Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General Considerations

Vinod P. Shah, Ph. D.
Senior Research Scientist
OPS/CDER/FDA

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General BA and BE Guidance

Outline

Chronology and Background
Important Features of the Guidance
Impact

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General BA and BE Guidance Chronology

- Advisory Committee meetings
- Draft Guidance – August 1999
- AAPS workshop in Montreal – August–September 1999
- Discussions at Advisory Committee Meeting – September 1999
- Discussions at AAPS annual meeting – November 1999
- Review of Comments
- Changes in Draft Guidance
- Final Guidance – October 2000

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BA and BE Studies General Considerations

- Uses sound scientific principles to reduce regulatory burden by lowering in vivo requirements, without sacrificing product quality
- Defines proportionally similar dosage forms
- Allows waivers of in vivo BE for higher strength of IR dosage form
- Allows waivers of in vivo BE requirements for lower strengths of IR and MR dosage forms
- Eliminates multiple dose BE study requirements for MR dosage forms

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General BA and BE Definitions

BA: BA focuses on the release of the drug substance from the drug product and its absorption into the systemic circulation. The process information related to formulation development has an effect on drug absorption, PK, PD or drug metabolites.

BE: BE focuses on the release of the drug substance from the drug product and its absorption into the systemic circulation. It is a comparative test that uses specified criteria, comparisons and predetermined BE limits.

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Proportionally Similar

All active and inactive ingredients are exactly in the same proportion.

Total weight remains nearly the same to accommodate the change in strength is obtained by increasing the amount of the active ingredient and one or more of the inactive ingredients.

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Documentation of Bioequivalence

In descending order of preference

- Pharmacokinetic Methods
- Pharmacodynamic Methods
- Comparative Clinical Trials
- *In Vitro* Studies

Pharmacokinetic Studies

- General considerations: study conduct
- Pilot and pivotal studies
- Study design - Single dose
  - Crossover design for IR products (ABE)
  - Replicate design for MR products (ABE)
  - Replicate design for highly variable drug products (IBE)
- PK measures of systemic exposure [peak (Cmax) and total (AUC) exposure]
- Statistical Analysis: 90% CI, 80-125% BE limits

Pharmacokinetic Studies
Measures of Systemic Exposure

- Early Exposure
  - Partial AUC with a cut-off at the median time to Tmax of the reference
- Peak Exposure (Cmax)
- Total Exposure (AUC)

Immediate Release Dosage Forms
General Considerations

- Focus is on the release of the active substance from the drug product into systemic circulation
  - *In vivo* single dose study
  - *In vitro* dissolution study
  - Exposure measures

Immediate Release Dosage Forms

Biowaivers (preapproval)

- For HS, HP, rapidly dissolving drug products (BCS)
- For lower strength(s)
  - Dissolution profile comparison – criteria
- For higher strength based on clinical safety/efficacy data and dose justification
  - Dissolution profile comparison – criteria

Biowaivers (post-approval)

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Modified Release Dosage Form

General Considerations

Bioavailability Studies

- A single dose fasting study on all strengths
- A single dose food-effect study at highest strength
- A steady state study using highest strength

Bioequivalence Studies

- A single dose replicate BE study at highest strength comparing T and R products
- A food-effect study at highest strength comparing T and R products

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Modified Release Dosage Form

Multiple-dose Bioequivalence study

- Because a single dose study is considered more sensitive in assessing the primary question in a bioequivalence study – release of the drug substance from the drug product into the systemic circulation, a multiple dose study is generally recommended.

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Modified Release Dosage Form

Biowaivers (preapproval)

- For lower strength(s) beaded capsules
- For lower strength(s) tablets
  - Same dosage form, proportionally similar in active and inactive ingredients, and the same drug release mechanism
  - Dissolution profile comparison in 3 media: pH 1.2, 4.5 and 6.8

Biowaivers (post-approval)

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Parent Drug vs Metabolite Measurement

BA Studies: Parent drug and metabolites

BE Studies: Measurement of only parent drug

- Measurement of a metabolite preferred when parent drug level are too low to allow reliable measurement in biological fluid. (Metabolite to meet criteria)
- When metabolite contributes meaningfully to safety and/or efficacy, parent drug and metabolite should measured. BE based on parent drug. Metabolite data provides supportive evidence.

