Biowaiver Monographs 2004-2012

Bringing essential medicines to those who need them most

Fédération Internationale Pharmaceutique

International Pharmaceutical Federation

1912 · 2012
100 YEARS OF
ADVANCING PHARMACY WORLDWIDE

Compiled and reviewed on the occasion of the FIP Centennial

PREFACE

For 100 years, the Federation International Pharmaceutique (FIP) has been at the forefront of innovations in pharmacy practice and the pharmaceutical sciences. This book commemorates the contributions of the FIP to the pharmaceutical sciences by documenting the results of just one of its joint programs with the World Health Organization: the Biowaiver Monographs.

Universal accessibility to quality medicines has been championed by both FIP and WHO since the early days of both organizations, but universal accessibility is only possible and achievable when medicines are affordable based on purchasing power parity of patients worldwide. Quality multisource or generic products with equivalent therapeutic interchangeability as compared to the respective brands have been the corner stone in achieving affordability. The development of pharmacokinetics, bioavailability (BA) and bioequivalence (BE) has made it possible to achieve therapeutically equivalent switchability (interchangeability). The Biowaiver seeks to streamline the introduction of these generic drug products and even further reduce the prices in the market place by circumventing pharmacokinetic-based bioequivalence studies, where appropriate, while still assuring (very good) drug product performance. Briefly, the drug properties of a drug product such as solubility, permeability through the intestinal membrane, therapeutic index and linearity of pharmacokinetics, as well as experience with the drug in the clinic and in pharmacokinetic studies are scrutinized to come up with an overall evaluation of the risks, if any, of determining similarity of products containing the drug using laboratory-based less expensive dissolution tests instead of a pharmacokinetic comparison. The Biowaiver was originally proposed by Amidon and co-workers in 1995[1] and subsequently adopted by the US-FDA, WHO and EMA for implementation in the approval of some generic drug products.[2-4] Many of the member countries of WHO also rely on the WHO Guidance to decide when a Biowaiver-based approval is appropriate for a generic drug product than having them subjected to *in vivo* bioequivalence studies.
In the early 2000s, a joint project was set up between the FIP and WHO to apply the Biowaiver concept to individual drug products. The idea was to provide assistance to national authorities by creating Biowaiver monographs which summarize the literature on a given active pharmaceutical product , and on the basis of this summary, draw a conclusion as to whether a marketing approval can be granted on the basis of similarity between the dissolution properties of the proposed drug product with the comparator drug product already on the market, or whether the equivalence of the two products must be decided in a bioequivalence study based on pharmacokinetic end points. Spearheading this initiative was Dr. Dirk Maarten Barends of the National Institute for Public Health and the Environment

(rivm) in the Netherlands and also a member of the FIP's Special Interest Group on BA and BE. Dr. Barends invited key scientists active in the field of BA and BE to join him in constructing the first Monograph, which covered drug products of Verapamil, Propranolol and Atenolol and which was published in 2004[5]. Following the success of this initial Biowaiver Monograph, a panel of fixed co-authors was established and a series of individual Monographs was underway. The initial panel of fixed co-authors included Gordon Amidon and Vinod Shah (both co-authors of the original concept paper), Kamal Midha, Hans Junginger, Sol Stavchansky, Jennifer Dressman, Sabine Kopp and Dirk Barends, thus bringing stakeholders from the regulatory authorities, along with experts in the fields of pharmacokinetics, bioequivalence, the Biopharmaceutics Classifications Scheme and in dissolution methodology, on board. This group, with the help of some very capable first authors, produced 24 Biowaiver monographs. In 2010, some changes were made to the group among fixed co-authors due to retirements etc. and at present the fixed co-authors are Bertil Abrahamsson, Jennifer Dressman, Kik Groot, Sabine Kopp, Peter Langguth, James Polli, Vinod Shah and Dirk Barends.

In a period of just seven years, a total of 32 Biowaiver Monographs have been published and the pipeline is full. The long term intention is to provide Monographs for all of the orally administered drug products on the WHOs Essential Medicine List (EML) plus some frequently used drug products that do not appear on the EML. This will obviously take some years and a lot of effort, but will provide an excellent database for national authorities, for the WHO and NGOs as well as for pharmaceutical companies and researchers working with these compounds.

None of this could have been possible without the foresight, organizational skills and large investment of time on the part of Dirk Barends and other contributors. It is worthy to mention Dirk Barends' vision and organizational skills in getting these Monographs started and maintaining excellent productivity, generating several Monographs every year. Moreover acknowledged are the rivm, for according Dirk the resources and time necessary to set up and maintain the project, as well as the FIP for supporting the efforts of its very active Special Interest Group "BCS and Biowaiver", which is now organized under the framework of Regulatory Sciences as a Focus Group in the FIP.

We look forward to another century of FIP and to a rich database of Biowaiver Monographs

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Dedicated to the memory of **Dr. Dirk Maarten Barends** (1925-2012),
founder of the Biowaiver Monographs

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BIOWAIVER MONOGRAPHS 2004 -2012

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THE BIOWAIVER MONOGRAPHS –
WHAT HAVE WE LEARNED?

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STARTING POINT OF THE PROJECT – 2004

In 2004, our first Biowaiver Monograph was published as a commentary in the Journal of Pharmaceutical Sciences. This commentary addressed the possibility of applying the biowaiver to three active pharmaceutical ingredients (API): verapamil hydrochloride, propranolol hydrochloride, and atenolol.[1]

Regulations on biowaivers already existed at that time, according to which an *in vitro* instead of an *in vivo* assessment could be used to assess bioequivalence for a new tablet or capsule, or a new formulation of an existing immediate release dosage form. On the basis of the *in vitro* assessment, a new drug product could be considered bioequivalent to its reference product, without having to perform a pharmacokinetic study in human volunteers. To generally describe the use of an *in vitro* assessment to waive the need for *in vivo* (bio) studies, the term "biowaiver" was coined. As this term was originally applied to waiving *in vivo* studies for registration of lower dosage strengths of drug products, the more precise term "BCS based biowaiver" is sometimes used to distinguish biowaivers based on BCS considerations from biowaivers used for the approval of lower dose strengths of a product.

As the various regulations described the *in vitro* methods to be used by the applicant, rather than providing data for actual drug substances or indicating specifically for which drug substances a BCS based biowaiver might be applicable, and since at that time open literature on the subject applying the biowaiver was scanty, it seemed logical to consider the BCS based biowaiver on a case by case basis. A further driving force for generating the Biowaiver Monographs was that the regulations differed among the various agencies and it was intended for the Biowaiver Monographs to provide a venue to open up a scientific debate about the differences in these regulations. Because of this lack of harmonization of existing guidances, it was also agreed to attempt to come to the best scientific decision for a given drug substance, based on existing information, rather than just applying one or more of the existing regulations unquestioningly. When the recommendation differs from one or the other of the guidances, this also provides an impetus to re-examine the basis of the particular guidance.

MAIN ITEMS OF THE BIOWAIVER MONOGRAPH PROJECT

Easier access to and better data regarding application of the BCS based biowaiver to drug substances

The regulatory guidances describe which data are needed to determine whether the BCS based biowaiver is applicable. The primary criteria which must be assessed to determine eligibility for the biowaiver relate to its BCS classification i.e. the solubility of the drug substance at different pH values and its intestinal permeability. Additionally, if the drug substance has a narrow therapeutic window and a very critical therapeutic indication, and/or if there have been a lot of unexplained failures to meet *in vivo* bioequivalence reported in the literature, it will generally not be eligible for a BCS based biowaiver. Each applicant has to make a case for his/her drug substance to be considered for a biowaiver and to support this case with the appropriate data and literature.

But as already mentioned, the regulations themselves do not reveal which APIs are eligible for the biowaiver, nor do they provide specific examples to guide applicants.

So, there was and is a need to apply the BCS based biowaiver concept to individual drug substances, both to see how the regulations play out in practice and to make these examples available in the open literature. With this intention, the idea for the Biowaiver Monographs was born.

Addressing an individual drug substance, the FIP Biowaiver Monograph reports all relevant data found in the open scientific literature, and also reviews critically the reliability of these published scientific data as well as identifying gaps. Where some data are lacking – very often the solubility data at some or all of the relevant pH values – this data may be additionally generated and included in the Monograph. In some cases, dissolution data is also generated to determine whether the drug substance itself or products containing the drug substance can meet the stringent release requirements necessary for approval based on the biowaiver methods. Based on the information summarized in the Monograph, the authors then weigh arguments about whether products containing the specific drug substance would be eligible for a biowaiver-based approval or not.

In this way, users of the FIP Biowaiver Monographs have access to a document summarizing all known information relevant to application of the BCS based biowaiver for a given drug substance. When the Monograph concludes that a biowaiver based approval would be appropriate, it also stipulates the conditions under which the biowaiver could be granted. Sometimes these conditions relate to which dissolution criteria must be applied, sometimes specific excipients are excluded and sometimes the product labeling can come into play. Although the Monographs do not have direct regulatory implications as to whether a given drug product could be approved according to the biowaiver or not in a specific jurisdiction, they can provide a good starting point for the applicant to make arguments for or against application of the BCS based biowaiver. Additionally, the Monographs serve as an efficient summary of relevant data for the drug substance and are therefore useful to regulators as a source of information.

The project was and is mainly intended to publish Biowaiver Monograph of drug substances which appear on WHO´s List of Essential Medicines[2]. Occasionally, other drug substances finding very common use can also be considered as candidates for generating a Biowaiver Monograph.

Best scientific review of the different regulations on biowaiving

As mentioned above, the regulations on BCS based biowaivers differ between the FDA, EU and WHO[3-5]. While the WHO regulations are applied by a large number of national regulatory agencies, the EU and FDA regulations are obviously still very important because of the large pharmaceutical markets they represent. The FDA allows the biowaiver only for drug substances that have high solubility at the different pH values as well as a high permeability, the so called BCS Class I drug substances. The regulations of the EU and WHO are somewhat different from those of the FDA, and have been revised since the instigation of the Biowaiver Monograph Project. For example, both the current WHO and EMA guidances allow products containing Class III drug substances to be considered for the biowaiver. Interestingly, Japan is yet to adopt a biowaiver procedure, although similar approaches are taken to determine what kinds of *in vivo* studies are necessary for proof of bioequivalence. In an accompanying chapter, Dr. Henrike Potthast has summarized the key differences among the different regulatory authorities with respect to applying the BCS based biowaiver and also discusses some of the challenges faced by both the regulatory authorities and applicants in applying the biowaiver.

Rather than merely checking compliance with the different regulations, the Biowaiver Monographs review the data from a scientific point of view. In that way, the recommendation reached in the Monograph is aimed to be the best scientific result. When there is a discrepancy between the various regulations with respect to eligibility for the biowaiver, or when a different conclusion is reached in the Biowaiver Monograph than that which would be reached by merely applying one of the individual regulations, the reasons for this are discussed. Thus the project additionally serves as an impetus for the various regulatory authorities to refine their biowaiver guidances to reflect the best scientific thinking. The long term aim of the Biowaiver Monographs is to optimize and harmonize biowaiver guidances on a global basis – by stimulating the best science to arrive at the best biowaiver regulations!

Defining risks associated with using the BCS Class alone to determine biowaiver eligibility

According to the FDA guidance, a drug substance can be BCS Class I, but still not be eligible for a biowaiver, after considering the therapeutic consequences of bioinequivalent drug products. Indeed, several regulatory guidances mention that risks of therapeutic consequences of bioinequivalent drug products should be considered, but on this point the guidances are general and tend to be rather vague. The same holds for the risks associated with the excipients present in the formulation, with the amounts of excipients and/or with the manufacturing of the drug product.

The WHO and EMA guidances consider the possibility of applying the biowaiver to BCS Class III drug substances, and the WHO guidance even extends this possibility to certain BCS Class II drug substances. But for BCS Class II and III the eligibility is more closely scrutinized and, especially for the BCS Class II substances, most candidates will fail to meet all of the criteria for a biowaiver.

In the FDA and in earlier WHO and EMA guidances, the risks associated with all the above mentioned areas were not well defined, so one of the tasks of the Biowaiver Monograph drafting committee was to try to establish clearer descriptions of these risks in a more formal and better structured way. Over time, discussions on this area have crystallized, leading to the current situation in which risk considerations are divided into three main areas:

- Risk of bioinequivalence between a test and a reference drug product due to excipients and/or manufacturing effects.

- Risk of approving a test product according to the biowaiver procedure, when in fact if it was compared with the reference product in an *in vivo* study it would fail to meet bioequivalence standards
- Risks to patients associated with a false, biowaiver-based acceptance of a drug product, which would actually fail to be bioequivalent to the comparator product in an *in vivo* study.

With the above risk considerations in mind, it is clear that merely classifying a drug substance according to the BCS is not a sufficient basis for determining whether products containing the substance can be biowaivered or not.

