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## BCS BASED BIOWAIVERS AND THEIR CURRENT REGULATORY ISSUES

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### ABSTRACT

To describe the region wise regulatory guidelines for carrying out biowaiver study in view to possible outcomes in the future along with its importance as major cost saving tool for industry. Bioequivalence is an important parameter in the process of drug development that is performed when there is a change in the formulation of dosage form. The biopharmaceutics classification system (BCS) is a scientific approach for classifying drug substances based on their solubility and intestinal permeability. The bio-relevance of the BCS properties and the in vitro release are best expressed through a correlation between in vitro and in vivo data. It has been estimated for waiving bioequivalence studies on the basis of the solubility and gastrointestinal permeability of drug substance and can be strategically avoided to save time and resources during drug development. 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. Instead of conducting expensive and time consuming in vivo studies, a dissolution test could be adopted as substitute basis for the decision as to whether the two pharmaceutical products are equivalent. Different regulatory authorities have given guidance for carrying out biowaiver study. The biowaiver approval criteria differ from region wise regulatory authorities. This article mainly outlines in detail aspects regarding biowaiver study and issues with regulatory authorities. BCS based biowaiver have given a lot range to generic industry to reduce cost and resources.

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## INTRODUCTION

Bioavailability and bioequivalence studies offer essential information in the whole set of data that assure the availability of safe and effective drugs to patients and practitioners. Bioavailability and Bioequivalence measures are frequently showed in optimal exposure measures, such as area under the plasma concentration-time curve and maximum concentration of drug. These measures of optimal exposure are assumed to co inside in certain way to safety and efficacy results that may be explained in terms of surrogate endpoints, biomarkers, or clinical advantage endpoints. Based on this assumption, Bioavailability and Bioequivalence information has been estimated to give practical and public health value for pharmaceutical sponsors, for regulatory authorities, and for patients and practitioners.

Bioavailability is defined in the Act as “the rate and extent to which the active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, Bioavailability may be estimated by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.” Bioequivalence is defined in the Act as “the absence of a significant difference in the rate and extent to which the 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

With the growth in bioanalytical capacity in the mid- 1950s, available data indicated that compromised product performance, as expressed in BA measures, might be more readily detected. These data led to national and international efforts to define BA and BE and to determine appropriate procedures for their assessment<sup>1</sup>. In 1967 the FDA defined criteria for possible 'problem' drugs, recognizing that bioequivalence is an important issue in drug development. Bioequivalence is even more important in the case of Narrow Therapeutic Index (NTI) drugs<sup>1</sup>.

Bioequivalence studies need to be performed when the formulation of the pharmaceutical dosage form has been changed. Typical examples are changes in the composition, production parameters or process technology. However, for New Chemical Entity's with a high solubility (i.e. the administered dose is soluble in the gastrointestinal fluids) and a high permeability of the gastrointestinal membrane.

Logically, the dissolution profiles of the different formulations should be equal to guarantee Bioequivalence. Thus, both BCS and the alternative linear pharmacokinetics approach require an evaluation of dissolution profiles. The justification of BCS is found in the permeability classification of the compound, those of the linear pharmacokinetics lies in the apparent lack of permeability problem. This may be treated likewise when complying with the aforementioned requirements.

A Biowaiver means that in vivo bioavailability and/or bioequivalence studies may be waived (not considered necessary for product approval). According to WHO it is defined as “The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than *in vivo* bioequivalence test”.

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<sup>2</sup>. At that time the Biowaiver was only considered for scale-up and post approval changes (SUPAC) to pharmaceutical products. More recently, the application of the Biowaiver concept has been extended to approval of certain orally administered generic products.

This article outlines the detail view of biopharmaceutical classification system and its biorelevance, BCS based biowaiver along with regulatory guidelines for carrying out study and its importance as major cost saving tool for industry.

## BASIC ASPECTS OF BIOWAIVER STUDY

The bio-relation of the BCS properties and the in vitro release are shown with a correlation between in vitro and in vivo data. Recently, BCS has been extended for waiving bioequivalence studies on the basis of the solubility and intestinal permeability of drug substance, which can be strategically applied to save resources during generic drug development. There are several basis on which biowaiver study depends.

