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*Review*

# Comparative analysis of biopharmaceutic classification system (BCS) based biowaiver protocols to validate equivalence of a multisource product

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**Biopharmaceutic classification system (BCS) is a substantial part of drug designing and generic product development and has been accepted as a technique to renounce in-vivo pharmacokinetic evaluation (biowaiver). It appeared to be worthwhile and time-saving by means of in-vitro studies in the presence of biorelevant physiological mediums that mimic not only the predictable solubility but also permeability of the multisource product. Such methodology is now applied as a regulatory stamp to support new and generic product approvals based on other than in-vivo equivalence testing. This article outlines the foundation of BCS, its implementation in granting biowaiver, adequacy of in-vitro bioequivalence studies, principles and requirements of BCS biowaiver by four regulatory agencies such as; Food and Drug Authority (FDA), World Health Organization (WHO), European medicine agency (EMA) and International Conference on Harmonization (ICH), potential effect of excipients on solubility and permeability of drug molecules and supplementary data provided by FDA regarding biowaiver approvals. Furthermore, supportive data provided by the International Pharmaceutical Federation (FIP) has also been given for biowaiver sanction of certain drug products. It has been concluded, that although biowaiver is a profitable methodology for generic and new drug product approval, the variance in the standards of governing bodies demands more critical assessment to establish some unified principles to be followed globally.**

**Key words:** Biopharmaceutics classification system, bioequivalence, biowaiver.

## INTRODUCTION

The clue about biopharmaceutic classification system (BCS) was first initiated by the American Department of Health and Human Services, Food and Drug Administration in 1995 with the intent of waiving in-vivo

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**Table 1.** Biopharmaceutic classification scheme (WHO, 2006; Lindenberg et al., 2004).

| BCS class | Criteria | Example |
|---|---|---|
| BCS Class I (high solubility - high permeability) | Rapidly dissolve with good absorption. The rate-determining steps are a dissolution or gastric emptying. The release is not related with dissolution so Precise dissolution studies must be performed to confirm bioavailability | Metoprolol, amlodipine, allopurinol, verapamil, propranolol, acetylsalicylic acid, etc. (WHO, 2006). |
| BCS Class II (Low solubility - high permeability) | Drugs are absorbed well (lower than class I) but inconsistent due to formulation and *in-vivo* factors. Dissolution is rate-dependent and it must have biorelevant dissolution media to mimic the in-*vivo* environment. Predictable in-*vivo* in-*vitro* relationship | Ibuprofen, naproxen, ketoprofen, ezetimibe, glibenclamide, carbamazepine, etc. (WHO, 2006). |
| BCS Class III (high solubility - low permeability) | The rate-determining step is permeability. Drug absorption could be non-uniform. Precise dissolution profile, partial or unpredictable *in vitro-in vivo* correlation | Cimetidine, ranitidine, vancomycin, chloramphenicol, acyclovir, abacavir, atenolol (WHO, 2006) |
| BCS Class IV (low solubility - low permeability) | Unreliable bioavailability and must require an alternate route of administration other than oral. Complications with drug delivery and un-predictable in-vitro-in-vivo association. | Hydrochlorothiazide, furosemide, indinavir, nelfinavir, ritonavir, aluminium hydroxide (Lindenberg et al., 2004). |

bioavailability and bioequivalence studies (Biowaiver). It is defined as a "technique where *in-vivo* bioavailability/bioequivalence studies are not obligatory for product approval" (Food and Drug Authority - FDA, 2017; WHO Biowaiver list, 2018; EMA, 2010; World Health Organization - WHO, 2015; International Conference on Harmonization - ICH, 2018). These biowaiver studies waive time-taken and burden of cost put away in pharmacokinetic studies and conduct only *in-vitro* dissolution test to determine whether drug products are bioequivalent or not (Ploger et al., 2018). Although the regulatory agencies documented that in-vivo bioavailability/bioequivalence studies are obvious for some products that preclude the prerequisite of *in-vivo* confirmation in some situations (FDA, 2017; WHO Biowaiver list, 2018; EMA, 2010; WHO, 2015; ICH, 2018).

