VIJAYA INSTITUTE OF PHARMACEUTICAL SCIENCES FOR WOMEN

BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUGS

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CONTENTS

INTRODUCTION

- Multi-source drug products need to conform to the same standards of quality, efficacy and safety of the innovator's product.
- In addition, reasonable assurance must be provided that they are, clinically interchangeable with market products.
- With some classes of products, including biologicals such as vaccines, animal sera, and products derived from human blood and plasma, and product manufactured by biotechnology, the concept of interchangeability raises complex and hence these products are consequently excluded from consideration.

DEFINITION OF TERMS

Explanation of certain pertinent terminology described below will facilitate the discussions on the approaches to the assessment of bioequivalence.

1. Bioavailability

2. Bioequivalence

3. Generic Drug Product

4. Innovator Drug Product

5. Interchangeable Pharmaceutical Product

5. Multi-source Pharmaceutical Products

6. Pharmaceutical Equivalence

7. Reference Product

8. Therapeutic Equivalence

METHODS TO DOCUMENT BA AND BE

• Several *in-vivo* and *in-vitro* methods can be used to measure product BA and to establish BE. In descending order of preference, these include:

1. **Pharmacokinetic Studies**
2. **Pharmacodynamic Studies**
3. **Comparative Clinical Studies**
4. ***In-vitro* studies.**

• Product BA and BE frequently rely on pharmacokinetic measures such as AUC and C_{max} that are reflective of systemic exposure.

PHARMACOKINETIC STUDIES

1. General Considerations

2. Pilot Study

3. Pivotal Bioequivalence Studies

4. Study Designs

5. Study Population

6. Single-Dose/Multiple-Dose Studies

7. Bioanalytical Methodology

8. Pharmacokinetic Measures of Systemic Exposure

GENERAL CONSIDERATIONS

- To measure product quality BA and establish BE, on pharmacokinetic measurements may be viewed as a bioassay that assesses release of the drug substance from the drug product into the systemic circulation.
- A typical study is conducted as a crossover study.
- In this type of study, clearance, volume of distribution, and absorption are determined by physiological variables (e.g. gastric emptying, motility, pH) are assumed to have less inter occasion variability compared to the variability arising from formulation performance.
- Therefore, differences between two products because of formulation factors can be determined.

PILOT STUDY

- If the sponsor chooses a pilot study, a small number of subjects can be carried out before proceeding with a full BE study.
- The study can be used to validate analytical methodology, assess variability, optimize sample collection time intervals, and provide other information.

PIVOTAL BIOEQUIVALENCE STUDIES

- General recommendations for a standard BE study based on pharmacokinetic measurements.

STUDY DESIGNS

- Non replicate crossover study designs are recommended for BE studies of immediate-release and modified-release dosage forms.

- The advantages of replicate designs over non-replicate designs includes:

(1) Allow comparisons within-subject variances for the test and reference products.
(2) Provide more information about the intrinsic factors underlying formulation performance.
(3) Reduce the number of subjects participating in the BE study.

STUDY POPULATION

➢It is related to the *in-vivo* BE studies be conducted in general population, taking into account age, sex and race.

1. Subjects recruited for *in-vivo* BE studies be 18 years of age or older and capable of giving informed consent. If the drug product is to be used predominantly in the elderly, the sponsor attempt to include as many subjects of 60 years of age or older as possible.

2. If the drug product is intended for use in both sexes, the sponsor attempt to include similar proportions of males and females in the study.

SINGLE DOSE/MULTIPLE DOSE STUDIES

- The single-dose pharmacokinetic studies for both immediate and modified-release drug products to demonstrate BE because they are *generally* more sensitive in release of the drug substance from the drug product into the systemic circulation.
- The multiple-dose study design is important, appropriate dosage administration and sampling be carried out to document attainment of steady state.

BIOANALYTICAL METHODOLOGY

- The bioanalytical methods for BA and BE studies are accurate, precise, selective, sensitive, and reproducible.

