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COMPARATIVE STUDY OF BCS BASED BIOWAIVER APPROACHES AND CURRENT DEVELOPMENTS TOWARDS HARMONIZATION

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ABSTRACT

Biowaiver on the basis of BCS is an important tool for pharmaceutical manufacturers and regulators to show equivalence of generic drugs to innovator or reference products. Various regulatory authorities such as USFDA, WHO and EMA put forward guidelines to practice this approach. However, these guidelines were differing in many ways to each other which created difficulties for manufacturers and regulators to follow different guidelines for different regions. To answer this question efforts have been made by different authorities to harmonize BCS based biowaiver on global basis. Recently USFDA has revised guideline to align with WHO and EMA with respect BCS based biowaiver request. Similarly, ICH also planned to publish a harmonize guidelines for biowaiver based on BCS to take advantage of harmonization for bioequivalence and save humans and financial resources by following different guidelines for BCS based biowaiver request. As a result, a harmonized approach for BCS based biowaiver is evolved which will be beneficial to both pharmaceutical manufacturers and pharmaceutical regulators globally and ease the registration process for drugs in different countries.

Keywords *– Biowaiver, Biopharmaceutical classification system, Bioequivalence, Harmonization, Pharmaceutical manufacturers, Pharmaceutical regulators.*

1. INTRODUCTION

Bioequivalence refer to no or minimal difference between two drug products on the basis of a study in which two similar drugs administer to human subjects under same conditions. It is a regulatory tool which is uniformly used by regulators to register a generic product in particular country. The purpose of bioequivalence is to document scientific evidence to assure that the generic drug product under question is equivalent to reference product (innovator, comparator, market leader product) in terms of efficacy, safety and quality. Bioequivalence is a mandatory requirement for product registration for generic oral dosage forms and it is quite impossible to register or market a drug product without bioequivalence study. Various guidelines to conduct bioequivalence study have been forwarded by global regulatory bodies including USFDA[1], WHO[2] and EMA[3]. There were number of differences among these guidelines to perform bioequivalence studies from study design to outcome of study. According to these guidelines the bioequivalence study is a time taking and quite expensive procedure which involve large amount of money, time and humans. As bioequivalence study is a mandatory requirement for drug applications approval and at the same time a long

process which delays the application process for drugs, regulatory bodies continuously search for alternate ways for BE. First solution to this issue was put forward by USFDA in 2000 to take the advantage of BCS classification of drug substances on the basis of their solubility, permeability and rate of dissolution. According to this a waiver to BE study for immediate release oral dosage forms can be requested on the basis of BCS classification subject to meeting other additional conditions. After USFDA approach, other regulatory bodies also contributed to bio waiver based on BCS classification and have formatted further guidelines to this question.

2. BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

Biopharmaceutical Classification System (BCS) scientifically classifies the drug substances on the basis of aqueous solubility and intestinal permeability[1, 2, 3]. Both these factors along with dissolution make BCS a governing system for the extent and rate of drug absorption for immediate release (IR) dosage forms. Division of drug substance according to BCS as follows:

Class 1: High Solubility – High Permeability

Class 2: Low Solubility – High Permeability

Class 3: High Solubility – Low Permeability

Class 4: Low Solubility – Low Permeability

This classification of drug substance can be used by applicants/sponsors to rationalize the request for biowaiver. However, only BCS classification of drug substance is not enough for request of biowaiver, some additional requirements also need to be fulfilled. Different drug regulatory bodies put forward guidelines to conduct the bioequivalence study along with biowaiver on the basis of BCS classification with certain additional requirements.

3. REGULATORY GUIDELINES

Worldwide there are three regulatory bodies along with ICH which govern the regulatory frame work of pharmaceutical industry in different regions. These are USFDA, WHO and EMA. Guidelines and recommendations by these bodies will follow by other countries. For instance, TGA Australia follows EMA for most of pharmaceutical industry aspects. This is also true in the case of biowaiver request. Guidelines by USFDA, WHO and EMA regarding BCS based biowaiver request are adopted and practiced by many countries in the world. But as there were some differences exist in these guidelines, countries which are following these guidelines also differ in their approach and practice on BCS based biowaiver. With increased export pharmaceutical business to Asian, African and Asia Pacific regions by Pakistani and Indian pharmaceutical industries there is a need to understand the BCS based biowaiver requirements for different countries and regions as this would provide better understanding and quick registration process in these countries.