BCS has played a key role in waiving bioavailability/bioequivalence requirements (Camenisch, 2016; Bodhe and Kaur, 2018). It is based on evidences that if (Liberti et al., 2010) (a) the two comparator immediate release (IR) products behave as oral liquid mixture within the gastrointestinal (GI) tract owing to their greater solubility and rapid dissolution; (b) the drug product does not precipitate in the alimentary canal after it is dissolved; and (c) to be bioequivalent both products show similar *in-vivo* performance at different intestinal pH with identical rate and extent of absorption (Amidon et al., 1995). In 1995, FDA presented the BCS system for giving biowaiver status and only class I drugs were allowed for biowaiver studies. Class I belongs to those active pharmaceutical ingredients (APIs) which are highly soluble with high permeability and are formulated in solid, immediate-release oral formulations (WHO, 2006; Camenisch, 2016; Levin, 2001). Thus, dissolution and permeability are two important parameters that control the absorption of drugs (Chen et al., 2011; Wu and Benet, 2005) as recommended by Amidon in 1995 following BCS. This statement was supported by Fick's first law of diffusion which states that permeability of drug and its concentration over GI tract follows parallel relationship expressed as; $J = P_wC_w$ (J = diffusion flux, $P_w$ = permeability, $C_w$ = concentration difference) (Shargel and Yu, 2005; Verbeeck and Musuamba, 2012). Therefore, BCS forms the technical foundation to classify drugs on the basis of their intestinal permeability and solubility (Shah et al., 2014; Sugano, 2016). This classification entitles drugs falling in any class ranging from I to IV (Chen et al., 2011; Ploger et al., 2018) shown in Table 1.

EMA and WHO has issued guidelines agreeing BCS biowaivers for drugs belongs to Class I and III (EMA, 2010; WHO, 2015). Previously, some weak acidic drugs that belongs to BCS class II were also considered by WHO as biowaiver candidate (Kanfer, 2015) but presently allows biowaiver for class I and III drugs. In 2017, FDA reviewed its BCS guidelines and biowaiver status was confined to class I and III substances (FDA, 2017). Besides this, both EMA and FDA has supported the concept of BCS based biowaivers and issued guidelines for particular products (EMA, 2015; FDA,2010). Additionally, 44 biowaiver monographs has been published by IPF (2015). Currently, BCS biowaiver system has been adopted by various developing nations, formed on the basis of WHO guiding principles or guidelines issued by specific governments. Hence, today BCS biowaiver is broadly recognized in the manufacturing, regulatory and academic zones for drugs, belongs to BCS class I and class III as given in Figure 1 (Chen et al., 2011; Shah et al., 2014; Helmy and El Bedaiwy, 2016). Though, consistent efforts have been made to establish harmonization between regulatory