EXPERIENCE WITH DRUG SUBSTANCES GATHERED IN THE PROJECT TO DATE

Until now, Biowaiver Monographs for more than 30 drug substances have been published. Due to a special arrangement with Wiley-Blackwell, the Monographs are not only published in the Journal of Pharmaceutical Sciences, but are also available free of charge on-line at the FIP website at www.fip.org/bcs . As part of the FIP Centennial celebration, they are now summarized in this Centennial Book.

The recommendations reached in the Monographs are summarized below in Table 1.

Table 1. BCS Classification and Recommendation for the Biowaiver According to the Biowaiver Monographs.

Drug substance	BCS classification	Risks	Biowaiver Recommendation	Further comments
acetaminophen	III	few	Yes	"rapid dissolution" and similarity between test and reference at all three BCS pH values is recommended as the pre-requisite.
acetazolamide	inconclusive	Possibly NTI	No	Conclusive solubility and permeability data are lacking, borderline NTI

Acetylsalicyclic acid	I	few	Yes	Dissolution requirements as per Guidances for BCS Class I
aciclovir	III (IV at 800mg dose)	few	Yes	Dissolution requirements per Guidances for Class III
amitriptyline	I/II Class I (WHO, EMA)*, Class II (FDA)	few	*Yes	Where applicable, dissolution requirements per Guidances for Class I
atenolol	III	few	Yes	Dissolution requirements per Guidances for Class III
chloroquine	I* *Solubilities have not been determined at all BCS relevant pH values.	Some toxicity concerns	Yes	Covers phosphate, sulphate and hydrochloride salts. Dissolution requirements per Guidances for Class I.
cimetidine	III	few	Yes	"rapid dissolution" and similarity between test and reference at all three BCS pH values is recommended as the pre-requisite.
ciprofloxacin	IV	N/A	no	Very poorly soluble at neutral pH
diclofenac	II	few	Yes	Dissolution requirements as per WHO Guidance for Class II weak acids. Applies to potassium and sodium salts.
doxycycline	I	few	Yes	Dissolution requirements per Guidances for Class I

ethambutol	III	NTI for ocular toxicity	Yes*	*Biowaiver only recommended if labeling is adequate for warning about ocular toxicity. Dissolution requirements per Guidances for Class III
furosemide	IV	few	No	Many reports of lack of bioequivalence, Class IV
ibuprofen	II	few	Yes	Dissolution requirements as per WHO Guidance for Class II weak acids.
isoniazid	I-III	few	Yes*	*Lactose accelerates decomposition of isoniazid and should be avoided as an excipient. Conclusive permeability data are lacking. Dissolution requirements per Guidances for Class III
ketoprofen	II	few	Yes	Dissolution requirements as per WHO Guidance for Class II weak acids.
lamivudine	III	few	Yes	Borderline permeability to Class I. Dissolution requirements per Guidances for Class III
levofloxacin	I	few	Yes	Dissolution requirements per Guidances for Class I
mefloquine	II-IV	few	No	Poor solubility at neutral pH, permeability not conclusive
metaclopramide	I-III	few	Yes	More conclusive permeability data are needed. Dissolution requirements per Guidances for Class III

metronidazole	I	few	Yes	Dissolution requirements per Guidances for Class I
prednisolone	*I	few	Yes	*Solubility within BCS limits at the highest dosage strength (but not at the highest single dose). Dissolution requirements per Guidances for Class I
prednisone	*I	few	Yes	*Solubility just fails BCS criteria at highest dosage strength (50mg), but authors concluded that risks associated with biowaiving are low. Dissolution requirements per Guidances for Class I
primaquine	I	few	Yes	Dissolution requirements per Guidances for Class I
propanolol	I	few	Yes	Dissolution requirements per Guidances for Class I
pyrazinamide	III	NTI according to some definitions	*Yes	*Biowaiver only recommended if labeling is adequate for warning about liver toxicity. Dissolution requirements per Guidances for Class III
quinidine	I-III	NTI	No	Although dissolution testing has been shown to be a reliable indicator of *in vivo* performance of quinidine, its NTI status precludes it from biowaiving

quinine	I-II	Dose-related toxicity at concentrations not far above therapeutic levels	No	Solubility at highest dose strength (300mg) passes D:S criteria at pH 6.8 but not pH 7.5. Dissolution is poor at pH 6.8 from marketed products.
ranitidine	III	few	Yes	"rapid dissolution" and similarity between test and reference is recommended as the pre-requisite.
rifampicin	II	Many reports of failure to meet BE	No	Poorly soluble API, unexplained lack of bioequivalence among products common
stavudine	I	few	Yes	Dissolution requirements per Guidances for Class I
verapamil	*I/II	few	YEs	*Meets solubility criteria at pH 6.8 but not pH 7.5 (not biowaivable according to FDA). Where applicable, dissolution requirements per Guidances for Class I

Of the Biowaiver Monographs published to date, most have recommended a biowaiver-based approval after a significant post-approval change or for approval of a generic version. This is largely because most of the APIs considered to date have been highly soluble over the BCS pH range and have a wide therapeutic index.

For seven of the 32 APIs considered to date, it was deemed inappropriate to recommend a biowaiver. In the case of ciprofloxacin, furosemide, mefloquine and rifampicin, the solubility of the drug substance was simply far too low at pH values typical of the small intestine to consider applying the biowaiver. Additionally for furosemide and rifampicin, there had been many reports of formulations failing bioequivalence studies published in the literature and moreover, these failures could often not be

explained by dissolution results. Quinine was an interesting case, because although the solubility at the highest dosage strength was able to meet BCS specifications, all marketed products tested release the API far too slowly at pH 6.8 to comply with the criteria for "rapidly dissolving". Since quinine also has dose-related toxicity at levels not far above therapeutic levels, it was deemed too risky to allow a biowaiver. Another drug substance for which a combination of inconclusive solubility data and possible problems with dose-related toxicity was identified, is acetazolamide. For these reasons, it too was excluded from the biowaiver. A more cut and dried example was quinidine, which because of its narrow therapeutic index and severe adverse reactions was not considered appropriate for biowaiving.

Two further compounds which are considered to have a narrow therapeutic index are ethambutol and pyrazinamide. In these cases the toxicities are well-characterized (ocular in the case of ethambutol and hepatic in the case of pyrazinamide) and package inserts are required to have a layman's description of symptoms which can alert the patient to consult his or her physician. Additionally, patients receiving these antitubercolitics are counseled by their physician to be aware of and recognize the symptoms. As the risk of bringing a bioinequivalent product on the market by virtue of an incorrect biowaiver-based decision is low for these two APIs (both are very highly soluble Class III APIs), as long as these precautionary counseling and labeling measures are taken, the potential risks to the patient associated with approving products containing either of these two drug substances was deemed to be acceptable.

For several drug substances, there was a discrepancy in eligibility for the BCS based biowaiver among regulatory guidances based on solubility criteria. These drug substances, which included amitriptyline, quinine and verapamil, were unable to meet the solubility criteria applied by the FDA but would meet the criteria applied by the WHO and EMA. They are all weak bases for which the ionization is not sufficient at pH 7.5 to effect a BCS conform solubility. However, it was reasoned that since the compounds should dissolve rapidly in the upper GI tract where the pH is either acidic (stomach) or almost neutral (average pH in the duodenum and jejunum is about pH 6-7), that the solubility at pH 6.8 is a more reasonable criterion to apply. Thus, amitriptyline and verapamil were recommended for the biowaiver. Because for quinine there was an additional complication due to the dose/toxicity profile, it was thought to be more appropriate to judge bioequivalence of products containing this API using pharmacokinetic studies in volunteers and the biowaiver was not recommended.

Last but not least, there were three APIs which failed to meet solubility criteria at low pH but which easily met the criterion at pH 6.8 and above. These were the three weakly acid anti-inflammatory drugs, diclofenac, ibuprofen and ketoprofen. As these APIs all have wide therapeutic indices and their dissolution is rapid at higher pHs, it was considered to be an acceptable risk to allow them to be biowaivered. Almost all published pharmacokinetic studies with formulations of these APIs show bioequivalence in AUC for the test and reference products. Occasionally the C_{max} is slightly out of the confidence interval for bioequivalence, and it is still not clear whether this can be detected with BCS conform dissolution testing[6,7] . However, since labeling indicates that these APIs can be taken with or without food, and since C_{max} is lower and occurs at a later time when the products are given with food, it seems highly unlikely that a small discrepancy in C_{max} would have any ramifications for therapy in clinical practice. This argumentation underscores recommendations of the WHO guidance, which allows APIs with such characteristics to be eligible for the biowaiver.

From the foregoing discussion it is obvious that there is more to biowaiving than just the BCS classification of the drug substance and that there is no "one-size-fits-all" approach to biowaiving. Instead, the approach of weighing up the risks and benefits for each individual drug substance has proven to be the more useful approach over the 32 compounds assessed to date.

Nevertheless it is interesting to consider the results for the 32 drug substances to date in the context of the BCS classification.

BCS Class I

Altogether 14 APIs in the dataset can be reasonably assigned to BCS Class I. These are acetylsalicylic acid, amitriptyline, chloroquine, doxycycline, levofloxacin, metronidazole, prednisolone, prednisone, primaquine, propranolol, quinidine, quinine, stavudine and verapamil. Of these, 12 were recommended for biowaivers and only two drugs, both with NTI status, were excluded from biowaiving.

Acetylsalicylic acid, doxycycline hyclate, propranolol hydrochloride, primaquine phosphate, and stavudine are highly soluble and highly permeable and BCS Class I, with no reports in the literature suggesting an impact of specific excipients on bioequivalence and which possess a wide therapeutic index. In general, as long as the excipients in the test product have already been used in products approved in ICH and

associated countries, and as long as these excipients are used in usual amounts for solid oral dosage forms, the risk of bioinequivalence appears to be very low and a biowaiver based approval was seemed appropriate. Only in the case where an excipient is known to affect motility/permeability in the upper GI tract must the excipient be used in the test as well as the reference product and preferably in the same or a similar amount. As all jurisdictions already apply the same criteria for BCS conform dissolution testing for products containing Class I APIs, the approach for biowaiving Class I drugs would be the easiest to harmonize on a global basis.

For other BCS Class I APIs, there are some specific and/or further restrictions to excipient use. Such restrictions tend to arise when the products approved in ICH and associated countries contain the so-called "critical excipients" i.e. those that can influence motility and/or permeability, neither of which can be detected with dissolution testing. For example, it has been noted that levofloxacin bioavailability can be affected by polysorbates (which can affect permeability) in the formulation, so amounts of this excipient should be similar in the reference and test formulations. Another drug substance classified as BCS Class I and having specific recommendations about excipients is metronidazole, for which amounts of sorbitol, sodium laurylsulfate and propylene glycol in the test drug product are recommended to be qualitatively and quantitatively identical to the comparator.

In the case of prednisolone, although the data on its solubility, oral absorption, and permeability were not totally conclusive, they strongly suggested the drug substance to be BCS Class I, hence it was concluded that biowaiver was acceptable under the usual restrictions with respect to the excipients present. This was also the case for prednisone, for which data on solubility, oral absorption, and permeability also were not totally conclusive, but which tended to be BCS Class I or borderline BCS Class I. Again, a biowaiver was concluded to be acceptable when the excipient requirements are met, also because in the very unlikely situation that an incorrect biowaiver decision would be reached, this would not subject the patient to any undue risks. Amitriptyline and verapamil represent two further cases where solubility is borderline at higher doses, particularly at higher pH values. Both are weak bases administered as hydrochloride salts, and as such, will be less soluble as the pKa is approached and exceeded. Like prednisolone and prednisone, however, the risks for the patient associated with a false bioequivalence decision based on biowaiving are considered to be too low to require pharmacokinetic studies of amitriptyline and verapamil products to prove bioequivalence.

For chloroquine phosphate, sulfate and hydrochloride, serious adverse effects have been reported, but only in cases of overdose, not as a result of relatively small fluctuations which would be associated with just failing to attain bioequivalence. By contrast, although quinidine sulfate is highly soluble and moderately to highly permeable, and thus assigned to BCS Class I, or at worst BCS Class III, it not only has a narrow therapeutic window but also a critical indication, and hence it was concluded that biowaiving would not be acceptable. That was also the conclusion for quinine sulfate, which is regarded as BCS Class I according to WHO and EMA guidances but BCS Class II according to the FDA as a result of the lower solubility at pH 7.5 than at pH 6.8. Although these solubility and permeability characteristics would suggest a low risk of bio*in*equivalence among oral quinine products, this narrow therapeutic index drug shows dose-related and, in some cases, irreversible side effects and toxicities at concentrations not far above the therapeutic concentration range. Therefore, the biowaiver was not deemed to be appropriate.