### In vitro/In vivo correlations

In vitro In vivo correlation has been defined as per FDA as “a prognostic mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response”. Generally; the in-vitro application includes the rate or extent of drug release while the in-vivo response is the amount of drug absorbed<sup>3</sup>.

The United States Pharmacopoeia also defines IVIVC as “the establishment of a relationship between a biological property, and a parameter derived from a biological property produced from a dosage form, and a physicochemical property of the same dosage form”<sup>4</sup>.

### Developing the correlation

The basic requirements for developing In vivo In vitro co relation are<sup>5</sup>

- Two or more drug product formulations with different dissolution rates are developed and there in vitro dissolution profiles generated using an appropriate dissolution method.
- Information obtained from human studies are required for regulatory consideration of the correlation
- The dissolution method use for all the formulations should be same.
- Plasma concentration data from a bioavailability study for each of the formulations.

### Models of IVIVC

The most basic IVIVC models are expressed as a simple linear equation between in vitro drug dissolved and in vivo drug absorption.

$$Y = bx + m$$

Where Y is the in vivo drug absorbed and x the in vitro drug dissolved, m the slope of the relationship and m the intercept. Ideally, b= 1 and m = 0, indicating a linear relationship.

This equation can applied to many of formulations with comparable in vitro and in vivo profiles<sup>6</sup>. However, for dosage forms with complicated mechanisms of release, which are usually of longer duration, in vitro release may not be on the same time scale as the in vivo release. Thus, in order to model such data, it is essential to include time-shifting and time-scaling parameters within the model.

While selecting any compound for biowaiver study IVIVC data is considered for assessment of similarity between two pharmaceutical products. IVIVC is major pedestal for biowaiver study.

## BIOPHARMACEUTICS CLASSIFICATION SYSTEM

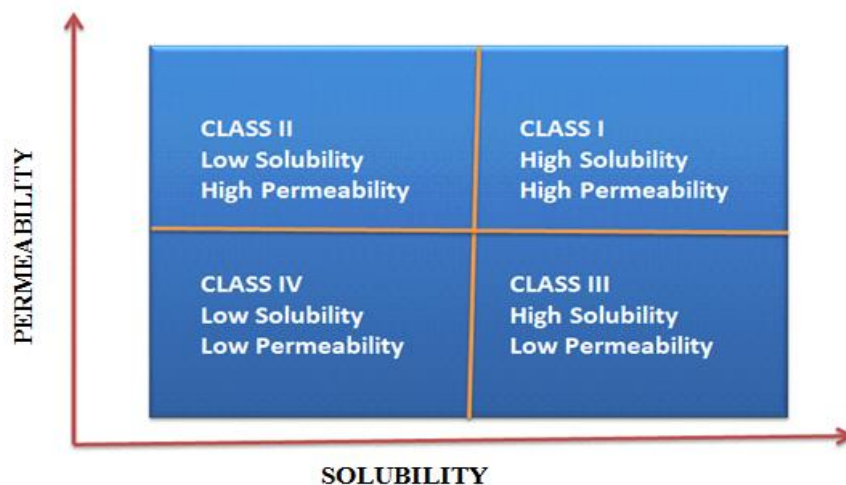
The BCS concept was developed by Gordon Amidon in 1995. The Biopharmaceutics Classification System is guidance for assessment of the drug absorption. It is classification system involving scientific framework of drug classification based on their aqueous solubility and intestinal permeability. There are three major pedestals of BCS that governs the rate and extent of drug absorption from dosage form. They are dissolution, solubility, and intestinal permeability<sup>7</sup>.

The BCS has taken up the interest of investigators because of its application in prior aspects of drug development. Nowadays a guidance document named "Waiver of in Vivo Bioavailability and Bioequivalence

Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties Based on a Biopharmaceutics Classification System" which extends the regulatory applications of BCS and also suggests methods for classifying drugs<sup>8</sup>. Drugs are divided into high or low-solubility and permeability classes. At present, BCS guidelines are provided by various regulatory authorities like World Health Organization and European Medicines Academy, U.S. Food and Drug Administration. The basic principle behind BCS is that drugs having yield the same solubility and permeability profile then they will result in the same plasma profile.

