 CFR 320.21(b)-***requires submission of evidence that the proposed drug product is bioequivalent to the reference listed drug or information supporting waiver of evidence demonstrating in vivo bioequivalence (i.e., 21 CFR 320.22).*
- **21 CFR 320.22***- contains requirements regarding the criteria for a waiver of the in vivo bioequivalence study requirement.*
- **21 CFR 320.23(b)-***contains requirements that:*
  - *Rate and extent of absorption do not show significant difference.*
  - *Bioequivalence may be demonstrated by scientifically valid methods for drug products not intended to be absorbed into the bloodstream.*
- **21 CFR 320.24(a)**
  - FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products.
  - Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available.

BE Studies that May be Submitted in Support of ANDAs

- 21 CFR 320.24(b)-Methods for demonstrating bioequivalence
  - In vivo test in humans measuring active ingredient/active metabolite in appropriate biological fluid as a function of time. (i.e., a pharmacokinetic [PK] study)
  - In vitro test
  - An in vivo test in human in which the acute pharmacological effect is measured (i.e., a pharmacodynamic study)
  - Clinical endpoint study
  - Any other method deemed appropriate by the Agency

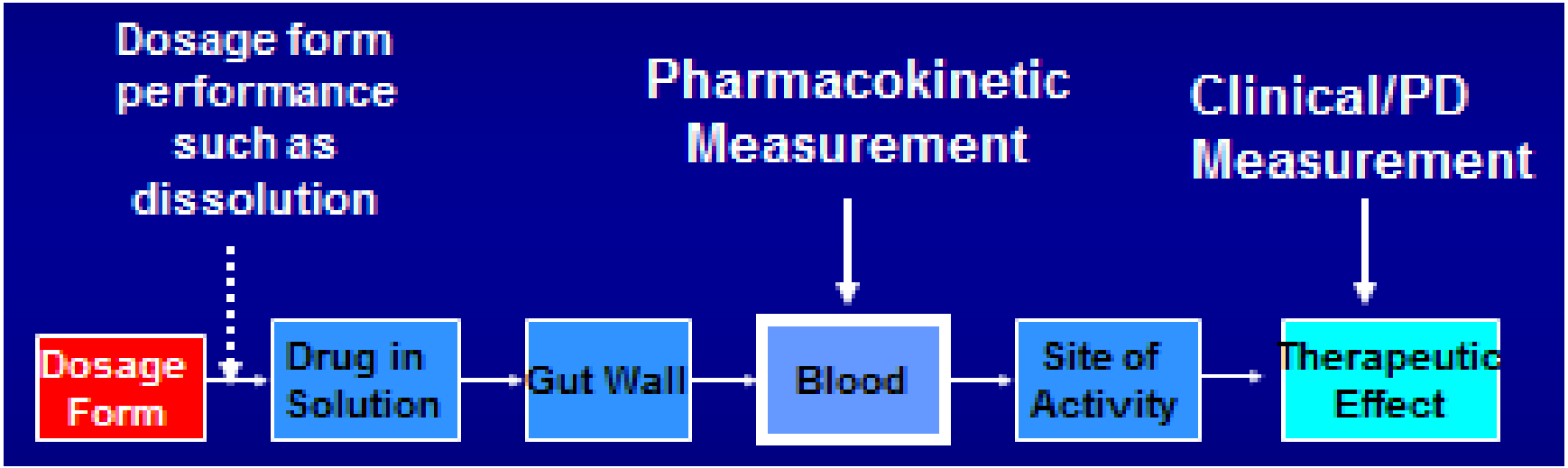
Product-Specific Guidances (PSGs) for Generic Drug Development

- Published in an incremental manner (approximately every three months)
- Agency's current scientific thinking on the most accurate, sensitive, and reproducible approach to demonstrate bioequivalence for a given product
- May recommend in vivo studies, in vitro studies, or a combination of the two
- May also recommend a waiver route

Considerations in Developing a PSG

- Mechanism of drug delivery and release
- Intended site of action
- Formulation design and composition
- Ability to measure drug availability systemically or at the site of action
- Available in vivo and in vitro tests

A PK study is *typically* the best BE method…



…but not always

Vancomycin HCl Capsules

Indications:

Treatment of *C. difficile*-associated diarrhea.

Treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains).

Mechanism of Action:

The bactericidal action of vancomycin against *Staphylococcus aureus* and the vegetative cells of *Clostridium difficile* results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis.

Vancomycin HCl Capsules

1. After oral administration, capsule releases drug in stomach and upper GI tract.
2. Drug is completely solubilized in GI fluids.
3. Solubilized drug is then transported in GI fluid to the site of action in the lower GI tract.
4. Vancomycin acts locally in the lower gastrointestinal (GI) tract.

- Vancomycin HCl is poorly absorbed after oral administration.

Vancomycin HCl Capsules

Thus, BE can be assured when:

- the effect of excipients on transport of drug to the site of action and/or on the effectiveness of drug at the site of action are similar between the test and reference products: *Q1 and Q2 sameness.*

- there is equivalent release of vancomycin from the test and reference products. *Similar T and R dissolution at all physiologically relevant pH ranges*

PK is not an effective way to assess BE in this example.

In vivo BE studies are not always necessary

21 CFR 320.22

A waiver of the in vivo bioequivalence study requirement maybe granted for the following products provided that certain conditions are met:

- Oral solution
- Parenteral solution
- Ophthalmic solution
- Otic solution
- Inhalation gas
- Products referencing a Drug Efficacy Study Implementation (DESI) effective drug product
- Non-biostudy strengths of a proposed immediate release product line
- Certain reformulated products

Biopharmaceutics Classification System (BCS) Waivers

Foundations of the Waiver
Permeability
Solubility
Dissolution

BCS Class 1: High Solubility – High Permeability
BCS Class 2: Low Solubility – High Permeability
BCS Class 3: High Solubility – Low Permeability
BCS Class 4: Low Solubility – Low Permeability

Why can waivers be based on solubility, permeability, and dissolution?

- The above three factors determine the absorption of a drug from a formulation.

- If a drug substance has high solubility, it is unlikely that formulation differences between test and reference product would affect the rate and extent of absorption of the API, provided that i) in vivo dissolution of both formulations is rapid or very rapid with respect to gastric emptying time and ii) there are no excipients that would affect absorption.

What products are eligible and ineligible for a BCS waiver?

Eligible:

- Immediate Release Solid Oral Dosage Forms with a BCS Class I drug substance that exhibit rapid dissolution or with a BCS Class III drug substance that exhibit very rapid dissolution are eligible. In both cases there should be no concerns regarding excipient effects on absorption.

Not Eligible:

- Modified release drug products
- Narrow therapeutic range drugs
- Dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets)

Highlights from the BCS Guidance

- High Solubility (BCS Class I and Class III)
  - Highly solubility is established when the highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1-6.8. **For a drug product where the highest single dose is higher than the highest strength, additional information may be necessary**.
  - **Equilibrium solubility should be measured using a shake-flask method (other methods can be used with justification).**

- High Permeability (BCS Class I only)
  - Mass balance studies
  - Intestinal permeability methods
  - **Expression of efflux transporters in cell culture systems**

Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (December 2017)

Highlights from the BCS Guidance

- High Permeability (BCS Class I only) (continued)
  - For cell culture methods, the method must be validated using a number of model compounds.
  - **Use a high and low permeability standard in pivotal study.**
  - **When intestinal permeability methods are used, drug stability in the GI tract must be documented.**

- Rapid (BCS Class I) or Very Rapid (BCS Class III) dissolution
  - Rapid (Mean of 85% in 30 min); Very Rapid (Mean of 85% in 15 min); Similar test and reference dissolution
  - Demonstrated in 0.1N HCl/SGF, pH 4.5, and pH 6.8 buffer/SIF
  - USP I at 100 rpm or USP II at 50 rpm using 500 mL
  - **Increase in speed to 75 rpm or in volume to 900 mL with justification**

Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (December 2017)

Highlights from the BCS Guidance

- Excipients
  - BCS Class I: The product does not contain excipients in amounts that will affect the rate or extent of absorption.
  - BCS Class III: The test product formulation is qualitatively the same and quantitatively very similar to that of the RLD product.

Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (December 2017)

Tips on BCS Waiver Studies

- Solubility Studies:
  - Equilibrium conditions
  - Saturated solutions
  - Measure pH
  - Use shake flask method
  - No surfactants

- Permeability Studies:
  - Internal standards that are not efflux transporter inhibitors
  - Citing literature data or labelling from non-US product is usually unacceptable

General Tips

- **Refer to the Product-Specific Guidance!**
  - Keep abreast of new and revised PSGs on our website.
  - Sign up for listservs that provide alerts on new and revised PSGs that have posted.
  - Certain PSGs have helpful recommendations on special BE considerations
    - (e.g., Highly Variable Drugs, Narrow Therapeutic Index Drugs, and Population Bioequivalence analysis)

- **Refer to the FDA Guidances for Industry on Biopharmaceutics**
  - Draft Guidance for Industry: Bioanalytical Method Validation (September 2013)
  - Draft Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (December 2013)

General Tips

- **Avail yourself of other resources when the PSG or general guidances do not address your situation**
  - First principles [21 CFR 320.24(a)]
  - PSGs for similar products
  - Draft Guidance for Industry: Controlled Correspondence Related to Generic Drug Development (November 2017)
  - Draft Guidance for Industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (October 2017)

- **Your application is only as strong as the data therein: Hire a good CRO!**

- **Reserve samples**
  - 21 CFR 320.63
  - Needed for all (in vitro and in vivo) BE studies

General Tips

- **Submit an organized and complete submission**
  - Clear, well-written study reports
  - All data needed for analysis
  - Complete summary tables
  - Draft Guidance for Industry: Content and Format of Abbreviated New Drug Applications (June 2014)
  - Complete site information (including street address) for all CROs who conduct BE studies (in vitro AND in vivo BE studies) and studies in support of BCS-based waiver requests

- **Draft Guidance for Industry: Good ANDA Submission Practices (January 2018)**

Concerns Noted by Our Assessors: In Vivo BE Studies

- **Statistical Analysis**
  - Incorrect model used
  - No pre-specified statistical analysis plan
- **Bioanalysis**
  - Missing long term storage stability data
  - Inadequate dilution integrity data
  - SOPs lack specific, complete, objective criteria, reasons for repeating sample analysis
  - Data for failed analytical runs not provided.
  - SOPs not provided
- **Study Design**
  - Inadequate sampling time

Submission Format for PK Data

Applicants whose studies started after December 17, 2016 must submit data in the data formats supported by FDA and listed in the FDA Data Standards Catalog.

See the following website for additional information:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Concerns Noted by Our Assessors: In Vitro BE Studies

- **Statistical Analysis-**
  - Incorrect method used
  - Missing justification for method used

- **Analytical Method-**
  - Quality controls not included
  - Method validation incomplete (e.g., all relevant parameters not validated)

Summary and Closing Thoughts

- Same goal
- Agency-provided resources
- Science
- Quality submissions

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http://www.ecfr.gov/cgi-bin/ECFR?page=browse

FDA Product-Specific Guidances for Generic Drug Development
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Listservs
https://www.fda.gov/AboutFDA/ContactFDA/ucm2005606.htm

Draft Guidance on Progesterone Capsules (Recommended April 2010, Revised February 2011) (Highly Variable Drug Products)
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf

Draft Guidance on Warfarin Sodium (Recommended Dec 2012) (Narrow Therapeutic Index Drug Products)
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201283.pdf

Draft Guidance on Budesonide (Recommended Dec 2012) (Population Bioequivalence Analysis)
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf

Vancomycin HCl Capsules-Labeling
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/050606s028lbl.pdf

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BCS Tips

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FDA Guidances for Industry: **Biopharmaceutics**
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm

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