BCS Class II

A total of five APIs were classified as Class II and three of these were recommended for the biowaiver. The FDA and EMA regulations do not allow biowaiving for BCS Class II drugs, but the WHO considers biowaiving of certain Class II compounds, as long as they are "highly soluble" at pH 6.8. In our Biowaiver Monographs, the scientific principles outlined in the WHO Guidance were underscored by the positive decisions reached with regard to biowaiving of three such drugs.

For the three APIs that are weak acids and thus exhibit poorer solubility at low pH but high solubility at pH 6.8, biowaivers were recommended even though the compounds formally belong to Class II. In accordance with the WHO guidance, it is expected that compounds with high solubility at pH 6.8 will be able to go quickly into solution in the upper small intestine and therefore be available for uptake. Thus, as long as an API has high permeability, poor solubility at gastric pH should not represent a significant barrier to absorption. Naturally, such cases still have to fulfill all other criteria with respect to therapeutic index, excipient effects, incidence of bioequivalence failures etc. For diclofenac potassium and sodium, the Monograph recommended the biowaiver for both salt forms, due to their therapeutic use, therapeutic index, and pharmacokinetic property profiles, as well as the lack of potential for excipient interactions, and reliable performance in bioavailability studies. The same holds for ibuprofen, also formally BCS Class II. Differences in composition and/or manufacturing procedures were reported

to have an effect on the rate, but not the extent of absorption; and furthermore such differences are likely to be detected by dissolution testing. Although there is not a perfect guarantee that the biowaiver would ensure *in vivo* bioequivalence, the Monograph accepted biowaiving. Similar arguments were used to recommend the biowaiver for ketoprofen.

Two further drug substances identified as BCS Class II were not deemed to be appropriate for the biowaiver. The first was rifampicin, for which many reports of failure to meet bioequivalence have been published and the reasons for these failures are insufficiently understood. Moreover, no reports were identified in which dissolution was shown to be predictive of lack of equivalence, therefore, it was recommended not to consider a biowaiver. The second was mefloquine, which is a weak base with insufficient solubility at pH typical of the small intestine (pH 6.8 and above). With its permeability inconclusive, it may even belong to Class IV. In any case, it cannot meet the BCS based biowaiver criteria for solubility in any jurisdiction and thus would not be eligible for the BCS based biowaiver.

BCS Class III

Of the Biowaiver Monographs to date, 10 addressed drug substances assigned to BCS Class III. These were acetaminophen, acyclovir, atenolol, cimetidine, ethambutol, isoniazid, lamuvidine, metoclopramide, pyrazinamide and ranitidine. Whereas the FDA regulations as of the time of this writing do not consider BCS Class III drug substances to be eligible for the biowaiver, the WHO and EMA guidances both do. After weighing the pros and cons for each of the 10 drug substances monographed to date, seven were recommended for a biowaiver, and the remaining three were recommended for the biowaiver if certain addition criteria could be met. In all cases where a biowaiver was recommended, it was noted that the excipients maybe more critical to bioequivalence for Class III than is the case for BCS Class I drug substances. For this reason, as well as recommending the use only of excipients which have already appear in products with a marketing authorization in an ICH or associated country, it is further recommended that types and amounts of excipients be similar in the test and the comparator product and that "critical excipients" i.e. those known to affect permeability or GI motility, be duplicated in so far as possible in the test product if they are present in the comparator product.

Acetaminophen and lamuvidine are both borderline high permeable compounds, with some studies showing almost 100% absorption and others just failing to meet the 85% absorption which is the criterion applied by the WHO and EMA. It was noted that, in the case of acetaminophen, Health Authorities often accepted differences between the rates of absorption from the drug products, as such differences are not considered to be therapeutically relevant. Ethambutol dihydrochloride was also identified to be a BCS Class III drug with a permeability approaching the border between BCS Class I and III. But this drug substance has a narrow therapeutic index, related to its ocular toxicity. In the Monograph, biowaiving was considered acceptable under the proviso that the Prescribers' Information indicate the need for testing the patient's vision prior to initiating ethambutol therapy and regularly during therapy.

Atenolol, cimetidine and ranitidine hydrochloride were also identified as BCS Class III but in these cases the permeability falls well below the criterion for highly permeable. On the basis of the scientific evidence in the literature with respect to excipient effects on absorption and risks to the patients, it was deemed appropriate to apply the biowaiver. In the case of cimetidine and ranitidine, it was even considered unnecessary to apply the "very rapidly dissolving criterion" for dissolution, instead, rapid dissolution profiles with f2 comparison was considered adequate.

Similarly, pyrazinamide is clearly BCS Class III, with linear absorption over a wide dosing range. Depending on the definition used, pyrazinamide can be classified as a narrow therapeutic index drug, which is usually a caveat to biowaiving. However, if the Prescribers Information for the test product stipulates the need for regular monitoring of liver function, the biowaiver can still be recommended. A further criterion is the ability of both the test and comparator product to fulfill the requirements for "very rapidly dissolving".

Aciclovir is also a drug substance for which the permeability is well below the cutoff value. At usually applied dosage strengths (up to 400 mg) it is therefore assigned conclusively to BCS Class III. However, in some countries 800 mg tablets are also available, which puts acyclovir just over the border into BCS Class IV. Since no examples of bioinequivalence have been identified in the open literature and since aciclovir has a wide therapeutic index, it was recommended to apply the biowaiver. Similarly to atenolol, both the test and comparator product must be very rapidly dissolving to conclude bioequivalence.

For metaclopramide and isoniazid, no conclusive data about permeability has been reported in the literature, so taking a conservative view, they were assigned to BCS Class III for the purpose of applying the biowaiver procedure. In line with this classification, and the pharmacokinetic properties, therapeutic use and therapeutic index, a biowaiver was recommended, as long as the test and comparator product are both very rapidly dissolving. In the case of isoniazid, formulations with lactose and other reducing sugars were explicitly excluded from the biowaiver, since such excipients accelerate the decomposition of the drug substance.

BCS Class IV

Two drug substances could be unequivocally assigned to BCS Class IV. Ciprofloxacin hydrochloride and furosemide were both identified as failing to meet the criteria for either high solubility or high permeability. Hence, biowaiving for these two drug substances was considered inappropriate.

BCS Class not defined

For acetazolamide, its solubility, oral absorption and permeability were not sufficiently conclusive to classify it with certainty according to the BCS. Furthermore it has toxicity issues and might be considered as borderline NTI. Taking a conservative view, a biowaiver was not considered justified. If further evidence comes to light about its solubility, permeability and toxicity properties, this conclusion could be revisited.

So what have we learned from our experiences with the BCS based biowaiver in over 30 drug substance cases?

First, it looks like the trend towards allowing biowaivers for Class III as well as Class I drugs is supported by our evidence to date. This is also reflected in the acceptance of the biowaiver procedure for Class III drugs substances by the EMA in 2010: already there have been approvals for drug products containing Class III drug substances such as acetaminophen in the EU. Moreover, the application of the biowaiver procedure to products containing Class III drugs appears to be under serious consideration by the FDA in the USA.

Second, for quite a few compounds there is a lack of clarity about the permeability. Especially for drug substances which undergo extensive first pass metabolism it

is often difficult to pinpoint whether an absolute bioavailability of less than 85% reflects less than "high" permeability or whether the drug substances is in fact highly permeable and the low bioavailability is solely due to first pass effects. Further, there are quite a few drug substances that cannot be administered intravenously (or have not been) due to unwanted reactions upon injection or to inability to formulate a parenteral version of the drug substance. In all these cases, it can be difficult to decide between a Class III and a Class I drug substance. In the USA this is crucial, since at the time of this writing, Class III drug substances are still excluded from biowaiving. In Europe, and in countries following the WHO guidances, the permeability is not so crucial, since both Class I and III drug substances can be considered for biowaivers. However, as the requirements to be satisfied for a biowaiver based approval are far more stringent for Class III drug substances, the classification is still quite important for the sponsor of the application. Also with respect to the permeability, there needs to be harmonization among the various regulatory authorities concerning the cutoff value for high permeability. Currently the cutoff is made at a fraction absorbed of 0.9 in the USA but at 0.85 in other jurisdictions. In the future, we will need to address a common standard cutoff value and also determine which value of fraction absorbed would be appropriate.

Third, based on current evidence, there seems to be little risk associated with applying the biowaiver to NSAIDs that are weak acids with adequate solubility at pH 6.8 and above. To date Biowaiver Monographs have been published for ibuprofen, diclofenac salts and ketoprofen. There is a large body of evidence in the literature which suggests that multisource products containing these drug substances tend to be bioequivalent. When lack of bioequivalence occurs, it is usually the C_{max} rather than the AUC which falls out of the limits for the confidence interval. In other words, it is the rate rather than the extent of absorption which can be a problem. On the one hand, a change in rate of absorption might be critical if a rapid onset of action is required, but on the other hand, these drugs can all be taken with or without food, which itself has a significant influence on the rate of emptying into the intestine and hence on the rate of absorption of drug substances belonging to this group. So it is not clear that a small change in the rate of absorption is clinically important. Mostly the BCS biowaiver dissolution tests can detect differences of this nature, though recent results from the Alvarez group show that this might not always be the case if the f2 statistic is applied to determine similarity of the dissolution profiles[6]. One suggestion might be to scale the data to 100% release from the reference formulation before applying the f2 statistic (since f2

represents an absolute rather than a relative difference). However, the discussion in this arena is ongoing and the best way to handle the data for products containing such drug substances still need to be agreed upon.

Fourth, we need a better way of handling drug substances that are available over a very wide range of dosage strengths, straddling the "high" and "not high" solubility categories. This problem was seen for aciclovir, prednisone and prednisolone and there are probably other cases as well. In such cases, a specific decision for the drug substance should be reached based on a risk-benefit analysis. A related problem exists for substances that have different dosage strengths in different jurisdictions. We have observed that the maximum dosage strength recommended on the WHO Essential Medicines List (EML) is often lower than the maximum dosage strength listed for use in the USA or in Europe. Substances with borderline solubilities may therefore qualify for the BCS biowaiver procedure in countries following the EML listing and WHO guidance, yet fail to meet the requirements e.g., in the USA. Yet another consideration is the "right" cutoff value for the dose-solubility ratio. Although this has been harmonized throughout all jurisdictions allowing the biowaiver at 250 ml, there has been some discussion in the literature about raising this value[8].

Fifth, the NTI classification is not consistent among jurisdictions and there is no real agreement on the definition. This is another point which needs to be clarified, as this is a crucial element of the biowaiver decision**.** One possibility would be to adopt the US-American approach of determining whether at doses twice or less of the therapeutic dose or at plasma concentrations twice or less of the therapeutic plasma concentrations, unwanted side-effects occur. Another possibility would be that the WHO produces a list of NTI compounds, to which the member countries could agree.

All in all, the experience with the Biowaiver Monographs has brought many issues to light, and these all need to be worked on in the coming years.

IMPACT OF THE BIOWAIVER MONOGRAPHS

The BCS based biowaiver and the Biowaiver Monographs have had a great impact on approval of multisource drug products. Drug products approved through the BCS biowaiver procedure and manufactured under Good Manufacturing Practice can be assumed to have the same quality as the reference product. When the reference

product has also been tested for safety and efficacy (as is the case when a generic drug product is compared against the innovator product, for example), quality means not only the manufacturing and quality control standards but also the safety and efficacy of the drug product. Since approval through the BCS biowaiver procedure circumvents the need to use human subjects, it offers the advantage of reducing the expense of bringing a new drug product to market and the time required to gain approval is also substantially reduced. Further, the ethical dilemma of subjecting human volunteers to medicines that they do not need and which may possibly result in unwanted side effects is not relevant if the biowaiver procedure is used. Thus, *in vitro* dissolution studies carried out by skilled scientists on validated equipment is an attractive alternative to proofing bioequivalence using pharmacokinetic methods. In developing countries, where resources and know-how to conduct pharmacokinetic bioequivalence testing are not always available, applying the BCS based biowaiver to approve drug products may even improve the quality of drug products available to the patients. Documentation of the number of drug approvals based on the BCS biowaiver procedure is not widespread and so it is difficult to get a clear understanding of how many products have been approved globally on this basis. However, some information has been published e.g. the FDA in the USA has indicated that 30 drug products had been approved through the BCS biowaiver procedure in the time frame 2000-2010 and that since 2008 the frequency of biowaiver based applications for ANDAs has increased substantially. The poster concluded that the "BCS biowaiver is becoming an effective tool for reducing the regulatory burden in the development of generic drug products"[9]. BCS principles have also been used in the IND/NDA process when BE studies are required. Likewise, the Prequalification programme of the WHO has adopted the BCS based biowaiver and publishes lists of products that can be prequalified according to this procedure. For example, in the antituberculosis programme, products containing ethambutol, isoniazid, levofloxacin, ofloxacin and pyrazinamide can be approved by the biowaiver procedure (http://apps.who.int/prequal/info_applicants/BE/BW_TB_2009February.pdf).