In consideration of bioequivalence that highly permeable, highly soluble drugs comes under the class of rapidly dissolving drug and both products will be bioequivalent and that, unless major changes are made to the formulation, dissolution data can be used as a surrogate for pharmacokinetic data to demonstrate bioequivalence of two drug products.

According to BCS, drug substances or active pharmaceutical ingredients are divided into high/low solubility and permeability classes as follow:



**Figure 1:** Graphical representation of Biopharmaceutical Classification system

This association of the system with drug absorption results in the identification of parameters controlling drug absorption.

### Solubility

The solubility class boundary is differing with regulatory authority guidelines. The class boundaries depend on the highest dose strength of drug. According to World Health Organization guidance an API is considered highly soluble when the highest dose is soluble in 250 ml or less of aqueous media over the pH range of 1.2-6.8. The pH-solubility profile of the API should be determined at  $37 \pm 1.8$  °C in aqueous media. According to U.S. Food and Drug Administration BCS guidance a drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. A minimum of three replicate determinations of solubility at each pH condition is recommended according to European Medicines Academy BCS guidance a drug substance is considered highly soluble if the highest single dose administered as formulation is completely dissolved in 250 ml of buffers within the range of pH 1-6.8 at  $37 \pm 1.8$  °C.

### Permeability

The permeability of drug is depends on extent of absorption of a drug substance in humans and the rate of mass transfer across gasointestinal membrane. According to World Health Organization guidance, a drug is considered highly permeable when the extent of absorption in humans is 85% or based on a permeability determination or in comparison with an intravenous comparator dose (absolute bioavailability). U.S. Food and Drug Administration considers BCS guidance which states absence of instability in the GI tract, a drug

substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on permeability determination or in comparison to an intravenous reference dose.

## **DETERMINATION OF PERMEABILITY**

Permeability along with solubility forms the backbone of BCS that helps in accessing oral absorption of drug molecules.

### **[i] Human Methods**

#### **Mass balance**

This method can provide highly variable estimates of drug absorption for many drugs. The mass balance studies provide the extent of absorption by using radio labeled drug or isotopes<sup>9</sup>.

#### **Absolute bioavailability**

Absolute bioavailability is determined by using intravenous administration as reference with oral administration<sup>10</sup>.

#### **In vivo intestinal perfusion**

Intestinal perfusion could be performed by a simple perfusion of an intestinal segment or by a double perfusion of the intestine and the vascular bed simultaneously<sup>11</sup>. The double perfusion has the advantage of measuring the substrate appearance in the vascular circuit.

### **[ii] Animal Methods**

#### **In vivo or In situ intestinal perfusion**

In this type of study animal intestine are isolated and treated with buffer solution containing drug. Intestine perfused in the buffer solution and sampling is done at proper interval<sup>12</sup>.

### **[iii] In Vitro Methods**

#### **Excised human or animal intestinal tissue**

It is intestinal tissue models based on the human adenocarcinoma cell line *Caco-2*. These cells are function as a model for intestinal tissue<sup>13</sup>. The Present researches on *Caco-2* cell lines have shown their ability to transport ions, sugars and peptides.

#### **Epithelial cell monolayer**

This study is carried out by culturing monolayers of animal or human epithelial cells are considered appropriate for passively transported drug<sup>14</sup>.

### **Requirements for a biowaiver study<sup>15</sup>**

- a) Permission of regulatory authorities like WHO, FDA, EMEA etc. Active pharmaceutical ingredient should have high solubility and high permeability according to bio-pharmaceutics classification system (BCS I). Other classes are part of current discussion.
- b) The In vitro dissolution study in Three different media (A. Buffer pH 1.2, Simulated Gastric Fluid without enzymes or 0.1N HCl, Buffer pH 4.5, C. Buffer pH 6.8 or Simulated Intestinal Fluid without enzymes) all in 900ml and at 37°C
- c) 12 Samples in each media, paddle 50rpm or basket 100rpm Sampling time: 10, 15, 20, 30, 45 and 60 minutes sampling time depends on type of dosage for according to WHO.
- d) The data of the test and reference products must be similar (in all three media).
- e) The products are considered similar if the similarity factor  $f_2$  is 50 or more and both drugs show 85% dissolution in 15 min.

For of a biowaiver request submission, it's essential to submit data supporting similarity in dissolution profiles between the test and reference products in each of the three media, using the  $f_2$  method. The total time requirement for the study is 7 hours.



