BCS-based Biowaivers

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ABSTRACT : A biowaiver has been regarded as an official approval of the waiver for conducting a bioequivalence study in the context of an application for drug approval process. Bioequivalence is an important parameter in the process of drug development that is needed to be performed when there is a change in the formulation of dosage form. It has been widely accepted that the in vitro tests for solubility, permeability and dissolution form the basis of a drug product's classification and qualification for biowaivers. The biopharmaceutics classification system (BCS) is a scientific approach for classifying drug substances based on their dose/solubility ratio and intestinal permeability. BCS has been widely implemented for waiving bioequivalence studies on the basis of the solubility and gastrointestinal permeability of drug substance. Hence, BCS-based biowaiver has become an important and cost-saving tool in approval of generic drugs. The present review critically aims to discuss various criteria and requirements for conducting biowaiver study along with various data to support request for biowaivers.

Key words: Biowaivers, BCS class, BABE studies, Drug development.

INTRODUCTION

Biowaiver

A Biowaiver means that in vivo bioavailability and/or bioequivalence studies may be waived (not considered necessary for product approval). Instead of conducting expensive and time consuming in vivo studies, a dissolution test could be adopted as the surrogate basis for the decision as to whether the two pharmaceutical products are equivalent. The risk of therapeutic non-equivalence of two immediate release products can never be reduced to zero, even if a full clinical study is performed. The conclusion of comparative clinical studies, in vivo bioequivalence studies, in vitro equivalence tests and biowaivers is based on statistics and scientific data that are assumed to be representative for the products at issue.[1-4]

Biopharmaceutics Classification System (BCS)[5,6,7]

Class I (High Permeability, High Solubility)

Drugs exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step. Rate of absorption is higher than rate of excretion. e.g. Metoprolol, Diltiazem, Verapamil, Propranolol.

Class II (High permeability, Low solubility)

drugs have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate limiting step for absorption except at a very high dose number. The absorption for class II drugs is usually slower than class I and occurs over a longer period of time. In vitro- In vivo correlation (IVIVC) is usually excepted for class I and class II drugs. e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine.

Class III (Low permeability, High solubility)

drugs, permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. e.g. Cimetidine, Acyclovir, Neomycin B, Captopril.

Class IV (Low permeability, Low solubility)

drugs exhibit a lot of problems for effective oral administration. Fortunately, extreme examples of class IV compounds are the exception rather than the rule and are rarely developed and reach the market. Nevertheless, a number of class IV drugs do exist. e.g. Taxol, Griseofulvin.

CRITERIA FOR BIOWAIVERS[8,9]

The in vivo bioavailability or bioequivalence of the drug product for certain drug products may be self-evident. FDA waives the requirement for the submission of evidence obtained during in vivo demonstrating the bioavailability or bioequivalence of these drug products.

a) If the drug product is a parenteral solution intended solely for administration by injection or an ophthalmic or optic solution.
b) If the drug product contains same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.

Additionally, FDA may waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability or bioequivalence of the drug products:

a) If they are highly soluble: Highest dose is soluble in 250 ml at pH 1.2-6.8.

b) If they are highly permeable: extent of absorption is greater than 85%.

c) If they are rapidly dissolving: 85% or greater by basket method at 100 rpm or by paddle method at 50 rpm in 900 ml at pH 1.2, 4.5, 6.8.

Moreover, for waiver of bioequivalence test and reference products, they should exhibit similar dissolution profile ($f2 \geq 50$).

REQUIREMENTS FOR A BCS-BASED BIOWAIVER STUDY INCLUDE[10]

1 Dissolution Test in 3 different media which are:
   - Buffer pH 1.2, simulated gastric fluid (SGF) without enzymes or 0.1N HCl
   - Buffer pH 4.5
   - Buffer pH 6.8 or simulated intestinal fluid (SIF) without enzymes, all in 900 ml and at 37°C

2 12 samples in each media, paddle rotating at 50 rpm or basket at 100 rpm

3 Sampling times are 10, 15, 20, 30, 45 and 60 minutes.

4 The profiles of the test and reference products must be similar in all three media.

5 The products are similar if the similarity factor f2 ≥ 50 and both products show ≥ 85% dissolution in 15 min

DATA TO SUPPORT REQUEST FOR BIOWAIVERS[11]

Quantities of data to support a request for biowaivers have to be submitted. The drug substance for which a waiver is being requested should be highly soluble and highly permeable. Sponsors requesting biowaivers based on the BCS should submit the following information to the Agency for Review by the Office of Clinical Pharmacology and Biopharmaceutics (for NDAs) or Office of Generic Drugs, Division of Bioequivalence (for ANDAs).

A. Data Supporting High Solubility

The following information should be included in the application:

a) A description of test methods including information on analytical method and composition of the buffer solutions.

b) Information on chemical structure, molecular weight, nature of the drug substance (acid, base, amphoteric or neutral) and dissociation constants (pKa).

c) Test results (mean, standard deviation and coefficient of variation) summarized in a table under solution pH, drug solubility (e.g., mg/ml) and volume of media required to dissolve the highest dose strength.

B. Data Supporting High Permeability

The following information should be included in the application:

a) For pharmacokinetic studies- information on study design and methods used along with the pharmacokinetic data

b) For direct permeability methods information supporting the suitability of a selected method that encompasses a description of the study method; criteria for selection of subjects, animals or epithelial cell line; drug concentrations in the donor fluid; description of the analytical method; and the method used to calculate extent of absorption or permeability

c) Information to support high permeability of a test drug substance should include permeability data on the test drug substance; the internal standards (mean, standard deviation and coefficient of variation); stability

information, data supporting passive transport mechanism where appropriate; and the methods used to establish high permeability of the test drug substance.

C. Data Supporting Rapid and Similar Dissolution

For submission of a biowaiver requesting an immediate release (IR) product should be rapidly dissolving. The following information should be included in the application:

a) A brief description of the IR products used for dissolution testing including information on batch or lot number, expiry date, dimensions, strength, and weight.

b) Dissolution data obtained with 12 individual units of the test and reference products using recommended test methods. The percentage of labelled claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, range (highest and lowest) of dissolution and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included.

c) Data supporting similarity in dissolution profiles between the test and reference products in each of the three media using f2 metric.

CONDITIONS OF GRANT FOR BCS-BASED BIOWAIVERS[12-14]

Dosage forms containing active pharmaceutical ingredients (APIs) which are highly soluble and highly permeable (i.e. BCS class 1), and are rapidly dissolving are eligible for a biowaiver based on the BCS, provided.

a) The dosage form is rapidly dissolving (i.e. no less than 85% of the labelled amount of the API dissolves in 30 minutes

b) The dissolution profile of the multisource product is similar to that of reference product at pH 1, 2; pH 4, 5; and pH 6, 8 buffer using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity, $f2 \geq 50$

If both the reference and the multisource dosage forms are very rapidly dissolving, i.e. 85% or more dissolution at 15 minutes or less in all 3 media under the above test conditions, the two products are deemed equivalent and a profile comparison is not necessary.

CONCLUSION

BCS biowaiver studies in preparing a submission for worldwide filing to satisfy US, European, and emerging market regulators. It is hoped that the availability of BCS Class I and Class III biowaivers in multiple jurisdictions will encourage more sponsors to request waivers of *in vivo* bioavailability/bioequivalence testing using the BCS approach.

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