PHARMACOKINETIC MEASURES OF SYSTEMIC EXPOSURE

- Both direct (e.g., rate constant, rate profile) and indirect (e.g., C_{max}, T_{max}, mean absorption time, mean residence time, C_{max} normalized to AUC) pharmacokinetic measures are used to assess rate of absorption. Exposure measures are defined relatively:

A. Early exposure

B. Peak exposure

C. Total portions of the plasma concentration-time profile

EARLY EXPOSURE

• An early exposure measure may be informative on clinical efficacy that measures drug absorption into the systemic circulation. It is recommended that, the use of partial AUC as an early exposure measure.

PEAK EXPOSURE

• For orally administered immediate-release drug products, BE can generally be demonstrated by measurements of peak and total exposure.

• Peak exposure assessed by measuring the peak drug concentration (C_{max}) obtained directly from the curve.

TOTAL EXPOSURE

For single-dose studies, the measurement of total exposure be:

• AUC_{0-t}, where t is the last time point with measurable concentration for individual formulation.

• $AUC_{0-\infty}$, where $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, C_t is the last measurable drug concentration and λ_z is the terminal or elimination rate constant calculated according to an appropriate method.

PHARMACODYNAMIC STUDIES

• Where a pharmacokinetic approach is not possible, suitably validated pharmacodynamic methods can be used to demonstrate BE.

COMPARATIVE CLINICAL STUDIES

• Where there are no other means, well-controlled clinical trials in humans can be useful to provide supportive evidence of BA or BE.

IN-VITRO STUDIES

• Under certain circumstances, product quality BA and BE can be documented using *in-vitro* approaches. This approach may also be suitable under some circumstances in assessing BE during the IND period, for NDA and ANDA submissions.

FOR NDA

- The pH, solubility profile of the drug substance.
- Dissolution profile at different agitation speeds (e.g., 100 to 150 revolutions per minute (rpm).
- 100 to 150 rpm for USP Apparatus I (basket), or 50 to 100 rpm for USP Apparatus II (paddle).
- Dissolution profiles at least in three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer).
- Water can be used as an additional medium. If the drug being considered is poorly soluble, appropriate concentrations of surfactants are recommended.
- It is recommended to select the agitation speed and medium.

FOR ANDA

➢ **For immediate-release drug products:**

• USP method can be submitted. If there is no USP method available, it is recommended for the FDA method for the reference listed drug be used.

• If the USP and/or FDA methods are not available, it is recommended for the dissolution method development report be submitted.

➢ **For modified-release products:**

• USP method can be submitted. If there is no USP method available, it is recommended for the FDA method for the reference listed drug be used.

• In addition, it is recommendable that profiles using at least three other dissolution media (e.g., pH 1.2, 4.5 and 6.8 buffer) and water be submitted.

• The dissolution data from three batches for both NDAs and ANDAs be used to set dissolution specifications for modified-release dosage forms.

COMPARISON OF BA MEASURES IN BE STUDIES

• An equivalence approach has been and continues to be recommended for BE comparisons.

• To compare measures in these studies, data have been analyzed **using an average BE criterion**.

DOCUMENTATION OF BA AND BE

• An ***in-vivo study*** is generally recommended for all solid **oral dosage forms** approved after 1962.

A. Solutions

• For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, ***in-vivo*** BA and/or BE can be used.

• Certain excipients, such as sorbitol or mannitol, that can reduce the bioavailability of drugs with low intestinal permeability in amounts sometimes used in oral liquid dosage forms.

B. Suspensions

• The BA and BE for a suspension generally be established for immediate-release solid oral dosage forms, and **both *in-vivo and in-vitro* studies** are recommended.

C. Immediate Release Drug Products

1. General Recommendations

• For BA and BE studies, a single-dose, fasting study be performed. It is also recommended that *in-vivo* BE studies be accompanied by *in-vitro* dissolution profiles on all strengths of each product.