## Dissolution Profile Comparison<sup>16</sup>

### Difference factor (f1)

Difference in percent dissolved between reference and test at various time intervals. The difference factor is important while comparing pharmaceutical products. The difference factor should not be more than 15%.

$$f1 = \left[ \frac{\sum_{t=1}^n |Rt - Tt|}{\sum_{t=1}^n Rt} \right] \times 100$$

### Similarity factor (f2)

It defines comparison of closeness of two comparative formulations. n=12 of reference and test or post change product. The results of 50 or greater indicate bioequivalence or similarity

$$f2 = 50 \times \log \left\{ \left[ 1 + \left( \frac{1}{n} \right) \times \sum_{t=1}^n (Rt - Tt)^2 \right]^{-0.5} \times 100 \right\}$$

Where

n = the number of dissolution time points

Rt = mean % drug dissolved of the reference product at time t

Tt = mean % drug dissolved of the test product at time t

## COMPOSITION PROPORTIONALITY

### Basis of biowaiver for strength

A prerequisite for qualification for a biowaiver based on dose-proportionality of formulations is that the multisource product at this strength has been shown to be bioequivalent to the corresponding strength of the comparator product<sup>17</sup>. The second requirement is that the further strengths of the multisource product are proportionally similar in formulation to that of the studied strength. When both of these criteria are met and the dissolution profiles of the further dosage strengths are shown to be similar to the one of the studied strength on a percentage released vs. time basis, the biowaiver procedure can be considered for the further strengths.

Three strengths, BCS class I API, RLD for two strengths- higher and middle, BE study waiver for lower strength is based on-

- (i) Acceptable bioequivalence studies on the higher strength,
- (ii) Proportional similarity of the formulations across all strengths, and
- (iii) Acceptable in vitro dissolution testing of all strengths.

All strengths composition is dose proportionate, except 10 % more ER polymer (SUPAC level II change) in lower strength

### Criterion for Active Pharmaceutical Ingredient and Excipients

While considering the criteria for API and Excipient there two things

1. They should be qualitatively same. It is necessary by means of if we have to justify the similarity between to pharmaceutical products.
2. They should be quantitatively proportional

### Excipients

- (i) Excipient which is to be used should not have any interaction with the pharmacokinetic of the active substance expected.
- (ii) Also should not affect the rate and extent of absorption
- (iii) In case of atypically large amounts of known excipients or new excipients being used, additional documentation has to be submitted<sup>18</sup>

## Regulatory necessities for Biowaivers

### A) Documentation while applying for biowaivers study

Amount of Information to support application for biowaivers have to be submitted. The active pharmaceutical ingredient for which a waiver is being requested should be highly soluble and highly permeable. Sponsors requesting the BCS based biowaivers 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)<sup>19</sup>

- (i) A detail of test methods including information on analytical method and composition of the buffer solutions.
- (ii) Test results arranged in a table under solution pH, drug solubility and volume of media required to dissolve the highest dose strength.
- (iii) Information on chemical structure, molecular weight, nature of the drug substance dissociation constants.
- (iv) A graphical presentation of mean pH-solubility profile.

### B) Documentation for Immediate and Similarity Dissolution

For submission of a biowaiver application an immediate release product should be rapidly dissolving. The following information should be included in the application [20]

- (i) A short description of the products used for dissolution testing including information on batch number, expiry date, dimensions, weight and strength.
- (ii) Dissolution results estimated with 12 individual units of the test and reference samples using suggested test methods. The percentage of labeled claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, range of dissolution and relative standard deviation should be arranged in table. The mean dissolution profiles for the test and reference products in the three media should also be included.
- (iii) Results supporting similarity in dissolution profiles between the test and reference listed products in each of the three media using similarity product (f2).

### Scale Up Post Approval Changes (SUPAC)

SUPAC-IR means for “Immediate release solid oral dosage forms: Scale-up and post-approval changes: chemistry, manufacturing, and controls, in vitro dissolution testing, and in vivo bioequivalence documentation”. The documents describe the required in vitro dissolution and in vivo bioequivalence studies for post approval changes. Possible changes are clustered in different sub-groups, for example changes in components and composition, site changes, changes in batch size and changes in the manufacturing method. Each sub-group is divided into several levels, and the complexity increases from levels 1 through 3. For each level the required data package to support a certain change is described, especially if there is an in vivo bioequivalence study necessary or if such a study can be waived<sup>21</sup>. The documents give detailed guidance to applicants and are very helpful for deciding to perform or to waive a bioequivalence study for post approval changes. Mostly, this approach is comparable to the EMEA, but in the US FDA there is simply more detailed guidance available.