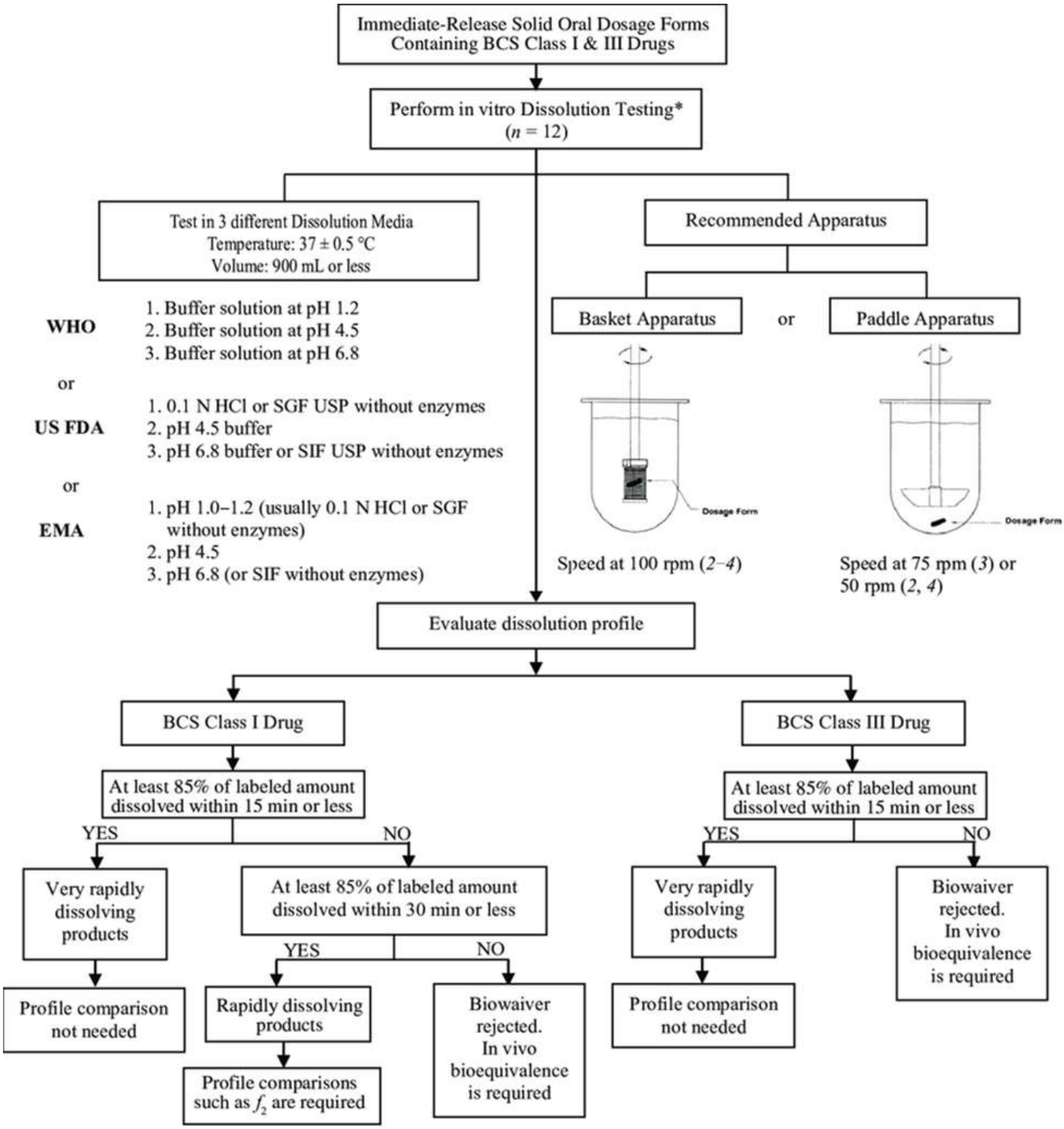


**Figure 1.** Comparative biowaiver guidelines for drugs belongs to BCS class I and class III.
Source: Helmy and El Bedaiwy (2016).

agencies on BCS biowaiver application, but still numeral variations exist among them, particularly in Japan, where BCS biowaiver has not been applied entirely. This must be a challenging scenario for companies, who pursue BCS biowaiver techniques for their innovator and generic products to be registered globally. Therefore, the purpose of current study was aimed to highlight the significance of BCS biowaiver study; competence of *in-vitro*

**Table 2.** Requirements for obtaining biowaiver based on BCS.

| Requirement | Regulatory agency | | | |
|---|---|---|---|---|
| | ICH M9 | FDA | WHO | EMEA |
| | BCS class | | | |
| | Class 1 & III | Class I & III | Class I, II & III | Class I & III |
| Solubility requirements | The highest single therapeutic dose is 48 completely soluble in 250 ml or less of aqueous media over the pH range of 1.2 - 6.8 at 37 ± 49 1°C | High solubility must be soluble in ≤ 250 ml, pH 1-7.5; the highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1 - 6.8 at 37 ± 1°C | For class II eligible only if D:S is 250 ml or lower at Ph 6.8 | The highest single dose must be soluble in ≤250 ml, pH 1.2 to 6.8, 37°C |
| Dissolution media | Buffer pH 1.2, pH 4.5, and pH 6.8 at 37 ± 1°C | Buffer pH 1.2, 4.5 and 6.8 at 37°C | Buffer pH 1.2 (0.1 N HCl), 4.5 and 6.8 at 37°C | Buffer pH 1.2, 4.5 and 6.8 at 37°C |
| Volume of medium | 900 ml or less | 500 mL or less (or 900ML) when properly justified | 900 ml | 900 ml |
| Apparatus and rpm | Paddle: 50 rpm Basket: 100 rpm | Paddle: 50 rpm<br>Basket: 100 rpm | Paddle: 75 rpm<br>Basket: 100 rpm | Paddle: 50 rpm<br>Basket: 50 rpm |
| Dissolution profiles | Not more than one mean value of ≥85% dissolved for any of the products | Rapidly dissolving; 85% in 30 min.<br>≥85% in 15 min (very rapidly dissolving) | Very rapidly dissolving; >85% in 15 min; Rapidly dissolving; >85% in 30 min | Very rapidly dissolving; >85% in 15 min. Rapidly dissolving; >85% in 30 min |
| No. of units | N/A | 12 | 12 | 12 |
| Dissolution profile comparison | *f*2 | *f*2 | *f*2 | *f*2 |