3.1. Comparison of USFDA, WHO and EMA Guidelines for BCS Based Biowaiver before December 2017

As earlier mentioned, that there were various underlying differences exist between three most renowned guidelines about biowaiver approaches, Table. 1 summarized the differences between three guidelines until December 2017. Biowaiver request on the basis of BCS classification depends on three major parameters related to drug substance and drug product. These are solubility and permeability of dug substance and dissolution of drug product.

3.2. Solubility

Solubility of drug substance is one of the two criteria as on which BCS classification is based. Therefore, solubility of drug substance considered to be most critical for BCS based biowaiver request. Three guidelines define criteria of highly soluble drug substance depending on volume and pH range of aqueous medium. However, some differences evident from Table. More wide

range of pH is proposed by USFDA as compared to WHO and EMA. In case of volume of aqueous solution, both WHO and USFDA consider high solubility in 250ml or less. In contrast, EMA proposed fixed volume of 250ml of aqueous solution without giving focus on solubility of drug substance in volume lesser than 250ml. Despite of these differences all three guidelines are equally practiced and implemented in most of the countries.

3.3. Permeability

Permeability is second factor which plays a decisive role in BCS classification of drug substances. Permeability is the rate or extent of absorption drug substance in humans. The only difference on the basis of permeability between three guidelines is cut off value to determine whether a drug substance is highly permeable or not. WHO and EMA used same cut off value of 85% absorption in humans for highly permeable drug substance. On the other hand, if rate or extent of absorption of drug substance is 90% or higher then drug substance is said to be highly permeable. This leads to quite a difficult position for drug manufacturer to decide what criteria to be followed. This situation becomes more worst when different countries follow different guidelines. Because, drug manufacturing companies need to adopt different BCS approaches for product registration in different countries for same drug product. Despite of these differences all three regulatory authorities have a consensus on method of determination of rate of absorption. Either mass balance study or comparative intravenous study with reference dose can be used to determine rate or extent of absorption of drug substance in humans.

3.4. Dissolution

To request a biowaiver on the basis of BCS classification, comparative dissolution profile between test and reference drug product is a mandatory requirement. Although it is very important and basic condition for biowaiver request, considerable differences between global guidelines still exist in different criteria and procedures. WHO and EMA classified drug products as rapidly dissolving and very rapidly dissolving on the basis of percent amount of drug substance dissolved in specify dissolution mediums. If 85% or more drug substance dissolves within 15 minutes under dissolution conditions defined by WHO and EMA, the drug is said to be very rapidly dissolving. The concept of rapidly dissolving drugs is not covered by USFDA guidelines. However, USFDA, WHO and EMA suggested uniform definition of rapidly dissolving drug substances. If 85% of drug substance dissolves within 30 minutes under prescribed dissolution conditions then product classified as rapidly dissolving.

It is quite evident that there are considerable differences for biowaiver requirements on the basis of BCS classification between three guidelines as shown in Table 1.

First of all, USFDA only consider BCS class 1 drug substances/products for biowaiver on the basis of dissolution profile comparison. In contrast, WHO not only consider BCS class 3 drug substances but also allow biowaiver for BCS class 2 drug substances with subject to high solubility of these drug substances in pH 6.8 buffer. This is proved to be a great advantage for pharmaceutical manufacturers and their regulatory departments to include such kind of drugs in biowaiver category. Finally, EMA, taking advantage of both WHO and USFDA guidelines to allow BCS based biowaiver for both BCS class 1 and BCS class 3 drug substances for biowaiver. In addition to differences on the basis of BCS drug substances and dissolution profile there are some other differences exist between leading pharmaceutical guidelines. For example, rpm requirements for paddle apparatus are different in WHO and USFDA guidelines via 75rpm and 50rpm respectively. Moreover, difference on the basis of high permeability values also found between these two guidelines. If rate or extent of absorption of drug in human is 90% or more it is considered to be highly permeable as per USFDA. On the other hand, as per WHO if absorption of drug product in human is 85% or more it is classified as highly permeable. This definition also adopted by EMA.