## Regulatory authorities and guidelines for biowaivers

### European Medicine Agency<sup>46,47</sup>

Similar to US FDA, Europe Medicines Agency also allows biowaivers for BCS 1 only, whereas, the proposed guidelines also permit BCS 1 and 3 biowaivers. However unlike US FDA guidance 85% absorption is considered as the permeability limit. However, there is a requirement for rapid drug product dissolution. The proposed guidelines define rapid as 15 min for both BCS classes. The media are slightly different; 1) pH 1.2 2) pH 4.6 and 3) pH 6.8 buffers.

The proposed guideline changes it to

- 1) pH 1.2 (0.1 N HCl)
- 2) pH 4.5
- 3) pH 6.8 or SIF without enzymes.

Moreover, the dissolution tests or bioequivalence studies are wanted when drug product performance could potentially be affected. These small processing changes such as embossing increased film coating weight and addition of a new test to the drug substance or excipient specifications.

**Table 1:** List Biowaiver monographs with BCS Class <sup>22-45</sup>

Sr. no	Biowaiver Monograph	BCS Class	Biowaiver Recommendation
1	Acetyl Salicylic acid	I	Possible
2	Doxycycline hyclate	I	Possible
3	Amitriptyline Hydrochloride	I	Possible
4	Quinine Sulphate.	II	Not Possible
5	Prednisolone	I	Possible
6	Ranitidine Hydrochloride	III	Possible
7	Chloroquine Phosphate	I	Possible
8	Prednisone	I	Possible
9	Cimetidine	III	Possible
10	Isoniazid	I	Possible
11	Furosemide	IV	Not Possible
12	Ibuprofen	II	Not Possible
13	Ethambutol Dihydrochloride	III	Possible
14	Ciprofloxacin Hydrochloride	II	Not Possible
15	Acetazolamide	IV	Not Possible
16	Aciclovir	III	Possible
17	Diclofenac potassium	II	Not Possible
18	Lamivudine	III	Possible
19	Quinidine Sulfate	III	Not Possible
20	Rifampicin	II	Not Possible
22	Mefloquine Hydrochloride	II	Not Possible
23	Stavudine	III	Possible
24	Metronidazol	I	Possible
25	Pyrazinamide	III	Possible

### United States Food and Drug Administration

The United States biowaiver guidance is based on the commonly known Biopharmaceutics Classification System. The US FDA allows biowaivers for only rapidly dissolving BCS 1 drug products. High permeability is defined as 90% absorption in tests outlined in the guidance document<sup>48</sup>. Rapidly dissolving includes that 85% or more of the dosage is dissolved in 30 minutes in three media;

- 1) 0.1 N HCl
- 2) pH 4.5 buffer
- 3) pH 6.8 buffer or simulated intestinal fluid (SIF).

### World Health Organization

The immediate release multisource product should possess very rapid in vitro dissolution in order to skip in vivo pharmacokinetic bioequivalence study. The demonstration of similarity by dissolution between the Reference Listed Drug and Generic products is mandatory for providing sufficient proof of exemption of bioequivalence testing.

### BCS based Biowaiver Criteria

Considerations of BCS based Biowaiver:



- (i) The excipients used in the formulation
- (ii) API solubility and permeability
- (iii) The similarity of dissolution profile between RLD and Generic drug product.
- (iv) The risks assessment of waiver study and impact of incorrect decision.

Conditions for BCS based biowaiver for solid oral dosage form<sup>49</sup>.

1. BCS Class 1 drugs which are rapidly dissolving are eligible for a BCS biowaiver based on the provided:
  - (i) The rapidly dissolving drug with similarity of RLD and Generic demonstrated in all three medias i.e. pH 1.2, pH 4.5 and pH 6.8 buffers using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity,  $f_2 \geq 50$ .
2. BCS Class III drugs of highly soluble and have low permeability are eligible for biowaivers criteria and the risk assessment based on amount and mechanism of absorption.