The Biowaiver Monographs themselves have been widely cited and are very popular as downloads. For example, the acetaminophen (paracetamol) biowaiver monograph has been cited in peer-reviewed scientific publications more than 50 times since it was published in 2006 (www.ncbi.nlm.nih.gov/**pubmed**/16307451, accessed 9th June, 2012) and has been downloaded in full text format from the Journal of Pharmaceutical Sciences website over 1500 times. All together, the biowaiver monographs are accessed more than 600,000 times a year (personal communication, J Pharm Sci), indicating

keen interest in them on the part of pharmaceutical scientists. They are also watched with interest by regulatory scientists, who find them to be a valuable resource when reviewing applications.

Last but not least, the BCS based biowaiver has helped to foster other ways of understanding the relationships between physicochemical characteristics of drugs and their physiological fate. From these considerations, the Biopharmaceutical Drug Disposition Classification System (BDDCS) was conceived[10]. It links a high tendency to undergo metabolism to high drug permeability through the gut wall. Conversely, drugs which have low permeability tend to be metabolized to a much lower extent. Such considerations can help to classify drug substances according to BCS and shed light on what can be expected when the drug is introduced into clinical trials. Last but not least, the BCS has also helped to understand better for which drugs an *in vitro-in vivo* correlation can be established, which is another way of reducing the need for bioequivalence studies during drug product development.

THE FUTURE OF BIOWAIVER MONOGRAPHS

Ongoing Biowaiver Monograph Activity

The Biowaiver Monograph project has already produced over 30 monographs and several are nearing completion. With regard to the published Biowaiver Monographs, many applicants have submitted dossiers which refer to the results summarized in the monographs, without being asked by the regulatory agencies to repeat the studies, thus saving the applicants time and money. In this way, preparation of regulatory work can be streamlined – and the data used are often better as they have already been through a scrutinizing and objective peer review. The overall value of the Biowaiver Monograph project will increase, as further drugs are monographed. The long term aim of the project is to complete monographs for all drugs on the WHO List of Essential medicines as well as for other drugs that are widely used.

Biowaiver Monographs for Fixed Dose Combinations

In fixed dose combinations (FDCs), a drug product contains more than one drug substance, in order to take advantage of synergies in the pharmacological activity of the individual drug substance, to reduce side-effects by reducing the doses of the individual drugs substances and to improve patient convenience and compliance. Accordingly, in the future, the Biowaiver Monograph project will no longer be restricted to single drug substances. We are currently starting to implement consideration of

FDCs, as well as products containing only a single drug substance in the Biowaiver Monographs. With more drug substances in a product, one is confronted with new challenges. To name a few examples: what if one drug is BCS Class I while the other is BCS Class II? Are there physical incompatibilities between the FDC partners? What should the comparators be – other FDCs or can one use the equivalent single drug products? These and other challenges will surely be the topic of intense discussion within the Focus Group as we move forward.

Should we consider highest dosage strength or highest single dose to calculate D:S?

In the Biopharmaceutical Classification System (BCS), an Active Pharmaceutical Ingredient (API) is classified according to its GI permeability and solubility. Solubility is expressed in Dose/Solubility (D/S), defined as the volume (ml) sufficient to dissolve the Dose. "Highly soluble" APIs are those with D/S at or below 250ml over the entire pH range defined in the guidance. The present FDA (2000) and WHO (2006) Guidances, as well as the former EMEA (2001) guidances, define Dose as the highest oral immediate release (IR) dosage strength, i.e. the tablet or capsule with the highest content of API. However, the recent EMA (2010) guideline defines Dose not as the highest oral IR dosage strength, but as the highest single oral IR dose administered, referring to the Summary of Product Characteristics (SmPC). This has resulted in a BCS Class change for several APIs, such as acetazolamide, metoclopramide and verapamil[11]. In the case of acetazolamide, the BCS based biowaiver had not been recommended due to its borderline narrow therapeutic index status and inconclusive solubility/permeability classifications, so the change in BCS Class did not affect the negative biowaiver recommendation. However, with the change in BCS Class for metoclopramide and verapamil, a biowaiver based approval would no longer be applicable in the EU, so the bioequivalence decision would have to be based on results of a comparative pharmacokinetic study. It is interesting that the same EMA guidance generally calls for the highest dosage strength to be used for a pharmacokinetic proof of bioequivalence, thus revealing a degree of inconsistency between the dose to be considered for *in vitro* and *in vitro* proofs of bioequivalence in this jurisdiction.

Discussion of the merits and disadvantages of the two ways of calculating the dose:solubility ratio is ongoing. On the one hand, it is the drug product, not the dosing instructions, which is being tested for bioequivalence and in *in vivo* BE testing it is usual to use the highest dosage strength for the study. On the other hand, particularly in

early clinical development, there is often a need to administer multiple dosage forms in Phase I studies or in order to arrive at a therapeutic dose in Phase 2 studies. In this case, the ability of the luminal fluids to adequately dissolve the drug may be challenged on a far different level than would be reflected by the highest dosage strength. Additionally, the SmPC might prescribe a single dose which requires more than one dosage form at the highest strength – as for example with prednisolone and prednisone. These and other challenges will be the topic of intense discussion for each Biowaiver Monograph where such considerations come into play, with a conclusion being reached only after considering the individual drug case as well as the various regulations.

Develop science-based risk calculations to make the biowaiver decision more objective

Since biowaiving is a surrogate for the *in vivo* proof of bioequivalence, accepting the *in vitro* biowaiver inherently has some risk that the biowaiver decision is not correct i.e., the two products are actually bioequivalent to each other but application of the BCS based biowaiver concludes that they are not bioequivalent, or, conversely, the two products are not bioequivalent to each other but application of the BCS based biowaiver concludes that they are bioequivalent with each other. Biowaiving is an *in vitro* surrogate for the *in vivo* proof of bioequivalence.

In the former case, the applicant is refused a biowaiver based approval and must perform an *in vivo* assessment of bioequivalence to obtain product approval, costing time and money, and the patient is deprived of the advantages of having more products available. In the latter case, the patient receives a product which is not bioequivalent to the comparator, and will be exposed to the risks associated with a higher than expected or lower than expected plasma concentration of the drug.

Currently we do not have enough information about the incidence of false biowaiver decisions and in which situations they are most likely to occur. One can speculate that this incidence may be dependent on the BCS Class of the drug and may be higher in the presence of excipients which can influence permeability or gut motility, as these effects cannot be assessed by the dissolution testing. Presently, there are simply not enough case examples in the open literature to make a statistical analysis. Once such a data set has been established, the acceptable risk level should be compared to the actual risk. But here too there is a dilemma – what is the acceptable risk? As the confidence

levels are set at 90% and the power level at 80% in *in vivo* studies, it is clear that reaching an inappropriate decision in an *in vivo* bioequivalence study is also possible, but is statistically definable. One approach to determining the acceptable risk for an inappropriate biowaiver decision would be to set it at the same level as an acceptable risk for a false decision made on the basis of an *in vivo* bioequivalence study.

In the future it is to be hoped that this risk calculation (risk of an incorrect bioequivalence decision based on the BCS biowaiver) can be put on a more formal basis and applied in a consistent way in the conclusions of the Biowaiver Monographs.

Of course, the *ramifications* of an incorrect biowaiver decision (such that a suprabioequivalent or subbioequivalent product enters the market) are highly dependent on the indication and therapeutic index of the drug. Thus, these risks need to be assessed on an individual drug basis.

Global Harmonization of Biowaiver Regulations

Perhaps most importantly, and in the interests of consistent global health policies, a key future activity in the BCS based biowaiver area should be to stimulate the various regulatory authorities to change and improve their regulations, so that they all apply "best science" practice to BCS biowaiving. This would eventually lead to a harmonization of biowaiver approaches throughout the world. It is to be hoped that all major jurisdictions, including Japan, will one day be able to agree on prerequisites and conditions for biowaiving, so that applicants and patients alike can benefit from this innovative concept on a global basis. Although currently there is still a diversity of opinion on the best scientific way forward, it is certain that through continued dialogue through the publication of Biowaiver Monographs and discussions in science and practice related conferences, this goal is achievable.

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UPDATE ON REGULATIONS ON *IN VITRO* EQUIVALENCE TESTING

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Disclaimer: This text reflects the personal opinions of the author, which do not necessarily represent the views or policies of the German Federal Institute for Drugs and Medical Devices (BfArM)

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INTRODUCTION

Almost two decades have passed since the Biopharmaceutics Classification System (BCS) was published by Amidon *et al.*[1] and introduced to reduce the need for *in vivo* bioequivalence studies, in particular for applications of generic drug products. Like bioequivalence studies the BCS concept aims to compare formulation effects. In short, the concept is based on the scientific rationale that rate and extent of drug absorption is assumed not to be dependent on product formulation as long as the drug substance is highly soluble and easily transported and is manufactured in immediate release dosage forms exhibiting similar, rapid *in vitro* dissolution characteristics. The approach is applicable for generic applications, to compare developmental products with to-be-marketed formulations during the development of new drugs, for certain line extensions and in cases where bioequivalence has to be demonstrated due to product variations. Since its introduction, the BCS based biowaiver has been implemented into guidance documents on bioequivalence in many jurisdictions, since the bioequivalence of oral dosage forms is the primary issue for which the BCS concept can be applied in a regulatory setting. However, differences among the various regulatory requirements are evident and are frequently criticized by pharmaceutical companies.

The following brief overview attempts to highlight the main guidance documents, along with their particularities, including more detailed information on the recently revised European guideline on bioequivalence. In addition, the distinction between the BCS based biowaiver approach and other situations is addressed where comparative *in vitro* dissolution aims to conclude on bioequivalence.

The US-FDA guidance

The US-FDA was the first jurisdiction that implemented regulatory requirements for BCS based biowaiver applications in a separate, comprehensive guidance document in 2000[2]. The guidance still restricts the eligibility of the BCS based biowaiver approach to BCS Class I drug substances in immediate release formulations and requires *in vitro* dissolution to be rapid, i.e. at least 85% dissolution of the labelled amount within 30 min or less.

In line with common understanding, the US-FDA guidance does not accept BCS based biowaivers for narrow therapeutic range drugs irrespective of their BCS classification.

Formulation-wise, products designed to be absorbed in the oral cavity (e.g. sublingual or buccal tablets) are also excluded from the BCS based biowaiver concept since absorption from such products may occur through the oral mucosa, and so their intended performance properties do not conform to the conceptual prerequisites of the BCS based biowaiver.

The definition of 'high solubility' refers to the highest dose strength of an immediate release product, which has to be soluble in 250 ml or less of aqueous media over the pH range of 1 – 7.5,. Solubility measurements should be performed at 37 °C using a stability-indicating, validated method. Further experimental requirements are extensively outlined and they are basically in line with pharmacopoeial recommendations.

The classification regarding high permeability refers to the extent of absorption in humans, i.e. high permeability is concluded if the extent of absorption in humans reaches at least 90 % of an orally administered dose. This conclusion may be based on either pharmacokinetic studies in humans (e.g. mass balance, or absolute bioavailability studies) or intestinal permeability methods like e.g. *in vivo* intestinal perfusion studies in humans or validated *in vitro* permeation studies across a monolayer of cultured epithelial cells.

Comparative *in vitro* dissolution investigations should ensure that no less than 85 % of the labelled amount is dissolved within 30 min in each of the required media: 0.1 N HCl, pH 4.5 and 6.8 buffers. Regarding experimental requirements, reference is made to the US Pharmacopoeia and the US-FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997)[3]. Resulting profiles should be compared using the similarity factor (f2), unless 85% or more of the labelled amount dissolves within 15 min from both products. The latter case would allow the conclusion that the investigated products are similar without requiring any further statistical calculations.

The US-FDA guidance requires that excipients be employed in usual quantities and consistent with their intended function, in order to exclude the possibility that particular excipient-driven effects occur *in vivo* which may not be detectable by means of *in vitro* dissolution experiments. New excipients and/or atypically large amounts of commonly used excipients require additional information and discussion. Relative bioavailability studies (i.e. using a simple aqueous solution as a reference)

may be requested to prove that certain excipients are not likely to have an impact on bioavailability.

Current Issues

Although the US-FDA guidance has been in place since the year 2000, BCS based biowaivers have been granted for only a limited number of drug substances [personal communication, US-FDA, [4]] up to now. However, increasing interest to use this approach is noted and generic approvals based on the BCS based biowaiver concept have increased since 2008 [5]. A revision of the guidance document is currently underway which might include a waiver possibility for BCS Class III drug substances [6], thereby addressing recent findings in this field and harmonizing with the revised EMA and WHO documents. Moreover, some criticism has been published regarding the definition of 'high permeability,' [7] emphasizing the need for a revision.

