Regulatory Requirements for BE

Nirmal Raj Marasine

Jaya pathak

BIOAVAILABILITY

- According to Food and Drug Administration (FDA) guidance, Bioavailability is defined as: —the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action
- According to World Health Organization (WHO) guidelines, Bioavailability is defined as: —the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action

BIOEQUIVALENCE

- According to Food and Drug Administration (FDA) Guidance, bioequivalence is defined as, —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

- ***Bioequivalence requirement:***A requirement imposed by the FDA for *in-vitro* and/or *in-vivo* testing of specified drug products, which must be satisfied as a condition for marketing.
- ***Bioequivalent drug products***. This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions

- For systemically absorbed drugs, the test (generic) and reference listed drug (brand-name) shall be considered bioequivalent if:

(1) the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses

- (2) the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional…..

, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

- When the above methods are not applicable (eg, for drug products that are not intended to be absorbed into the bloodstream), other *in-vivo* or *in-vitro* test methods to demonstrate bioequivalence may be appropriate.

- Terms use in the *Bioequivalence studies:*

- *Brand name*. The trade name of the drug.
- This name is privately owned by the manufacturer or distributor and is used to distinguish the specific drug product from competitor's products (eg, Tylenol, McNeil Laboratories).
- *Chemical name*. The name used by organic chemists to indicate the chemical structure of the drug (eg, N-acetyl-*p*-aminophenol).

- ***Abbreviated New Drug Application*** **(ANDA**). Drug manufacturers must file an ANDA for approval to market a generic drug product. The generic manufacturer is not required to perform clinical efficacy studies or nonclinical toxicology studies for the ANDA.
- *Drug product*. The finished dosage form (eg, tablet, capsule, or solution) that contains the active drug ingredient, generally, but not necessarily, in association with inactive ingredients.

- ***Generic name***. The established, nonproprietary, or common name of the active drug in a drug product (eg, acetaminophen).
- *Generic substitution*. The process of dispensing a different brand or an unbranded drug product in place of the prescribed drug product. The substituted drug product contains the same active ingredient or therapeutic moiety as the same salt or ester in the same dosage form but is made by a different manufacturer.

- **Pharmaceutical euqivalence**:this term implies that two or more drugs products are identical in strength quality ,purity,content uniformly and disintegration and dissolution characteristics .
- They may, differ in containing different excipients.
- **Therapeutics equivalance**:this term indicates that two or more drugs that contain the same therapeutically active ingredient elicit identical pharmacological effects and can control the disease to the same extent.

Reference Product

- A reference product is a pharmaceutical product with which the new product isintended to be interchangeable in clinical practice.
- The reference product would normally be the innovator product for which efficacy, safety and quality have been established.

- When the innovator product is not available the product which is the market leader may be used as a reference product, provided that it has been authorized for marketing and its efficacy, safety and quality have been established and documented

- Generic products Products whose active pharmaceutical ingredients, dosage form strengths and regimen are the same as those of new products.
- Generic and new products should be the same in the application area of dosage and their physiochemical characteristics should be similar to those of new products.
- Bioequivalence range31 Acceptable range of bioequivalence is generally 0.8% - 1.25% for the test or reference ratio of average values, when the parameters are logarithmically transformed.

- The acceptable range is generally ± 0.2 for the relative difference *in vivo parameters between reference and test products, when the raw data are used*

Bioequivalence: FDA Regulatory Overview

- *INDs-NDAs*
- BE documentation may be useful during the IND-NDA period to establish links between:

  (i) early and late clinical trial formulations;

  (ii) formulations used in clinical studies and stability studies, if different; and

  (iii) clinical trial formulations and the to-be-marketed drug product. In each comparison, the new formulation or new method of manufacture is the test product, and the prior formulation or method of manufacture is the reference product.

- It may not be possibl to conclude BE because the test product produces higher or lower measures of rate and extent of absorption or because the performance of the test or reference is more variable.
- In some cases, "bio*equivalence" is observed because of inadequate* numbers of subjects entered into the BE study
- ***ANDA****s* Sponsors of ANDAs are required to establish BE between a pharmaceutically equivalent generic drug product and the corresponding listed drug

- ***Postapproval Changes*** Information on the types of *in vivo BE studies and in vitro dissolution needed for postapproval changes to drug* products approved as either NDAs or ANDAs are provided in **FDA guidances**
- In the presence of certain major changes in components and composition, and/or method of manufacture after approval, *in vivo BE between pre- and postchange* product may need to be re established.

- Under such circumstances, for approved NDAs, the drug product after change should be compared with the drug product before change, whereas for approved ANDAs, the drug product after change should be compared with the reference listed drug
- **TEST PROCEDURES**
- Several *in vivo and in vitro methods are appropriate* to document BA and BE

- In descending order of preference, the US regulations include pharmacokinetic, pharmacodynamic, clinical, and *in vitro studies .*
- . *Willingness to rely on* test procedures other than clinical studies is based on the assumption that pharmacokinetic and pharmacodynamic approaches and/or *in vitro approaches, along with appropriate* goalposts, adequately reflect clinical safety and efficacy outcomes

- **Pharmacokinetic Studies**

The statutory definition of BA and BE, expressed in rate and extent of absorption of the active moiety or ingredient to the site of action, emphasizes the use of pharmacokinetic measures to indicate release of the drug substance from the drug product with absorption into the systemic circulation.