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Enantiomers vs Racemates

BA Studies: Measurement of both enantiomers

BE Studies: Measurement of racemate using an achiral assay

Measurement of enantiomers in BE are recommended when ALL of the following conditions are met:

- Enantiomers exhibit different PD characteristics
- Enantiomers exhibit different PK characteristics
- The primary efficacy/safety activity resides with minor enantiomer
- Non-linear absorption is present for at least one of the enantiomers

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Long-half Life Drugs

BA: Characterization for half-life of the drug

BE: Collection time adequate to ensure completion of GI transit time of the drug product and absorption of the drug substance. AUC truncated to 72 hours

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BA and BE Studies General Considerations

The General BA and BE guidance (October 2000) will replace:

- Guidelines for the evaluation of controlled release oral dosage products (April 1984)
- Oral extended (controlled) release dosage form: In vivo bioequivalence and in vitro dissolution testing (September 1993)
- Statistical procedures for bioequivalence studies using a standard two-treatment crossover design (July 1992)
- Drug specific BE guidances (CDER/FDA)

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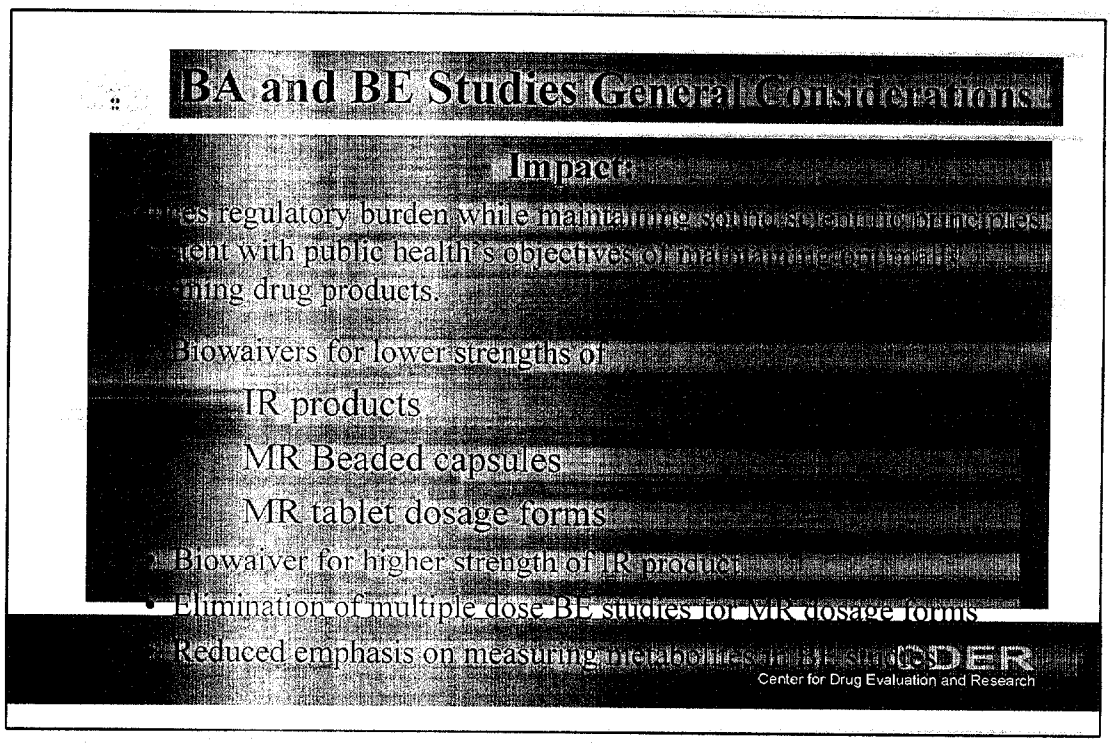
BA and BE Studies General Considerations
Impact:
es regulatory burden while maintaining scientific principles
ent with public health's objectives of maintaining control
ming drug products.
Biowaivers for lower strengths of
IR products
MR Beaded capsules
MR tablet dosage forms
Biowaiver for higher strength of IR product
Elimination of multiple dose BE studies for MR dosage forms
Reduced emphasis on measuring metabolites in BE studies
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