Further, reference is made to the US-FDA website, where product-specific recommendations are publicly available describing which bioequivalence investigations are expected. Some of them include a hint that the BCS based waiver approach could be used. Even though this information already entails the principle acceptance of the drug substance as fulfilling the BCS Class I criteria, applicants are requested to support the classification by means of their own experimental data. In general, in addition to data on solubility, results of Caco-2 experiments are often submitted for this purpose, irrespective of any previous classification in terms of permeability which has been accepted by the US-FDA.

As a particular surrogate for bioequivalence between a test and a reference, the BCS based biowaiver is accompanied by other regulated approaches using *in vitro* dissolution as a tool to waive *in vivo* equivalence testing. These have been reviewed, for example, by Gupta et al. and include SUPAC rules, waiver based on proportionality considerations and *in vitro/in vivo* correlations [8].

The European Guidance

In August 2011 a revised version of the European note for guidance (NfG) on bioequivalence testing came into operation [9] addressing the BCS based biowaiver approach more comprehensively in a separate appendix including relevant modifications to the previous NfG published in 2002 [10].

Similar to the US-FDA guidance, therapeutic aspects are addressed first, i.e. the drug substance in question should not have a narrow therapeutic index (NTI). This recommendation is meant to serve as an initial risk assessment since as of this writing it has not been proven that the BCS based biowaiver is eligible even when narrowed acceptance limits (i.e. 90 – 111%) for AUC and/or C_{max} are required *in vivo*.

Solid oral formulations other than immediate release products are excluded from the biowaiver approach but it is specifically mentioned that it could be used for orodispersible formulations provided it can be shown that the drug is not absorbed across the oral mucosa.

Another particularity of the revised EMA guideline refers to the EU directive (2001/83/EC, Article 10(2)(b) allowing a generic to contain different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance. Appendix 3 therefore clarifies that this general definition of the 'same active substance' can not be applied for a generic applying the BCS based biowaiver concept. Instead, only different salts, both of which are shown to be BCS Class I drug substances, are considered acceptable. All of the other variations on the active substance mentioned above do not qualify for the biowaivers since potential bioavailability differences would not be detectable by means of investigations relevant for the BCS based biowaiver concept.

Class boundaries and formulation-related requirements have been modified and specified as follows:
The criterion for high solubility refers now to the *highest single dose* (rather than the highest dose strength), and a physiological pH range between pH 1 – 6.8. It is expected that not only usual three media are used (pH 1.2, 4.5, and 6.8) but that solubility should also be investigated at the pKa, if applicable.

It is interesting to note that the European guidance particularly requires information on absorption rather than demonstration of high permeability. According to section *III.2* the extent of absorption should reach at least 85 % in order to classify for high permeability. This interpretation of the permeability approach is in line with a paper published by Benet et al. [7] where the 'ambiguous' definition of high permeability has been criticised. In contrast to US-FDA and WHO requirements, absorption characteristics can only be substantiated by means of human data, i.e., cell culture investigations could be supportive but are not considered valid as stand-alone

information on absorption. Absolute bioavailability and masS balance studies in humans are mentioned as acceptable data to support near complete absorption. In addition, an explanation is given as to how metabolites may be considered if masS balance results are presented. Furthermore, reported bioequivalence between orally administered aqueous solutions and immediate release solid formulations could be supportive as this indicates rather minor formulation effects on absorption.

Since the EMA guideline allows the BCS based biowaiver approach not only for BCS Class I but also class III compounds, it is not necessary to have complete knowledge about absorption. However, if this is the case or complete absorption (at least 85 %) can not be demonstrated, more restrictive requirements have to be met regarding product comparison *in vitro* (see below).

Comparative *in vitro* dissolution of the products in question should aim to demonstrate absence of differences with respect to formulation characteristics. As a fundamental prerequisite the batches used for such experiments should be representative for the products compared, as is required for *in vivo* bioequivalence studies. Therefore, reference is made to section 4.1.2. of the main guideline text, as this paragraph outlines respective requirements for adequate 'biobatches'. In addition, it is considered advisable to investigate more than one batch in order to ensure that the batches are indeed representative for the applied product.

In vitro dissolution should not only be investigated using generally employed media (pH1.2, 4.5, and 6.8) but also at pH values where the minimum solubility of the compound in question could be relevant (e.g. torasemide) [11] . The description of basic experimental conditions includes a reference to current compendial standards in general. Stating the agitation to be 'usually' 50 rpm for the paddle apparatus and 'usually' 100 rpm for the basket apparatus provides some flexibility as to e.g. account for situations where coning effects might be relevant. A sampling schedule is given as an example (10, 15, 20, 30, and 45 min) indicating the necessity to provide a complete dissolution profile. As an expected general rule Ph.Eur. buffers are recommended and surfactants are definitely discouraged.

General requirements regarding data evaluation are in line with other guideline documents, i.e. very rapidly dissolving drug products are those reaching 85 % within 15 minutes and can be considered similar without further statistical evaluation, whereas

in other cases the dissolution may take longer but not more than 30 min to achieve 85 % dissolution. The latter case would require demonstration of test *vs.* reference profile similarity by means of f_2-testing unless the profiles are superimposable. However, the evaluation of comparative *in vitro* dissolution emphasizes the notion that an absence of differences is the goal when using the BCS based biowaiver concept. Consequently, it is particularly stated that discussion of profile differences in terms of the *in vivo* relevance is considered inappropriate. This statement appears rather strict but in essence reflects perfectly that the BCS based biowaiver approach provides a means to ensure that neither the drug substance itself nor formulation characteristics are likely to affect bioavailability of test and reference.

In contrast to the previous guideline text, requirements on excipients are specifically addressed in a separate paragraph. In general applicants are advised to use the most similar excipients whenever the BCS based biowaiver approach is applied. However, there is a differentiation between BCS Class I and III drug substances as to how critical possible differences are considered. In case of BCS Class III drug substances, the guideline requires qualitatively the same and quantitatively very similar excipients while somewhat more flexibility is possible for BCS Class I drug products. As an additional general rule, excipients that might affect bioavailability should be both qualitatively and quantitatively the same in test and reference. In essence this would probably require "reverse engineering" of the reference product but also reflects the limited knowledge available for specific impact of such excipients on bioavailability. Furthermore, applicants are expected to provide comprehensive information and thorough evaluation of all excipients used in the composition under discussion.

Current Issues

The first BCS based biowaiver for a generic drug product e.g. in Germany was granted already in 2002 based on the previous guideline [12]. Meanwhile, and particularly related to the revised guideline, the industry has shown rising interest in the possibility of filing BCS based biowaiver for generic drug applications and in the development of new drugs.

There are still some unresolved and/or controversial issues in using this approach, like questions regarding convincing data on human absorption leading to BCS Class I or III classification since this has consequences with respect to requirements for comparative *in vitro* dissolution. There are also discussions on whether a failed study

may be substituted by filing a BCS based biowaiver for the product in cases where the reason for failing *in vivo* could be explained e.g. by outliers or analytical limitations.

With respect to orodispersible formulations, convincing and generally accepted ('compendial') *in vitro* dissolution methods are still lacking thereby substantially limiting the use of the BCS based biowaiver approach. However, there are proposals to require two comparative tests, i.e. *in vitro* dissolution combined with disintegration (personal communication).

Further discussions arise when the concept is used to compare aqueous solutions with solid formulations - which is clearly not acceptable, neither according to the underlying waiver concept nor according to the guideline, as the formulation difference is not sufficiently covered by BCS based waiver related investigations.

Assessment of BCS based biowaiver documentation has revealed that data variability should be part of thorough evaluation. This includes looking at individual results rather than mean values only. As an example, upon request one company indicated that some (seemingly 'minor') process modifications led to an obvious reduction in data variability. However, it is important to see test product characteristics that are representative for the to-be-marketed product.

Another issue came up through interactive assessment of *in vitro* dissolution data provided for the BCS based biowaiver and those proposed for product specifications, i.e. batch release. It seems prudent that *in vitro* dissolution specifications should not exceed acceptance criteria applicable for the BCS based biowaiver, i.e. a maximum time of 30 min to reach at least 85 % of the labelled amount dissolved for BCS Class I compounds and a maximum time of 15 min to reach that limit for BCS Class III compounds. However, since usual pharmacopoeial requirements for batch release are usually more relaxed this issue is still provoking discussion.

Although the revised EMA guideline aims to consider current scientific knowledge and findings the respective WHO document on the BCS based biowaiver is still the guidance with the most relaxed approach to biowaiving. Efforts are still ongoing to implement the biowaiver concept in the regulatory framework of developing countries in order to facilitate respective applications and thereby product quality. (see chapter by Jan Welink in this book)

Other Jurisdictions

Some countries are considering the BCS based biowaiver concept by adopting either one of the three main guidance documents (US-FDA, EMA, WHO) or a combination of specific requirements.

Brazil may be viewed as one particular example of a 'threshold-country' which has specified respective regulatory requirements on how to apply for a BCS based biowaiver following intense discussions and an assessor's meeting on this topic in 2009. Additional background information on the development of the legislation for generic drugs in Brazil can be found in [13]. Meanwhile, the Brazilian authority (ANVISA) implemented the BCS based biowaiver and published a guideline on this issue in 2011 [14]

Regarding the general BCS classification of active substances ANVISA already identified those that would be acceptable and listed them in the guideline as follows:

- Acetyl salicylic acid
- Propranolol hydrochloride
- Doxycycline hydrochloride
- Dipyron
- Estavudine
- Fluconazol
- Isoniazid
- Levofloxacin
- Metoprolol
- Metronidazol
- Paracetamol
- Sotalol

These drugs are proposed based on (publicly) available data for the listed active substances regarding extent of absorption, therapeutic window, history of bioequivalence problems and solubility. Accordingly, extent of absorption should reach at least 85 %, the therapeutic window should be wide, and bioequivalence problems should be absent. Applicants are supposed to demonstrate high solubility despite the listing, since the guideline text indicates that 'high solubility' has been assumed. The reason for handling the solubility this way relates to the lack of solubility data that would meet specified BCS criteria, e.g. solubility in three buffers at 37 °C. It is mentioned that solubility refers to the highest single dose. Conditions of solubility investigations

like shake-flask method or phase-diagram are specifically mentioned as being suitable to demonstrate 'solubility at equilibrium'.
Required conditions for comparative dissolution testing are basically in line with US-FDA requirements, except that the Brazilian Pharmacopoeia and those accepted by ANVISA should generally be followed.

ANVISA also requires thorough comparative evaluation of excipients but this seems less strict than e.g. the European regulation. Accordingly, excipients that might affect bioavailability should be qualitatively the same in test and reference and quantitatively compatible with the intended function. It is stated that other excipients may be different but should be well-established for the dosage form, route of administration, and the drug substance under investigation. For isoniazid it is particularly stated that respective formulations should not contain any saccharides.

In summary, the Brazilian guideline combines certain aspects taken from all three, the US-FDA (e.g. BCS Class I only) guideline, the EMA (e.g. requirements on 85 % absorption and consideration of the highest single dose rather than the strength), and WHO guideline (e.g. providing a list of drug substances eligible for the BCS based waiver). Overall, the Brazilian requirements look rather conservative except handling of excipients which seems less restrictive than e.g. in Europe.

Australia and *ASEAN (the Association of Southeast Asian Nations) countries* adopted the previous European guideline, thereby allowing application of the BCS based biowaiver for BCS Class I drug substances in immediate release dosage forms. For example, in 2000 *Malaysia* and in 2009 *Thailand* have published bioequivalence guidelines in line with the unrevised European guideline. However, Singapore published a guidance document dated February 2007 referring to both the US-FDA and EMA guideline.

Regarding *South Africa* the BCS based biowaiver approach is mentioned in a guidance on Biostudies effective since June 2007 [15]. The BCS biowaiver approach is also implemented in a guideline on 'Dissolution' that includes the BCS concept among other biowaiver options [16]. This guidance document came into operation in July 2008. Both documents basically refer to the US-FDA guidance on the BCS based biowaiver.

India drafted a document "Guidelines for Bioavailability & Bioequivalence Studies" (March 2005)[17] where the basic requirements on solubility, absorption and *in vitro*

dissolution are rather briefly mentioned as an option to prove bioequivalence. Basic requirements are in line with the current US-FDA guidance on BCS based biowaiver.
The *Pan American Health Organization* Working Group on Bioequivalence, drafted a document "Science based criteria for bioequivalence *in vivo* and *in vitro*, Bio-waivers, and strategic framework for implementation" basically adopting US-FDA recommendations as far as the BCS based biowaiver is concerned [18].