3.5. Regional Differences

Differences among global regulatory authorities are so diverse that it is quite impossible to draw a general approach using guidelines by these bodies. This leads to variation in practicing biowaiver approach in different regions and countries. For example, Saudi Arabia a member country of GCC allow biowaiver request only for BCS class 1 drugs[4]. On the other hand there are also some countries which allow biowaiver for both BCS class 1 and class 3 drug products but not for BCS class 2 drugs as proposed by WHO[5, 6, 7, 8]. However, Egypt

Table. 1: Comparison of different BCS based biowaiver approaches by different regulatory athorities before December 2017

Parameters	USFDA[1]	WHO[2]	EMA[3]	Remarks
Solubility	a- Highest dose strength b- Volume: 250ml or less c- pH range: 1-7.5	a- Highest dose strength b- Volume: 250ml or less c- pH range: 1-6.8	a- Highest dose strength b- Volume: 250ml c- pH range: 1-6.8	i- Difference in pH range between USFDA and WHO& EMA ii- EMA excluded the word less from USFDA and WHO criteria
Permeability	a- Cutoff value of absorption in human for high permeability is 90% or more b- Determination method: mass balance study or intravenous comparative study with reference dose	a- Cutoff value of absorption in human for high permeability is 85% or more b- Determination method: mass balance study or intravenous comparative study with reference dose	a- Cutoff value of absorption in human for high permeability 85% or more b- Determination method: mass balance study or intravenous comparative study with reference dose	i- Difference between cutoff values of absorption between USFDA and WHO & EMA.
Dissolution	a- Rapidly dissolving: 85% or more of labeled amount of drug in 30 minutes b- Dissolution conditions: rpm: 100rpm for apparatus I 50rpm for apparatus II Volume: 900ml or less pH range: 0.1N HCl pH 4.5 buffer pH 6.8 buffer	a- Very rapidly dissolving: 85% or more of labeled amount of drug in 15 minutes b- Rapidly dissolving: 85% or more of labeled amount of drug in 30 minutes c- Dissolution conditions: rpm: 100rpm for apparatus I 75rpm for apparatus II Volume: 900ml or less pH range: 0.1N HCl solution or buffer pH 4.5 acetate buffer pH 6.8 phosphate buffer	a- Very rapidly dissolving: 85% or more of labeled amount of drug in 15 minutes b- Rapidly dissolving: 85% or more of labeled amount of drug in 30 minutes c- Dissolution conditions: rpm: 100rpm for apparatus I 50rpm for apparatus II Volume: 900ml or less pH range: 0.1N HCl pH 4.5 buffer pH 6.8 buffer	i- USFDA not defined very rapidly dissolving drug products ii- Difference in rpm for apparatus II between USFDA & EMA and WHO.
BCS Based Biowaiver	BCS class 1	i- BCS class 1 and 3 ii- BCS class 2 in pH 6.8 buffer	BCS class I and III	i- Different BCS based biowaiver approached adopted by three regulatory authorities.

Table 2: Regional BCS based biowaiver approaches

S. No.	Region	Adopted Guideline	BCS Based Biowa1ver
1	Australia	EMEA	BCS Class 1and BCS Class 3
2	ASEAN	EMEA	BCS Class 1and BCS Class 3
3	Canada	EMEA	BCS Class 1and BCS Class 3
4	GCC	EMEA	BCS Class 1
5	SADC	USFDA/EMEA/WHO	BCS Class 1and BCS Class 3
6	Egypt	WHO	BCS Class 1 and BCS Class 3, BCS class 2 as per WHO criter1a