Sources: Arrunátegui et al. (2015), Davit et al. (2016) and Rohilla et al. (2012).

bioequivalence studies, principles and requirements of BCS biowaiver by various regulatory agencies, need of harmonization among them for BCS biowaiver protocol and to understand the possible effects of excipients on solubility and intestinal permeability of active drug ingredients.

## TECHNICAL BASIS FOR BIOWAIVERS

A thorough evaluation of literature was performed in pursuit of a technical foundation that allowed the presentation and discussion of the laws cited which were mainly reported by the FDA, WHO, EMA and ICH (Table 2). Besides using BCS as the underlying principle for waiving bioequivalence studies it has been proposed that biowaivers can also be approved for data based on standard pharmacokinetics. Presence of rapid dissolution profile and if a drug displays dose-linear pharmacokinetics, it is absolute that the drug produces no hassle with respect to its absorption (WHO, 2006). “Two drug substances are thought to be comparable/alternative/substituent to one another in terms of peak drug concentration in blood vs. time (AUC; area under the curve) after administration of the identical single dose following similar settings and their bioavailabilities are comparable at a point where they give identical profiles” (WHO, 2006). Identical dissolution profiles can justify the bio-equivalence of two products. Thus, BCS and alternative linear pharmacokinetic methodology require an assessment of dissolution profiles (Faassen and Vromans, 2004; Charalabidis et al., 2019), therefore bioequivalence can also be obtained by using dissolution data as an alternative of pharmacokinetic data (Dressman et al., 2001).

Similarity among the dissolution profiles were calculated by applying difference factor ($f_1$) and similarity factor ($f_2$). Difference factor ($f_1$) indicates the average difference in the percentage of drug dissolved at all time points, its value is between 0 and 15 if the reference and test product release profiles are indistinguishable. It can be increased consistently with increasing dissimilarity (Anderson et al., 1998; Charalabidis et al., 2019). Whereas, “similarity factor $f_2$” is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves. Its value is between 50 and 100 for equivalent dissolution profiles” (FDA, 2017; Charalabidis et al., 2019). In cases where both products dissolve ≥ 85% in 15 min in biowaiver buffer mediums than $f_2$ comparison is not mandatory (WHO, 2006; FDA, 2017; EMA, 2010). FDA identifies both but generally, $f_2$ is preferred (O’Hara et al., 1998).

Mainly, parameters affecting the technical basis for

biowaiver extension of drugs are solubility, permeability and BCS classification. The BCS class I immediate release product may be accepted as biowaiver, if it encompasses excipients with no impairment on the absorption rate and extent of oral drugs. Also, such drugs must not be a narrow therapeutic index drug with good stability in the GI tract. For biowaiver allowance, it must not have absorption in the oral cavity. This makes an impression for BCS class I drugs that the difference in the rate and extent of absorption of pharmaceutically alike drugs is due to the difference in the *in-vivo* drug dissolution (Yu et al., 2002).