Argentina adopted the WHO guidance to a great extent and published a respective guidance document in 2009 [19]. However, the BCS based biowaiver is accepted for BCS Class I and III drug substances and a specific list of drugs is presented in addition mentioning the following compounds:

- Propranolol
- Salbutamol
- Tamoxifen
- Amitriptylin
- Diazepam
- Atenolol
- Ethambutol
- Hydralazine
- Flucytosine
- Methyldopa
- Clormipramine
- Biperidone
- Quinine bisulfate

Saudi Arabia drafted a guideline in 2005 also implementing the possibility to apply the BCS based biowaiver in line with WHO requirements, i.e. allowing the waiver approach for BCS Class I, III and some of BCS Class II drug substances ("Guidelines for Bioequivalence Studies for Marketing Authorization of Generic Products") [20]. The document is effective since January 2010.

In appendix 4 of its guidance document on bioequivalence dated 2008 *Korea* has implemented the US-FDA requirements on how to apply for a generic based on the BCS based biowaiver concept, i.e. allowing this approach for BCS Class I drug substances only [21].

Other jurisdictions do not accept the BCS based biowaiver approach or any of the current guidelines that have implemented it. *Switzerland*, *Canada*, and *Japan* have not yet implemented the BCS based biowaiver as a means to ensure bioequivalence of different drug products in any shape or form. However, *Canada* has conducted a workshop on this topic in order to at least identify the need and the possibility to employ the approach in their regulatory framework. Referring to *Japan* the situation is rather similar to what has been reviewed by Gupta *et al.* [8]. The "Guideline for Bioequivalence Studies of Generic Products", 2006 [22] states under section 1: Introduction: For oral drug products, dissolution tests should be performed, since they provide important information concerning bioequivalence", although not on a stand-alone basis. However, the BCS based biowaiver concept has been implemented at least to a limited extent in the process of justification of minor product variations according to the respective guidance document published in December 2006 [23].

Following a first draft in 2008 without implementing the BCS based biowaiver option, *Russia* has recently drafted a new guideline basically following the WHO recommendations [24]. However, this draft guidance is not yet in the implementation phase (personal communication). In contrast, *China* published a guideline on bioequivalence but do not seem to having implemented the BCS concept as a surrogate for *in vivo* bioequivalence like other jurisdictions.

DISCUSSION

Proving bioequivalence in various regulatory circumstances without conducting an *in vivo* study is highly appreciated by applicants in order to save relevant resources. Almost two decades ago the BCS based biowaiver was invented as a surrogate for *in vivo* bioequivalence and is now being increasingly utilized. However, divergent requirements in various jurisdictions seem to be still the most relevant reason that the approach is not employed as much as it could be. Obviously, the risk of a failed application and related loss of time on the market do not outweigh pronounced cost savings for generic companies [4].

Possible reasons include different views on whether using published data for drug substance classification is appropriate as compared to always requesting experimental results for this purpose. For example, in regulatory pratice the US-FDA is requesting

Caco-2 permeability on a regular basis while the EMA guideline requests information on human absorption, discouraging attempts to report the results of cell-culture investigations as stand-alone data. In view of these differences, the question has been raised from companies as to whether Caco-2 permeability could ever result in a false positive, i.e. indicating high permeability when absorption in humans does not support high permeability. There seem to be no final answer to this question yet, since arguments to date are based on a few well-known drug substances only. However, scientific discussions on the BCS concept including sub-classifications and classifications based on metabolic properties (e.g. Benet [25], Fagerholm [26]) may have at least contributed to a better understanding of the concept.

With respect to dissolution test requirements, part of the diversity in opinion arises from their several-fold applications in the pharmaceutical sciences: for example to test pharmaceutical quality, to assess limits to *in vivo* performance, and to demonstrate absence of differences within the BCS based biowaiver concept. As a result, *in vitro* dissolution experiments required in the framework of BCS based biowaiver may not necessarily meet the same criteria applied to test pharmaceutical quality. This could lead to the situation that a BCS based biowaiver is accepted and at the same time quality control methods employed for batch release of the particular test product may be much more relaxed in terms of *in vitro* dissolution since respective specifications often follow usual pharmacopoeial criteria. This example highlights the need for further specific recommendations clarifying this matter in order to prevent non-bioequivalent batches being released onto the market.

Furthermore, there seems to be a tendency of 'over-using' (if not misusing) the BCS based biowaiver approach. In its introduction to appendix III the EMA guideline explicitly mentions that the concept is applicable only to oral solid dosage forms. However, in various instances, appicants have tried to utilize the BCS based biowaiver to avoid *in vivo* comparison between solid and liquid formulations, i.e. studies on relative bioavailability. This approach is considered unacceptable and would in fact jeopardize the correct use since possible differences between such different dosage forms can not be addressed by means of the BCS based waiver 'tools'.

Besides using the BCS based biowaiver approach for generic applications, line extensions, and comparisons of developmental and to-be-marketed formulations it is also implemented in justifying unchanged bioavailability following relevant product

variations. In this context it is generally expected that a modified generic would again be compared to the innovator product, while the reference for a modified innovator product would be the non-modified formulation. Product variations that are considered 'minor' are usually addressed without questioning bioequivalence, i.e. by means of *in vitro* dissolution investigations. In different regulatory circumstances and jurisdictions the principles of the BCS based biowaiver like the multimedia testing have been implemented in various ways probably to strengthen the validity of comparative *in vitro* dissolution [see e.g. Ref. [8]]. This also includes the possibility of waiving additional comparative *in vivo* studies based on proportionality within a (generic or innovator) product series. Although BCS based drug substance classifications as such are generally considered rather supportive, implementing the BCS based biowaiver related multimedia testing as it is done for these various objectives remains open to question for the following reasons:

- For products containing 'highly' soluble drugs the multimedia testing will hardly be critical and/or discriminative when using it 'outside' the BCS based biowaiver considering all its specific prerequisites. For products containing 'low' solubility drug substances it is generally expected that companies develop the optimal discriminative experimental *in vitro* dissolution method considering basic knowledge on such experimental settings like e.g. sink conditions. However, the additionally requested use of the multimedia testing 'borrowed' from the BCS based biowaiver approach would ignore whether sink conditions are achieved and would strongly discourage any use of surfactants. This could lead to dissolution results which reflect drug substance solubility rather than biopharmaceutic product performance or at least a mixture of both. Instead, respective results are used to find possible signals for biopharmaceutic differences as an 'alarm' to request further *in vivo* studies as indicated in section 4.2.2 of the EMA guideline [9]. In several cases, diverging results generated with a product-related method and multimedia testing led to controversial discussions and a number of referral procedures at the EMA (personal communication). The situation is getting even more complex and questionable considering that e.g. in paragraph 5.1 the European guideline on modified release dosage forms [27] refers to the above mentioned section of the EMA guideline on bioequivalence for immediate release formulations.
- Furthermore, using the f_2 in cases when *in vitro* dissolution is very low due to reasons as described above would lead to questionable results. The f_2 will be positive as long as the mean differences do not exceed 10 % which could already mean doubling the dissolution with low solubility drugs.

- In several jurisdictions the request on multimedia testing relates to particular quantities of excipients [see e.g. Gupta et al. Ref. [8]]. Respective evaluations of excipients may be questioned since knowledge on particular effects of excipients on certain drug substances is rather limited and therefore to a great extent based on assumptions. It is thus considered difficult to interpret these multimedia results in terms of their meaning for the *in vivo* situation.

Therefore, it is emphasized that employing the multimedia testing outside the BCS based biowaiver framework must be scrutinized carefully. The ultimate goal of the BCS based approach should be focussed on demonstrating bioequivalence by justifying the absence of differences between two formulations considering specific prerequisites. It is highly appreciated that this viewpoint has been clearly implemented in the latest revision of the European guideline.

SUMMARY AND FUTURE PERSPECTIVE

To date the BCS based biowaiver concept has been implemented in several regulatory guidance documents worldwide. Appropriate use of this possibility to e.g. apply for approval of generic drugs is still limited however, slowly increasing. Like with bioequivalence in general, the need for harmonizing divergent requirements is obvious. It may be hoped that harmonization processes would include the BCS based biowaiver as a means of proving bioequivalence where necessary, thereby reducing the number of unnecessarily performed *in vivo* bioequivalence studies. The intention of the US-FDA to revise its first regulatory guidance on BCS, as already expressed at the AAPS/FDA meeting on bioequivalence and BCS in May 2007 [28] and elsewhere has been welcomed but is still awaited. At the same time it seems necessary to keep underlying principles and to use the BCS based biowaiver according to its capacity regarding bioequivalence testing.

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THE BIOWAIVER MONOGRAPHS: BCS BASED BIOWAIVERS

A REGULATORY OVERVIEW [1]

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INTRODUCTION

The demonstration of bioequivalence (BE), as defined by the US Food and Drug Administration's (FDA's) Guidance for Industry [1], has been an essential regulatory requirement for approval of generic drugs and significant pre- and post approval changes for both new and generic drugs. It is critical for ensuring that patients receive therapeutically equivalent products which perform as indicated by the label. Since Congress initiated the concept of prescribing "generic drugs" in the 1960s, the comparison of systemic concentration profiles between generic and the reference listed drug (RLD) using *in vivo* human studies has become the usual standard to demonstrate BE [2]. Nevertheless, with the advance in regulatory science, our reliance on *in vivo* BE studies can be reduced due to ethical considerations and the availability of scientific criteria, such as the Biopharmaceutics Classification System (BCS) based biowaiver, that replace unnecessary human studies.

The BCS [3] classifies active pharmaceutical ingredients (APIs) into one of four categories: Class I, high solubility and high permeability; Class II, low solubility and high permeability; Class III, high solubility and low permeability; and Class IV, low solubility and low permeability. BCS based biowaivers (i.e. waiver of an *in vivo* BE study based on *in vitro* data), in general, are granted for rapidly dissolving drugs with highly soluble and highly permeable APIs. The rationale behind this practice is: 1) observed *in vivo* differences in bioavailability (BA) from two pharmaceutically equivalent solid oral products is likely due to differences in drug dissolution *in vivo*; and 2) for a rapidly dissolving IR oral dosage form with highly soluble and highly permeable API, BA is unlikely to be dependent on drug dissolution and/or gastro-intestinal (GI) transit time [3-5].

In recent years, there has been growth in the worldwide acceptance of BCS based biowaivers. While the central concept of this framework (high permeability, high solubility, rapid dissolution) is universally endorsed by major regulatory bodies, the particular definition of BCS Classes and the detailed submission requirements differ from region to region. This paper presents an overview of the global regulatory guidance pertaining to BCS based biowaiver, focusing on US-FDA's perspective on the application of BCS based biowaiver in regulatory submissions. Regulations concerning the general biowaiver practice for immediate release solid oral dosage forms in the US, European Union (EU), Japan and the World Health Organization (WHO) were reviewed elsewhere [6].

Regulations in the United States

Published US-FDA guidances that consider BCS based biowaivers are: 1) Waiver of *in vivo* bioavailability (BA) and bioequivalence studies for immediate release solid oral dosage forms based on a Biopharmaceutics Classification System (the BCS Guidance, published in 2000) [4]; 2) the Food-effect bioavailability and fed bioequivalence studies (the Food Effect Guidance, published in 2002) [7]; and 3) Bioavailability and bioequivalence studies for orally administered drug products–general considerations (the General Guidance, published in 2003) [1].

The BCS based biowaiver is applicable for BE studies in New Drug Applications (NDAs) for pre- and post approval changes (e.g. changes in composition, manufacturing site, batch size and manufacturing process), or for BE studies in Abbreviated New Drug Applications (ANDAs). To be eligible, the drug substance has to be BCS Class I compound, the product has to be rapidly dissolving, and the test and reference formulations should be pharmaceutical equivalents and show rapid and similar dissolution.

According to the BCS guidance [4], BCS Class I drugs are those with high solubility (the highest strength should be soluble in 250mL or less of aqueous media over the pH range of 1-7.5; if 3<p*K*a<5, solubility should be determined at pH = 1, p*K*a-1, p*K*a, p*K*a+1, and 7.5), high permeability (90% or greater fraction absorbed as determined by mass balance or absolute bioavailability studies in human, or properly designed *in vivo* or *in vitro* intestinal permeability studies). Rapid dissolution is defined as 85% dissolution in 30 minutes in 900mL or less of 0.1N HCL or Simulated Gastric Fluid, in pH 4.5 buffer, and in pH 6.8 buffer or Simulated Intestinal Fluid. FDA also requires data showing the stability of the drug substance in the GI tract.

BCS based waivers are not applicable for the initial *in vivo* bioavailability characterization for NDAs. Other restrictions of application include: 1) narrow therapeutic index (NTI) drug; and 2) drug products intended to be absorbed in the oral cavity. Similarly, prodrugs and excipients require special consideration. In case of prodrugs, whether to measure the prodrug or the drug for permeability determination will depend on where the conversion occurs. Excipients should be known to have no effect on the rate and extent of drug absorption and should be used in quantities that are in line with their intended function.