ASEAN: Association of Southeast Asia Nations (Brunei Darussalam, Combodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, Viet Nam, GCC: Gulf Cooperation Council (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arabia Emirates)

SADC: South African Development Community (Angola, Botswana, Democratic Republic of Congo, Lesotho, Madgascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, United Republic of Tanzania, Zambia, Zimbabawe allows BCS based biowaiver for BCS class 2 drugs as well in addition to BCS class 1 and 3 drug products[9]. This means that drug manufacturers have to follow different product registration practices for different countries. This kind of varied requirements involve more healthy humans, cost and time. Regulatory authorities continuously working to resolve this issue and ultimately, they are about to come at an agreement.

4. CURRENT DEVELOPMENTS

In 2015 USFDA has put forwarded a draft guideline which not only include BCS class 3 drugs for biowaiver on the basis of BCS classification but also modify the criteria for high permeability and maximum volume requirements for dissolution profile[10].In previous guideline, USFDA considered a product highly permeable if its rate or extent of absorption is 90% or more in humans. While in draft guidelines they revised the minimum percent requirements for highly permeable drugs. According to this draft drug product considered to be highly permeable if rate or extent of drug found to be 85% or more. This approach is similar to WHO approach. However, USFDA introduced a new variation between WHO and USFDA approaches on the basis of volume employed for rapidly and rapidly dissolving drug definition. Earlier USFDA recommended 900 ml volume of aqueous solution for dissolution very similar to WHO. However, in this draft guideline USFDA revised the volume requirement for dissolution which is 500ml[10]. Despite of this difference USFDA attempt to harmonize with WHO by allowing 75 rpm for apparatus II as well.

However, in December 2017, USFDA has finalized their draft guideline for biowaiver request on the basis of BCS classification[11]. In this guideline USFDA aligned their requirements for biowaiver request completely with WHO and EMA by allowing BCS class III drug products for biowaiver request if these substances meet other conditions in addition to BCS class I. USFDA has also allowed provision for dissolution volume of 900 ml. After this development the only difference exist between USFDA and WHO guidelines for biowaiver request based on BCS classification is the conditional provision of BCS class II drug substances for biowaiver request. All other differences between these two major guidelines overcome by this effort. Similarly, USFDA and EMA are now become completely aligned with each other in terms of BCS based biowaiver request. Therefore, all three main regulatory guidelines for biowaiver request are harmonized with respect to requirements for biowaiver request as shown in Table. 3.

Considering variations about theoretical and practical approaches about BCS based biowaiver among regulatory authorities ICH intervene to resolve this issue. ICH introduced a concept paper to resolve the global issue of diverse guidelines and practices about BCS classification and biowaiver request[12]. This guideline will harmonize the supportive data requirements for classification of drug products in to one of the BCS class. This guideline also aims to put forward a uniform supportive data for biowaiver request. Guideline will consider solubility of highest therapeutic dose or highest strength of drug product to decide whether the product is classified as highly soluble or low soluble. As discussed above different methods exist to determine permeability of drug products. Harmonized guide will also address in vitro data or in vivo data or both could be used to determine permeability. Selection of appropriate method and cut off values also will be the subject of proposed guideline. Global regulatory guidelines also found different in terms of in vitro dissolution conditions. Different approaches about dissolution conditions will be discussed and to decide whether different dissolution conditions could be applicable or not. If applicable then what should be the type of justification. Clarification about application of BCS biowaiver only to pharmaceutical comparatives will be provided by harmonized

guideline. Addition to this if a comparator formulation marketed in multiple strengths then what will be the procedure of BCS based biowaiver request. Whether a single strength dissolution comparison profile is enough or each of comparator strength should be matched with that of test formulation.

Table. 3: Comparison of different BCS based biowaiver approaches by different regulatory athorities after December 2017.