In case of BCS class II drugs, technical justification for biowaiver allowance is still debatable. This class of drugs shows limited oral absorption by *in-vivo* dissolution. Intestinal absorption of class II drugs is mainly influenced by pH and nature or type of surfactant. The presence of certain excipients in the formulation might produces effects on the solubility and permeability of these drugs. It is believed that addition of suitable surfactants, for example, sodium lauryl sulfate (SLS) or any other surfactant can mimic *in-vivo* solubilization and also sustain sink conditions for absorption. For example, the amount of SLS in the dissolution medium is 0.5, 0.75, 1 and 2% for medroxyprogesterone acetate tablet, danazol capsule, carbamazepine tablet, and flutamide tablet respectively (USP 24-NF19, 2001). However, the addition of a surfactant is not only sufficient for predicting the *in-vivo* dissolution. Considerable efforts and research in this perspective is still needed to develop such a dissolution medium which mimic *in-vivo* dissolution condition (Yu et al., 1999). Dissolution studies based on “Biorelevant Dissolution Medium” (BDM), with/without physiological modeling and *in-vivo* bioequivalence test were also performed, to evaluate bioavailability and pharmacokinetics of BCS class II drugs in humans (Khandelwal et al., 2007).

High-soluble low-permeable BCS class III drugs can be granted a biowaiver if it follows similar standards as given for class I drugs (Blume and Schug, 1999). The permeability factor will limit the absorption which is less likely to be affected by formulation factors, whereas *in-vivo* permeability determines bioavailability (Blume and Schug, 1999; Polli and Ginski, 1998). FDA has conducted survey for about 10 BCS class III drugs. The results showed that these drugs demonstrate site-dependent absorption characteristics, which are not affected by the nature of used excipients, rather they may affect motility and permeability (Lee, 2000; Wacher et al., 2001). Certain excipients reduce the GI transit period, therefore, GI transit period serves as a critical factor for bioequivalence proposing more strict criteria for dissolution to make sure complete dissolution in the stomach (Koch et al., 1993). Apart from *in-vivo* pharmacokinetic studies, presently only Caco-2 permeability studies are endorsed in the ICH harmonised guideline (ICH, 2018; Jarc et al., 2019). A study conducted to determine consequence of Caco-2 permeability for some formulation excipients showed that permeability across Caco-2 monolayers did not aggravate by such excipients (Rege et al., 2001). Excipients like sugar, alcohols (Adkin et al., 1995), sodium acid pyrophosphate may influence small intestine transit period (Koch et al., 1993). Therefore, transit-influencing excipients like alkanoyl surfactants, mucoadhesive polymers, medium-chain glycerides, cholines, steroidal detergents, acylcarnitine, and fatty acids should be excluded from class III for biowaiver allowance (August, 2000).

Some factors can influence the request of biowaiver for *in-vivo* bioavailability and bioequivalence studies of immediate-release oral solid dosage forms as follows.

## Excipients

Organic solvents are not suitable, and surfactants should not be added. All the samples should be filtered when collected. The use of enzymes might be suitable for gelatin capsules or tablets having gelatin coatings, where cross-linking has been established if reasonably justified (ICH, 2018). The selection of excipients as per different regulatory bodies has been given in Table 3. As mentioned previously, frequency and degree of absorption of drugs are significantly changed by excipients excluding those that are currently accepted by the FDA to be intended for IR oral solid dosage form (FDA, 2017). Any deviation for example use of such excipients in large quantity or incorporation of any new excipients will require additional information with respect to the effect on bioavailability. BCS class III drugs because of low permeability must contain excipients that are similar qualitatively and quantitatively with reference product for a biowaiver to be scientifically justified because excipients may have a great impact on absorption of BCS class III drugs (FDA, 2017; WHO, 2019).

## Fixed-dose combinations

FDA also established certain guidelines for immediate release fixed-dose combination drugs such as;

a. if the combination is composed of entirely BCS class I drugs having no pharmacokinetic interaction; can be a successful candidate for biowaiver. In the case of any pharmacokinetic interaction, excipients would otherwise fulfill the FDA’s criteria for excipients otherwise *in-vivo* bioequivalence testing is obligatory (FDA, 2017).

b. BCS class III or a combination of class I and III immediate release fixed-dose combination are appropriate for biowaiver, provided the excipients must fulfill the FDA’s criteria for excipients otherwise *in-vivo*