Regulations in the European Union

In January 2010, the European Medicines Agency (EMA) published the Guidance on the Investigation of Bioequivalence [8], which includes recommendations on BCS based biowaiver. As in the United States, BCS based biowaivers in the European Union (EU) are intended to prove bioequivalence between early clinical trial products and to-be-marketed products (in NDAs), generics and innovator products (in ANDAs), and in the case of variations (i.e. pre- or post-approval changes) that require bioequivalence testing. BCS based biowaiver are forbidden for drug substances with critical therapeutic range (NTI drugs) or sublingual, buccal, and modified release formulations [8].

In terms of technical requirements, there are small differences between FDA and EMA guidance that arouse discussions in the scientific community and the regulatory domain. First, the EMA Guidance defines "highly soluble" as "the highest single dose administered as immediate release formulation(s) is completely dissolved in 250 ml of buffers within the range of pH 1–6.8", whereas the FDA guidance requires the highest dosage strength to be completely dissolved in 250 ml over the pH range of 1-7.5. Second, the EMA Guidance considers a drug substance as "highly permeable" if the urinary recovery is above 85%, whereas the FDA threshold is set at 90%. Third, the EMA Guidance defines two new terms, "very rapid" dissolution, which refers to "greater than 85% of the labeled amount to be dissolved within 15 min", and "rapid dissolution", which refers to greater than 85% dissolved within 30 min (same as required by FDA). Fourth, the EMA Guidance specifically states that sound peer-reviewed literature may be accepted for known compounds to determine their BCS classes. Last, in addition to BCS Class I drugs, the EMA would grant BCS based biowaiver for drug products containing BCS Class III APIs if very rapid dissolution is established and excipients are qualitatively (Q1) and quantitatively (Q2) the same or very similar (depending on its nature).

WHO Regulations

The WHO is a non-government agency that publishes technical reports and guidances as recommendations to national regulatory bodies. WHO documents pertaining to BCS based biowaiver include: 1) Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability (the 2005 Guideline) [9]; and 2) General notes on Biopharmaceutics Classification System (BCS) based biowaiver applications (the 2011 Notes) [10]. The 2005 Guidelines recommend more relaxed criteria than FDA and EMA guidance in the following aspects.

1. “high solubility”. The 2005 Guidelines request solubility data in a narrower pH range (pH 1.2-6.8) than both FDA and EMA.
2. “high permeability”. Like the EMA Guidance, the 2005 Guidelines define high permeability as greater than 85% absolute bioavailability or absorption in mass balance studies,
3. “rapid dissolution”. Like the EMA Guidance, the 2005 Guidelines define two levels of “rapid dissolution”: “very rapid dissolution” if no less than 85% dissolves within 15 min in pH 1.2, 4.5 and 6.8 buffers, and “rapid dissolution” if no less than 85% dissolves within 30 min in pH 1.2, 4.5 and 6.8 buffers. The agitation condition required by WHO is 75 rpm for the paddle apparatus while that by FDA and EMA is 50 rpm.
4. Per the 2005 Guidelines, BCS based biowaiver can be considered for BCS Class II drugs with weak acidic properties, if rapid dissolution is proven in pH 6.8 buffer.

Like the FDA and EMA guidance, the 2005 Guidelines do not consider BCS based biowaiver for narrow therapeutic drugs, and information regarding excipients effect on absorption will always be requested.

In the 2011 Notes, the WHO Prequalification of Medicines Program published a list of APIs to be eligible for BCS based biowaiver applications and clarified the submission requirements for BCS based biowaiver applications [10]. The reliance on peer-reviewed literature data in the development of WHO approved BCS Class I and III drug list is explicitly stated.

In accordance with WHO guidelines on BCS based biowaiver, as of March 2012, 28 Biowaiver Monographs for immediate release solid oral dosage forms have been published in the Journal of Pharmaceutical Sciences for determining the BCS classes of 33 APIs based on carefully scrutinized literature data and labeling information [11] (Table 1). The publication of these monographs has played an important role in assisting the easy approval of qualifying WHO Essential Drugs, especially in developing countries, by reducing the number of unnecessary human studies while ensuring product quality on the market.

The publication of FDA, EU and WHO guidances has had a substantial influence on the implementation of BCS based biowaivers worldwide. A summary of similarities and discrepancies between these major guidances are summarized in Table 2.

Table 2. Comparison of FDA, EU and WHO guidance on BCS based biowaiver.
SGF: Simulated Gastric Fluid; SIF: Simulated Intestinal Fluid; RLD: the reference listed drug.

Parameters	FDA	EU	WHO
Allowed classes	1	1 and 3	1, 2 (weak acids), and 3
High solubility Highest strength completely dissolved in 250mL of aqueous media at 37 °C ± 1 °C.			
pH range	pH 1-7.5, and pH = p*K*a, p*K*a±1 (if 3 < p*K*a < 5)	pH 1-6.8, and pH=p*K*a (if 1 < p*K*a < 6.8)	pH 1.2-6.8
High permeability	>90% absolute BA or mass balance study	>85% absolute BA or mass balance study	
Other acceptable methods (the sponsors need to justify the use of these methods)	in vivo intestinal perfusion in human in vivo or in situ intestinal perfusion studies in animal in vitro permeation studies using excised human or animal intestinal tissues in vitro permeation studies across cultured epithelial cells	None.	in vivo intestinal perfusion in humans in vitro permeation using excised human or animal intestinal tissue
Rapid dissolution			
Media (studies should be conducted at 37 ± 1 °C)	900 mL or less aqueous media (0.1N HCl or SGF; pH 4.5 buffer; and pH 6.8 buffer or SIF)	900 mL or less aqueous media (pH 1.0-1.2 buffer, usually 0.1N HCl or SGF; pH 4.5 buffer; and pH 6.8 buffer or SIF)	900 mL or less aqueous media (pH 1.2 HCl solution; pH 4.5 acetate buffer; and pH 6.8 phosphate buffer)
Criteria	>85% in 30 min in 3 media	Class 1: >85% in 30 min in 3 media (Rapid) Class 3: >85% in 15 min in 3 media (Very Rapid); or, >85% in 30 min and similar dissolution profile to RLD (Similarly Rapid)	Class 1: >85% in 30 min in 3 media (Rapid) Class 2: >85% in 30 min in pH 6.8 medium and similar dissolution profile in 3 media Class 3: >85% in 15 min in 3 media (Very Rapid)

Apparatus (APP)	USP APP I - 100 rpm USP APP II - 50 rpm	Paddle APP - 50 rpm Basket APP - 100 rpm	Paddle APP - 75 rpm Basket APP - 100 rpm
Other considerations on excipients	Need to justify the use of new excipients or atypically large amounts of common excipients	Class 3: qualitatively and quantitatively the same or similar to RLD	Class 2 and Class 3: qualitative and quantitative composition will be critically evaluated
Restrictions	Narrow therapeutic drugs Oral products intended to be absorbed in the oral cavity Modified release drug products		

Regulations in the other Pan America Countries

The registration of drug products on the Pan American regions is heterogeneous. Nevertheless, there is increasing recognition of the importance of BCS based biowaivers. In 2008, the Pan America Health Organization published the *Framework for Implementation of Equivalence Requirements for Pharmaceutical products* [12] which aims at harmonizing bioequivalence criteria in the Pan America countries. The *Framework* proposed to endorse the WHO's criteria of exempting *in vivo* BE studies. According to this publication, major challenges in this area are the lack of proper technical documentations to back up the BCS classification of marketed drug products, and the lack of qualified personal with biopharmaceutical education. The publication of Biowaiver Monographs is expected to very positively influence the development of biowaiver regulations in these regions.

Regulations in Asia

The Association of Southeast Asian Nations

In 2004 the Association of Southeast Asian Nations (ASEAN) published its requirements for exemption of *in vivo* bioequivalence study to harmonize the biowaiver practice in its ten member states (i.e. Brunei Darussalam, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand and Viet Nam) [13]. These requirements include the demonstration of high solubility in 250mL aqueous buffers over the pH range 1-8 (preferably at pH 1, 4.6 and 6.8), indication of high permeability by linear and complete absorption, and similarly rapid dissolution (greater than 85% dissolved in 15min within pH range 1-8). This guideline does not define the term "highly permeable", nor the acceptable methodologies for permeability evaluation, therefore, the BCS

classification of approved drug substances would not be feasible. Although these requirements do not represent a typical BCS based waiver practice, similar to the FDA, EMA and WHO guidances, this guideline requires thorough investigation into the excipients effect on drug pharmacokinetics as well as the risk of therapeutic failure due to bioinequivalence.

China

Despite of a lack of established guidances on relevant matter, technical requirements for BCS based biowaiver were proposed in 2010 by researchers from Chinese regulatory agency and academic institute [14]. In general, BCS based biowaiver will not be applicable to drugs used for life-threatening diseases, NTI drugs, or drugs reported with bioinequivalence. Solubility tests will be performed in pH range 1-6.8, while permeability determination will rely on absolute bioavailability or masS balance studies in human. In China, a BCS based biowaiver is likely to be an option for Class III drugs with rapid dissolution and proper amount of excipients, but is unlikely to be extended to Class II drugs. Rapid dissolution will be defined as no less than 85% release in 30 minutes for Class I drugs and in 15 min for Class III drugs.

India

In March 2005, the Central Drugs Standard Control Organization (CDSCO) of the Indian government published its Guidelines for Bioavailability and Bioequivalence Studies [15]. The CDSCO guideline partially adopts US FDA's definition on "high permeability" (i.e. greater than 90% absolute bioavailability or greater than 90% absorption by mass balance determination; *in vitro* permeability data will not be accepted). The definition of "rapid dissolving" differs from both FDA and EMA guidance in that it requires no less than 80% dissolution in 15 min. In alignment with FDA guidance, BCS based biowaiver can be granted to only BCS Class I drugs, and its application does not extend to NTI drugs and drug products to be absorbed in the oral cavity.

Japan

As of the end of 2011, there is no publicly available guidance dedicated to BCS based biowaiver in Japan. While the great contribution of BCS in mechanistic understanding of drug absorption and its success in reducing unnecessary *in vivo* BE studies has been well acknowledged by the Japanese pharmaceutical regulation agency, BCS based biowaiver has not been introduced because the extensively applied multimedia dissolution tests in Japan have proved to be capable of ensuring BE even for generic

IR products that differ in formulation and manufacturing [16]. Furthermore, the Japan agency recognizes the difficulty in acquiring permeability data for many drugs, and decides not to pursue further exploration on permeability characteristics of drug substances, because it believes that the differences in bioavailability between test and reference products are driven by formulation changes [6,16].

Nevertheless, the Japan guidance for generic drugs and formulation changes aligns with FDA and EMA guidance in several aspects [17,18]. For example, biowaivers are not considered for drug products containing low solubility API or NTI drugs, and to be eligible for consideration, the drug product must dissolve more than 85% in multiple media within 30 min.

FDA IMPLEMENTATION OF BCS BASED BIOWAIVER

The BCS Committee

To promote research on potential biowaiver extensions, provide expert advice on BCS based biowaiver applications, and proactively interact with external constituents on BCS related policies, the FDA formed the Center of Drug Evaluation and Research (CDER) BCS Committee in March 2004. Dr. Mehul Mehta and Dr. Lawrence Yu are the co-chairs of the Committee. Members of BCS Committee come from the Office of Testing and Research, the Office of Clinical Pharmacology, the Office of Generic Drugs, and the Office of New Drug Quality Assessment.

The Review Process

The Committee meets periodically to evaluate BCS based biowaiver requests and to determine if a BCS Class I classification could be granted to a given API. Based on sponsor request and available data for BCS determination, primary reviewers will decide whether a summary package should be submitted to the committee for review (Figure 1). For each presented case, each committee member has a vote of Yes, No, or Insufficient Data for BCS Class 1 determination; the final decision is by majority. Official record of each consult is kept with the summary report, discussion, vote and outcome. The outcome is communicated back to the review team and to the sponsor via the review division.

FDA provides guidance on bioequivalence requirements for specific products [19] and for some of these products, the option of BCS based biowaiver has been provided as a result of the outcome of the findings of the BCS Committee.

Table 1. The BCS classification as determined by the Biowaiver Monographs.
Including a category for inconclusive evidence (I.E.) for classification.