Parameter	USFDA[11]	WHO[2]	EMA[3]	Remarks
Solubility	a- Highest dose strength b- Volume: 250ml or less c- pH range: 1-6.8	a- Highest dose strength b- Volume: 250ml or less c- pH range: 1-6.8	a- Highest dose strength b- Volume: 250ml c- pH range: 1-6.8	i- Difference in pH range excluded by USFDA in revised guideline and now become similar WHO& EMA ii- EMA excluded the word less from USFDA and WHO criteria
Permeability	a- Cutoff value of absorption in human for high permeability is 85% or more b- Determination method: mass balance study or intravenous comparative study with reference dose	a- Cutoff value of absorption in human for high permeability is 85% or more b- Determination method: mass balance study or intravenous comparative study with reference dose	a- Cutoff value of absorption in human for high permeability 85% or more b- Determination method: mass balance study or intravenous comparative study with reference dose	i- Difference between cutoff values of absorption omitted by USFDA and become equivalent to WHO & EMA.
Dissolution	a- Very rapidly dissolving: 85% or more of labeled amount of drug in 15 minutes b- Rapidly dissolving: 85% or more of labeled amount of drug in 30 minutes b- Dissolution conditions: rpm: 100rpm for apparatus I 50rpm for apparatus II or 75rpm Volume: 500ml or less or 900ml pH range: 0.1N HCl pH 4.5 buffer pH 6.8 buffer	a- Very rapidly dissolving: 85% or more of labeled amount of drug in 15 minutes b- Rapidly dissolving: 85% or more of labeled amount of drug in 30 minutes c- Dissolution conditions: rpm: 100rpm for apparatus I 75rpm for apparatus II Volume: 900ml or less pH range: 0.1N HCl solution or buffer pH 4.5 acetate buffer pH 6.8 phosphate buffer	a- Very rapidly dissolving: 85% or more of labeled amount of drug in 15 minutes b- Rapidly dissolving: 85% or more of labeled amount of drug in 30 minutes c- Dissolution conditions: rpm: 100rpm for apparatus I 50rpm for apparatus II Volume: 900ml or less pH range: 0.1N HCl pH 4.5 buffer pH 6.8 buffer	i- USFDA defined very rapidly dissolving drug products in revised guideline in addition to rapidly dissolving criteria ii- Difference in rpm for apparatus II has been addressed by USFDA and provide provision to become align with EMA and WHO.
BCS Based Biowaiver	BCS class I and III	i- BCS class 1 and 3 ii- BCS class 2 in pH 6.8 buffer	BCS class I and III	i- Different BCS based biowaiver approached adopted by three regulatory authorities.

Even though the scientific data to support BCS based biowaiver is uniform but interpretation of this data is different among different regulatory authorities. Harmonization will bring uniformity of BCS based biowaiver application and requirements for biowaiver. This harmonization not only beneficial to ICH countries but also could be used by other countries as a guideline for BCS based biowaiver.

There are some clear tactical benefits associated with this harmonization. First of all, exposure of healthy humans to drug product could be reduced as in vitro studies will be sufficient to justify bioequivalence of drug product. In developing countries cost associated with in vitro bioequivalence studies is a big concern which hinders the introduction of good quality drug products in these regions. Harmonization will bring down this cost as in vitro study will take place of in vivo studies which leads to high quality drug product at low cost in the reach of developing countries people. Pharmaceutical companies will also beneficial to this harmonization as they will follow the same guiding principles for BCS based biowaiver in different regions which will speed up the availability of high-quality drug products to general public.

5. CONCLUSION

Biowaiver on the basis of BCS is an important tool for pharmaceutical manufacturers and regulators to show equivalence of generic drugs to innovator or reference products. Various regulatory authorities put forward guidelines to practice this approach. However, these guidelines differ in many ways to each other which creates difficulties for manufacturers and regulators to follow different guidelines for different regions. To answer this question efforts have been made by different authorities to harmonize BCS based biowaiver on global basis. Recently USFDA has revised guidelines to include BCS class III drug substances to match with WHO and EMA. Similarly, ICH has also planned to publish a harmonize guidelines for biowaiver based on BCS to take advantage of harmonization for bioequivalence and save humans and financial resources while following different guidelines for BCS based biowaiver request.

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