**Table 3.** Excipients recommendation as per regulatory agencies.

| Excipients | ICH (%) | FDA (%) | WHO | EMEA |
|---|---|---|---|---|
| **Filler** | ±10.0 | ±10 | Absence of excipients that have an impact on bioavailability. | Absence of excipients that have an impact on bioavailability, e.g. s*orbitol, mannitol, sodium lauryl sulfate or other surfactants*. |
| **Disintegrant** | | | | |
| *Starch* | ±6.0 | ±6 | | |
| *Other* | ±2.0 | ±2 | | |
| **Binder** | ±1.0 | ±1 | | |
| **Lubricant** | | | | |
| *Ca or Mg stearate* | ±0.5 | ±0.5 | | |
| *Other* | ± 2.0 | ±2 | | |
| **Glidant** | | | | |
| *Talc* | ±2.0 | ±2 | | |
| *Other* | ±0.2 | 0.2 | | |
| **Film coat** | | ±2 | | |

bioequivalence is required (FDA, 2017).

### Prodrugs

The mechanism and conversion site of prodrug to active moiety must be known for biowaiver study. Some prodrugs convert before intestinal permeation, whereas some after intestinal absorption. In both cases the permeability of either prodrug or active drug moiety must be measured (FDA, 2017).

### Exceptions

Narrow therapeutic index drugs and products designed to be absorbed in the oral cavity are excluded from BCS-based biowaiver studies, however, biowaiver can be considered for orally disintegrating tablets if their absorption from the oral cavity is averted (FDA, 2017).

## MONOGRAPHS FOR BIOWAIVER APPROVAL

They are also referred to as literature reviews and designed for newly formulated active pharmaceutical ingredients which include the open-access data of various drugs. These monographs were established for consideration of queries regarding biowaiver recommendations for such formulations. Various pharmaceutical characteristics are discussed in this literature such as; solubility, permeability, dissolution, pharmacokinetics, bioavailability, bioequivalence, clinical indication, the therapeutic index of drugs and information on drugs excipient interactions. FIP in this regard, initiated the collection of freely available information on essential medicinal drug products based on their BCS classification. This has been facilitated by FIP's special interest group on BCS and biowaiver. Whereas, further assistance has been provided by other regulatory authorities including WHO, FDA and EMA. The technical advancements in the domain of biowaiver have also made its contributions and so far, nearly 50 biowaiver monographs have been published (Table 4). The drug approvals have been supported by the WHO model list of essential medicines with the purpose to establish reliable access to drug products for developing countries (FIP, 2015).

## HARMONIZATION AMONG INTERNATIONAL REGULATORY AGENCIES

Despite being based on the same principles, BCS-based biowaivers are interpreted and regulated differently among international regulatory agencies. The Bioequivalence Working Group (BEWG) of the International Generic Drug Regulators Programme (IGDRP) compared the criteria for BCS-based biowaivers applied by the participating regulators and organizations. Differences and similarities regarding solubility, permeability, dissolution, excipients and fixed-dose combination products were identified and compared in a detailed survey of each participant's criteria for BCS-based biowaivers. These criterias were determined based upon the participant's respective regulatory guidance documents, policies and practices (Van et al., 2018).

The most important difference that hinders harmonization of BCS-based biowaiver requirements relates to whether solubility is classified using the highest strength or the highest single therapeutic dose of the