Commonly the risks of reaching an unsuitable biowaiver verdict require to be more seriously evaluated when the extent of absorption is lower (especially if  $f < 50\%$ ), if the sites of absorption are restricted to the proximal regions in the gastrointestinal tract and if the mechanism of absorption is subject to competition. If it is believed that the risk of attainment of a wrong biowaiver decision and its associated risks to public health and for individual patients is acceptable, the multisource product is eligible for a biowaiver based on BCS.

APIs having high solubility at pH 6.8 but not at pH 1.2 or 4.5 and with high permeability are appropriate for a BCS based biowaiver provided that criteria, that the API has high permeability and a dose: solubility ratio of 250 ml or less at pH 6.8, and that the multisource product<sup>50</sup>

- a. It should be 85% soluble in pH 6.8 buffer.
- b. The Generic product shows similar dissolution profiles,  $f_2$  value should be to those of the Reference Listed product in buffers at the three pH values (pH 1.2, 4.5 and 6.8).

### Therapeutic Goods Administration- Australia

TGA has considered the criteria of European medicine agency guideline with some modification. Generic applications requires demonstration of bioequivalence versus the reference Listed product. The guidelines states "biopharmaceutics data are not normally required" a number of applications for which bioequivalence studies can usually be waived<sup>51</sup>.

- API Solubility
- Therapeutic index
- Similarity proven in comparison of in vitro dissolution profiles across pH range 1 - 7.5 between the products being considered

### Agencia Nacional de Vigilancia Sanitaria- Brazil<sup>52, 53</sup>

In case of Brazil BCS based biowaiver is explained in resolution – RDC N° 37. Only active pharmaceutical ingredients of BCS class 1 are acceptable for this biowaiver. The drugs qualified as candidates for a BCS based biowaiver is published in normative instruction – N° 4, 3. As usual, for BCS based approaches the following data need to be provided:

- Information to estimate the high solubility and permeability of the drug substance
- Information to show immediate and identical dissolution across pH 1.2 – 6.8 between test and reference products
- Data to prove that the excipients do not affect bioavailability (preferably the same excipients should be included in the test and reference product)

Fixed combinations are explicitly mentioned as having access to a BCS based biowaiver if the criteria are met for all drug substances included in such a fixed combination. The BCS based biowaiver is not applicable for substances of low therapeutic index, for certain product categories (contraceptives, vitamins) and for modified release dosage forms.

### Food and Drug Regulations- Canada

Food and Drug Regulations do not clearly state biowaiver preferences, apart from the over passing approach<sup>54</sup>. But in principle there is an opportunity to waive unnecessary bioequivalence studies, for example for specific dosage forms like oral solutions, for additional dose strengths and for scale up and post approval changes if certain prerequisite are satisfied. The basics are comparable to those in the EU or USA. The BCS concept is still not applied in Canada. However, the basic BCS considerations, for example the solubility and permeability of the drug substance, the in vitro dissolution behavior of the drug product and some other product specific characteristics play an important role for the bridging approach. The generic applicant must submit a justification for not performing a bioequivalence study versus the Canadian reference product, but instead versus another reference product from a highly regulated market. Such a justification should address all of the above mentioned criteria.

### CONCLUSION AND FUTURE PERSPECTIVES

The article concludes biowaiver as trending regulatory issue for generic industry. Currently there are several application are under review for waiving bioequivalence for many new or generic drug formulations. BCS based biowaiver has major advantage of cost and resource reduction. It avoids ethical problem comes with unnecessary testing of drugs on human subjects. Logically small change in formulation should not affect the performance of drug so similarity can be proved with in vitro dissolution study. The regulatory authorities have given certain guidelines for carrying out the biowaiver study, along with criteria for drug for study. The difference in regulatory allowance still is major part of discussion.

It is expected in upcoming time the regulatory authorities will consider other classes of BCS for biowaiver study based on risk assessment. The lowering of regulatory burden will result in regulatory relief without loss of product quality. The regulatory authority still reviewing several drugs for biowaiver study but still distance to go for product approval based on in vitro data.

### Authors' Statements

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### Competing Interests

The authors declare no conflict of interest

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