This approach rests on an understanding that measurement of the active moiety or ingredient at the site(s) of action is

generally not possible and that some predetermined relationship exists between the drug concentration at the site of action relative to that in the systemic circulation.

- A typical BE study is conducted as a crossover study, in which clearance and physiologic variables (*e.g., gastric emptying, motility, and pH)* are assumed to have less interoccasion variability within an individual compared with variability between individuals

- Where needed, a pilot study may be useful to validate analytic methodology, to assess intra- and intersubject variability in systemic exposure measures, and to optimize sample collection times
- Although some authors have stated that multipledose studies are useful in establishing BA and BE , singledose studies to document BE may be preferred because they are generally more sensitive in assessing *in vivo release of the* drug substance from the drug product A goal in BA and BE studies is to assess rate and extent of drug absorption.

- Extent of absorption is readily measured by AUC either to the last sampled time point (AUC0-t) or following extrapolation to time infinity (AUC0)
- Measurement of the true rate of absorption is difficult, given that rate varies continuously over time . A recent FDA guidance, therefore, has recommended that measures of systemic exposure be used to reflect clinically important differences between test and reference products in BA and BE studies .

- These measures include (i) total exposure (AUC0-t or AUC0- for single-dose studies and AUC0-t for steady-state studies), (ii) peak exposure (Cmax), and (iii) early exposure (partial AUC to peak time of the reference product for an immediate-release drug product).
- Reliance on systemic exposure measures will reflect comparable rate and extent of absorption, which in turn, will achieve the underlying goal of assuring comparable therapeutic effects

- **Pharmacologic Effect (Pharmacodynamic) Studies**

Locally acting drug products include oral inhalation drug products, such as metered dose inhalers and dry powder inhalers, and topically applied dermatologic drug products such as creams and ointments.

- .These drug products deliver an active moiety or active ingredient to local sites of action where they exert their primary clinical effects. Pharmacokinetic studies measure systemic exposure but are generally inappropriate to document local delivery BA and BE.

- In such cases, BA may be measured, and BE may be established, based on a pharmacodynamic (PD) study, providing an appropriate PD endpoint is available, which can be studied with sufficient accuracy, sensitivity, and reproducibility.
- Bronchodilator drug products, such as albuterol metered dose inhalers, produce relaxation of airway smooth muscle

- For these drug products, a PD endpoint, based either on increase in forced expiratory volume in 1 s (FEV1) or on measurement of PD20 or PC20 (the dose or concentration, respectively, of a challenge agent) (17,18), is clinically relevant and may be used for BA and BE studies
- An essential component of a BA or BE study based on a PD response is documentation of a dose-response relationship

- The dose-response curve should be characterized as part of the study. In the absence of other evidence, the commonly used Emax model is assumed as the default model.
- To establish BE, the study is conducted in the sensitive region of the dose-response curve .
- A BE study conducted near the plateau of response will be insensitive to differences in drug delivery between the test and reference products and will, thus, require increased numbers of subjects to detect product differences.

- PD response measurements of the test and reference products determined in the BE study may be converted to estimates of delivered dose of the test and reference products by using a dose-scale approach .
- The benefits of the dose-scale approach to BE assessment arise from the translation of nonlinear PD measurements to linear dose measurements

Comparative Clinical Trials

- In vitro bioequivalence studies :
- in viitro studies ,i.e dissolution studies can beused in ileu of in vivo bioequivalence under certain circumstances called as biowaivers (exemptions)-

1) the drugs product differs only in strength of the active substances it contains ,provided all the following conditions hold……..

- Pharmacokinetics are in linear
- The qualitative composition is the same
- The ratio between active substanceand the excipients is the same ,or the ratio between the excipients is the sme
- Both products are produced by the same manufacturer at the same production site.
- A bioavailability or bioequivalence study has been performed with the original product .

- under the same test conditions ,the in vitro dissolution rate is the same

2)The drugs product has been slightly reformulated or the manufacturing method has been slightly modified by the original manufacturer in ways that can convincingly be agrued to be irrelevant for the bioavailability.

3.The drugs product meets all of the following requirements….

- The product is in the form of solution or solubilised form (elixir ,syrup tincture ,etc).

- the product contains active ingredient in the same concentration as the approved drug product.
- The product contains no excipients known to significantly affect absorption of the active ingredient

4. An acceptable IVIVC and the invitro dissolution ratte of the new product is equivalent with that of the already approved medicinal product

More ever ,

- The product is intended for topical administration (cream ,ointment,gel ,etc)for local effect.
- The product is for oral administration but not intended to be absorbed (antaacid or radio – opaque medium)
- The product is administered by inhalation as a gas or vapour

REFERENCES

- U.S. Food and Drug Administration, Title 21 CFR 21 CFR 314.50(d)(1)–(6), Office of Federal Register, National Archives and Records Administration (2001).
- U.S. Food and Drug Administration, Title 21 CFR 314.94, Office of Federal Register, National Archives and Records Administration (2001).
- World Health Organization. *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability.*

- 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
- Rani S, Pargal A. Bioequivalence: An overview of statistical concepts. *Indian J Pharmacol. 2004;36:209–216*

- Guideline for Bioequivalence Studies of Generic Products (December,2006). National Institute of Health Sciences. Japan NIHS. http://www.nihs.go.jp/drug/be-guide(e)/be2006e.pdf. Accessed December 8, 2010.

- Bioequivalence Requirements Guidelines, Saudi Food and Drug Authority Drug Sector. 2005, 5-8.