**Table 4.** Biowaiver monographs offered by FIP **(***http://www.fip.org/bcs_monographs*).

| S/N | Drug product | BCS classification |
|---|---|---|
| 1 | Acetaminophen | BCS Class III |
| 2 | Acetylsalicylic acid | BCS Class I |
| 3 | Acyclovir | BCS Class III/IV |
| 4 | Amitriptyline hydrochloride | BCS Class I/ II |
| 5 | Amodiaquine hydrochloride | BCS Class III/IV |
| 6 | Amoxicillin trihydrate | BCS Class I/II/IV (dose dependent) |
| 7 | Atenolol | BCS Class III |
| 8 | Bisoprolol fumarate | BCS Class I |
| 9 | Chloroquine phosphate/sulfate/hydrochloride | BCS Class I |
| 10 | Cimetidine | BCS Class III |
| 11 | Ciprofloxacin hydrochloride | BCS Class IV |
| 12 | Codeine phosphate | BCS Class I |
| 13 | Diclofenac sodium/potassium | BCS Class II |
| 14 | Doxycycline Hyclate | BCS class I |
| 15 | Efavirenz | BCS Class II/IV |
| 16 | Enalapril Maleate | BCS Class III |
| 17 | Ethambutol Dihydrochloride | BCS Class III |
| 18 | Fluconazole | BCS Class I |
| 19 | Folic acid | BCS Class IV |
| 20 | Furosemide | BCS Class IV |
| 21 | Ibuprofen | BCS Class II |
| 22 | Ketoprofen | BCS Class II |
| 23 | Isoniazid | BCS Class I/III |
| 24 | Lamivudine | BCS Class III |
| 25 | Levetiracetam | BCS Class I |
| 26 | Levofloxacin | BCS Class I |
| 27 | Metoclopramide hydrochloride | BCS Class III |
| 28 | Metronidazole | BCS Class I |
| 29 | Nifedipine | BCS Class II |
| 30 | Piroxicam | BCS Class II |
| 31 | Prednisolone/prednisone | BCS Class I |
| 32 | Primaquine diphosphate | BCS Class I |
| 33 | Proguanil hydrochloride | BCS Class III |
| 34 | Propranolol hydrochloride | BCS Class I |
| 35 | Pyrazinamide | BCS Class III |
| 36 | Quinidine sulfate | BCS Class I |
| 37 | Quinine sulfate | BCS Class I/ II |
| 38 | Ranitidine hydrochloride | BCS Class III |
| 39 | Ribavarin | BCS Class III |
| 40 | Rifampicin | BCS Class II |
| 41 | Stavudine | BCS Class I |
| 42 | Verapamil hydrochloride | BCS Class I |
| 43 | Zidovudine | BCS Class I |

reference product. Other complicating factors include, differences in *in-vitro* permeability data can be accepted to support a permeability classification and the necessity of conducting comparative dissolution testing among the test and local reference product in each jurisdiction (Van et al., 2018; FDA, 2017).

The survey identified several areas for potential regulatory harmonization or convergence. The greatest similarities in the approach to BCS-based biowaivers were observed between New Zealand, Australia, Canada, Colombia, Taiwan, EU, South Africa, Switzerland, and the WHO because of the use of a similar pH range

for the solubility classification, similar requirements for permeability data and the same cut-off point for the permeability classification at 85%. Except for Taiwan, all of these participants base the solubility classification on the highest single dose stated in the reference product labeling. Furthermore, these participants accept BCS Class III biowaivers. Harmonization with Singapore is possible because of the same cut-off value for permeability classification (85%) and pH range for solubility classification (1.0 to 6.8). Singapore currently, accepts only BCS Class I biowaivers and is reviewing its position on BCS Class III biowaivers. In contrast, harmonization with Brazil will be more challenging because of the acceptability of BCS-based biowaivers is limited to those BCS class I drug substances listed in their regulations. Similar challenges exist for South Korea and the US, based on a different cut-off value for the permeability classification (90%) and the wider pH range (1.0 to 7.5) for the solubility classification. Additionally, the US requires experimental data for the permeability classification, unless the absolute bioavailability is stated in the labeling of the reference product. However, they continue to make strides towards harmonization. This is evident from the recently revised draft BCS guidance document published by the US in 2015 (Van et al., 2018; FDA, 2017).

## CONCLUSION

Extensive evaluation of biowaiver guiding principles proposed by regulatory agencies around the globe (FDA, WHO, EMA and ICH) do not come to an agreement on a single approach, to grant biowaiver to multisource drug product regulated by BCS classification. Furthermore, contradiction was also observed among the participants of IGDRP regarding solubility and permeability classification values and pH-range approved for solubilty determination of the drug product, which forms the foundation for biowaiver approval. Thus, a need of convergence among regulatory authorities in many areas is necessary for avoiding costly and time consuming *in-vivo* studies in order to produce safe, efficacious and quality generic product.

## CONFLICT OF INTERESTS

The authors do not have any conflict of interests.

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