2. Waivers of in-vivo BE Studies (Biowaivers)

a. INDs, NDAs, and ANDAs: Preapproval

• For preapproval, the *in-vivo* BE demonstrate based **on dissolution tests and an *in-vivo*** study on the highest strength.

• For an NDA, appropriate **dissolution** method has been established, the f_2 test can be used to compare dissolution profile of different strengths of the product. An f_2 value is >50 then the further *in-vivo* studies are not needed.

• For ANDA, conduct an ***in-vivo*** study on any strength of the product.

b. NDAs and ANDAs: Post approval

• For post approval, the *in-vitro* comparison made between the prechange and postchange products. Where dissolution profile comparisons are suggested, it is recommended for the f_2 test. An f_2 value is > 50 then there is no further *in-vivo* studies are needed.

D. Modified Release Products

• Modified-release products include delayed-release products and extended release products.

• Extended-release products can be capsules, tablets, granules, pellets, and suspensions.

• If any part of a drug product includes an extended-release component, the following recommendations are applied :

1. NDAs: BA and BE Studies

• An NDA can be submitted for a previously unapproved new molecular entity, new salt, new ester, prodrug, or other non-covalent derivative of a previously approved new molecular entity formulated as a modified-release drug product.

• The following BA studies can be conducted for an extended release drug product submitted as NDA:

• A single-dose, fasting study on all strengths of tablets and capsules and highest strength of beaded capsules.

• A single-dose, food-effect study on the highest strength.

2. ANDAs: BE Studies

For modified-release products submitted as ANDAs, the following studies are recommended:

(1) A single-dose, non-replicate, fasting study comparing the highest strength of the test and reference listed drug product .

(2) A food-effect, non-replicate study comparing the highest strength of the test and reference product.

3. Waivers of in-vivo BE Studies (Biowaivers): NDAs and ANDAs

a. Capsules

Highest strength - a single-dose, fasting BE study be carried out only.

Lower strength - dissolution profiles.

b. Tablets

- Highest strength - a single-dose, fasting BE study be carried out only.
- Lower strengths - dissolution profiles.

Postapproval Changes

• For postapproval, the *in-vitro* comparison made between the prechange and postchange products.

• Where dissolution profile comparisons are suggested, it is recommended for the f_2 test. An f_2 value of >50 suggests no further *in-vivo* studies are needed.

E. Miscellaneous Dosage Forms

- The rapidly dissolving drug products, such as buccal and sublingual dosage forms (and chewable tablets), be tested for *in-vitro* dissolution and *in-vivo* BA and/or BE.
- The *in-vitro* dissolution test conditions for chewable tablets be the same as for non-chewable tablets of the same active ingredient or moiety.

CONCLUSION

• This is the guidance which will be useful for the applicants planning to conduct BA and BE studies for orally administered drugs during the IND period for an NDA, BE studies intended for submission in an ANDA, and BE studies conducted in the postapproval period for certain changes in both NDAs and ANDA.

REFERENCES

1. Investigation of bioavailability and bioequivalence: The rules governing medicinal products in European Community. Vol. III, addendum 2, 149-169, 1991.
2. Food and Drug Administration (FDA), Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products general considerations. Informal communication by the Center for Drug Evaluation and Research (CDER), March 2003.
3. Food and Drug Administration (FDA), Guidance for Industry: Statistical approaches to establishing bioequivalence. Informal communication by the Center for Drug Evaluation and Research (CDER), January 2001.
4. Food and Drug Administration (FDA), Guidance for Industry: Food-Effect bioavailability and bioequivalence studies, Draft Guidance, Informal communication by the Center for Drug Evaluation and Research (CDER), October 2001.
5. Food and Drug Administration (FDA), Guidance for Industry: Bioanalytical method validation. Informal communication by the Center for Drug Evaluation and Research (CDER), May 2001.


Thank
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