Drug Name	BCS Classification	Reference
Acetaminophen	3	37
Acetazolamide	I.E.	38
Aciclovir	3 or 4	39
Amitriptyline Hydrochloride	1 or 2	40
Atenolol	3	41
Chloroquine Hydrochloride	1	42
Chloroquine Phosphate	1	42
Chloroquine Sulfate	1	42
Cimetidine	3	43
Ciprofloxacin Hydrochloride	4	44
Diclofenac Potassium	2	45
Diclofenac Sodium	2	45
Doxycycline Hyclate	1	46
Ethambutol Dihydrochloride	3	47
Furosemide	4	48
Ibuprofen	2	49
Isoniazid	1 or 3	50
Lamivudine	3	51
Levofloxacin	1	52
Mefloquine Hydrochloride	I.E.	53
Metoclopramide Hydrochloride	3	54
Metronidazole	1	55
Prednisolone	I.E. (borderline BCS Class 1)	56
Prednisone	I.E. (borderline BCS Class 1)	57
Primaquine Phosphate	1	58
Propranolol Hydrochloride	1	41
Pyrazinamide	3	59
Quinidine Sulfate	1 or 3	60

Quinine Sulfate	1 or 2	61
Ranitidine Hydrochloride	3	62
Rifampicin	2	63
Stavudine	1	64
Verapamil Hydrochloride	1	41

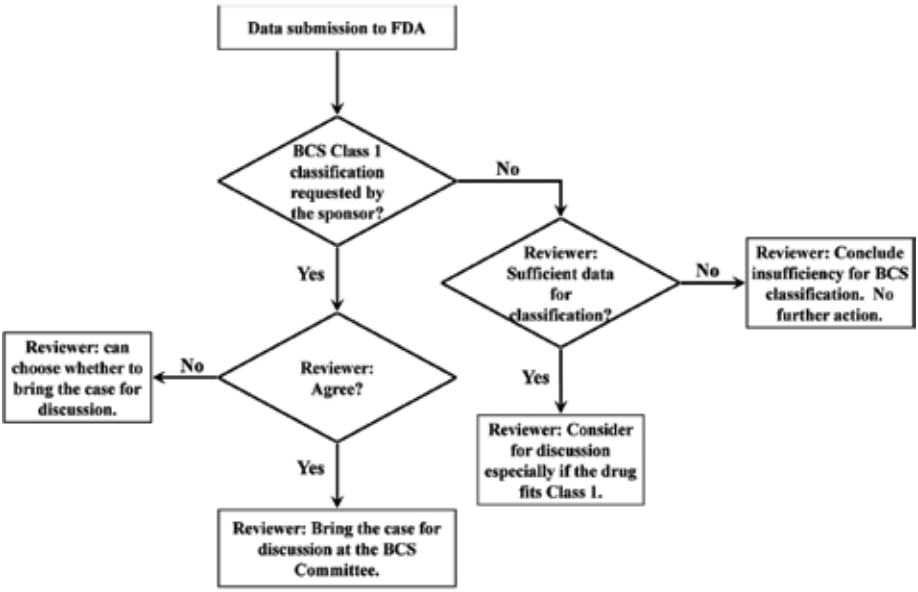

Figure 1. Decision point for requesting BCS Class I determination.

Major Considerations in BCS Determination

Determination of permeability class is central to the BCS classification. The term "permeability" is initially used as a measure of velocity for a compound to pass through a membrane. For a typical oral drug penetrating human jejunum, the value is typically on the order of 1×10^{-4} cm·s^{-1} [20]. Because a compound with high fraction of dose absorbed usually have high *in vivo* permeability [21-23], in the FDA guidance [4], the permeability class boundary is defined by the extent of absorption or by measurements of the rate of mass transfer across human intestinal membrane.

It has also been demonstrated that, for certain class of compounds, an excellent relationship exists between *in vivo* human permeability and results from alternative non-human systems, including intestinal perfusion studies in rat and *in vitro* epithelial cell culture methods [23-25]. Therefore, FDA accepts permeability assessment based on non-human experiments, but the suitability of such methods needs to be justified. For example, a proper set of standard compounds should be included in the protocol for classification and reproducibility purpose. The expression of active transporters in the *in vitro* system should be characterized. In addition, stability data of the compound should be provided to support claims on its stability in the gastro intestinal tract. Literature reports in peer-reviewed journals often fail to provide sufficient details to justify the applicability of the data to regulatory decision making. Hence, FDA generally has concern in using literature data alone for BCS classification.

Examples

Here are a few interesting examples that highlight complexities involved in the BCS determination of drug products.

1. Drug A exhibited high permeability in *in vitro* permeability studies. Additionally, in the mass balance study, greater than 90% radioactivity was recovered in the urine. However, careful evaluation of the stability data indicated that the drug extensively degrades in pH 1 aqueous solution and the *in vitro* permeability study could be done only at pH 6.0 and 7.4, thus raising the concern whether the drug would be highly permeable *in vitro* across the physiological pH range. Moreover, in the mass balance study, there was no breakdown of the radioactivity in the urine in terms of parent and metabolites. Thus, even though on the face of it, the drug appeared to be highly permeable, on careful evaluation, it was classified as low permeability.

2. The permeability of Drug B was evaluated in mass balance study in six healthy subjects. A two treatment (oral and intravenous solution), randomized crossover design was explored. Total radioactivity in whole blood and urine was analyzed. The ratio of radioactivity after oral and intravenous administration were greater than 0.9 in both blood and urine samples. Because the sponsor had analyzed urine for the parent drug, the major metabolite and the conjugates, the permeability study design was deemed suitable, and Drug B was classified as high permeability.

3. Drug C is a substrate of an efflux transporter. At concentrations 1 and 50 μM, its *in vitro* permeability is less than 1 and 8×10^{-6} $cm \cdot s^{-1}$, respectively. Without further information, Drug C would be classified as low permeability compound. However, the suitability of the *in vitro* permeability study was not properly justified. The permeability of Drug C is concentration dependent; therefore, the *in vitro* study should be conducted at clinically relevant concentrations. At clinically relevant concentration (>3000mM), the drug exhibits close to 100% absolute bioavailability. Drug C was therefore classified as a BCS Class I compound.

FDA'S FUTURE CONSIDERATIONS

Since its publication in 2000, the FDA BCS Guidance has aroused extensive research and discussion within FDA, academia and industry regarding its applicability to a broader range of drug products. In 2002, Yu *et al.* published a commentary, "*Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions*" [5] that identified possibilities for biowaiver extensions beyond the original FDA guidance. This paper has likely served as the scientific basis for BCS based biowaiver guidelines by many policy development bodies including EMA and WHO. Meanwhile, FDA has also been carefully evaluating emerging evidence and the proposed extension criterion [5] to identify and reduce the number of unnecessary *in vivo* BE studies for specific drug products. FDA's future considerations on BCS based biowaiver practice will be focused on but not limited to the following aspects.

Permeability, Solubility, and Dissolution Boundaries

Under the current FDA BCS classification, a drug is considered highly permeable if the fraction of intestinal absorption is equal to or greater than 90%. Because the experimentally determined fraction-of-dose-absorbed is less than 90% for many drugs which are generally considered as completely or well-absorbed, it was suggested in the Commentary that a boundary of 85% might be more appropriate in defining high permeability. This suggestion has been reflected in EMA and WHO guidelines in defining high permeability drugs.

Current BCS Guidance requires that the highest strength of a drug substance is completely soluble in 250mL or less of aqueous media over the pH range of 1.0–7.5. Because under the fasting condition the pH range varies from 1.4 to 6.6 in the stomach to the jejunum and it generally takes approximately 85min for a drug to reach the ileum

[26, 27], for a rapidly dissolving drug with no less than 85% dissolved within 30min, it is likely completely dissolved by the time it reaches the ileum. Therefore, the Commentary recommended a pH range of 1.0-6.8 for the solubility studies. The EMA guideline fully adapted this suggestion, while the WHO guideline pushed the range slightly narrower to 1.2-6.8.

FDA is also considering redefining the dissolution testing condition from 50 to 75 rpm (for USP Apparatus II) as it has been reported that the higher paddle speed may reduce system artifacts due to improved hydrodynamics in the dissolution vessel. The balance between the discrimination power of these conditions and their potential impact on dissolution profiles for different formulations is under careful evaluation.

Biowaiver Extension Potential to BCS Class III Drugs

The absorption of a Class III drug is likely limited by its permeability and less dependent upon its formulation. Therefore, if the *in vitro* dissolution of a Class III drug product is rapid under all physiological pH conditions, and the amount and the nature of excipients is not expected to affect bioavailability, its *in vivo* behavior will be similar to oral solution [5, 28]. For instance, Jantratid *et al.* reported that the *in vivo* absorption performance of ten rapidly dissolving IR products containing cimetidine (a BCS Class III compound) were similar despite considerable differences in their *in vitro* dissolution profiles [29]. Likewise, simulations have shown that formulations of metformin (a BCS Class III drug) that release 100% *in vitro* in a time period equal to or less than two hours are indicated to be bioequivalent [30].

Although the idea of "very rapid dissolution" (i.e. >85% in 15min) [5] is adopted by EMA and WHO to ensure complete dissolution is reached before gastric emptying, and the Q1Q2 requirements on excipients are already in place in the EMA guideline to eliminate excipient effects on drug absorption, FDA is considering a series of studies to more rigorously evaluate the validity of the 15 min boundary and the necessity of Q1Q2 requirements. In these studies, information on the composition, dissolution, and *in vitro/in vivo* permeability of nominal BCS Class III drugs will be collected from in-house data with FDA, EMA and WHO publications, and literature reports. Major questions of interests are: 1) the contribution of intestinal transporter and metabolism at gut wall on drug absorption; 2) the interaction of excipients with intestinal transporters or metabolic enzymes; and 3) dissolution profiles of these drug products in relation to drug absorption. Based on these studies, FDA intents to publish a list of commonly used

excipients with information on their effect on drug absorption, and to determine the sensitivity of *in vivo* BE study to variations in *in vitro* dissolution.

BCS Class III drugs account for a significant portion of orally administered drugs appearing on world's top oral drug list [31]. It was estimated that if BCS Class III compounds are granted waivers, a direct savings of over 60 million dollars would be realized [28].

Biowaiver Extension Potential to BCS Class II Drugs

BCS Class II drugs have high permeability and low solubility. Their oral absorption is determined by the rate and extent of *in vivo* dissolution and solubility in the GI tract. FDA has concerns that rapid dissolution and similar dissolution profiles to RLD in different pH media do not guarantee similar *in vivo* dissolution.

The absorption of BCS Class II drugs is sensitive to the solubility at the absorbing region in the GI tract. The solubility can be affected by many physiological factors (e.g. pH, surfactant, etc.) in the region that are difficult to simulate in an *in vitro* solubility test. Likewise, dissolution media covering physiologically relevant GI regions are yet to be developed and validated. Hence, similarities *in vitro* dissolution profiles may not correlated with *in vivo* dissolution and solubility over the GI tract.

The WHO guidelines grants BCS based biowaiver to BCS Class II drugs with weak acidic properties, if rapid dissolution is proved in pH 6.8 buffer and similar dissolution profile to RLD is demonstrated in pH 1.2 and 4.5 media. These requirements mirror the proposal of an intermediate solubility class based on the site of solubilization (e.g. either the intestine or the stomach) [5]. FDA intends to further explore the feasibility of extending biowaiver to BCS Class II drugs based on similar dissolution profiles and intermediate solubility classification, together with Q1Q2 requirements.

Fraction of Metabolism as a Measure of Absorption

In 2005, Wu and colleagues proposed the Biopharmaceutical Drug Disposition Classification System (BDDCS) to predict drug disposition and potential drug-drug interactions in the intestine and/or liver based on solubility and metabolism characteristics [32]. It has been demonstrated that extensive drug metabolism (≥90% of the dose) is likely to dictate a high extent of absorption (≥90%), but not vice versa.

For instance, some metabolic enzymes such as P450 3A4 are known to exhibit stereoslective metabolism on their substrates. One substrate is metabolized much faster than its enantiomer, although both two enantiomers exhibit the same extent of oral absorption [33, 34]. Therefore, while BDDCS based metabolism has been strongly advocated as a surrogate for the extent of drug absorption and in support for a waiver of *in vivo* bioequivalence studies [35], it should be operated with the caution that BDDCS may have a tendency to misclassify high permeability drugs as low permeability drugs [36].

CONCLUSIONS

The biowaiver approach is now established across different regions of the world and the BCS framework has resulted in eliminating many unnecessary human trials. The US FDA has created a centralized BCS evaluation process to assure consistency and transparency across all therapeutic areas in BCS based biowaiver decisions. While the permeability classification of drug substances relies extensively on *in vivo* studies, *in vitro* permeability studies are well adapted in many cases to provide pivotal information and to resolve uncertainties from *in vivo* data. For timely evaluation of BCS based biowaiver application, applicants should submit all necessary information. It is especially important to address the suitability of *in vitro* methods and to provide appropriate stability data. FDA is also actively exploring the possibility of extending biowaivers beyond BCS Class I drugs.

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THE BIOWAIVER MONOGRAPHS:
THE VISION OF THE PHARMACEUTICAL INDUSTRY

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INDUSTRIAL BENEFITS OF BCS BASED BIOWAIVERS

The concept of BCS based biowaivers, i.e. *in vitro* based bioequivalence (BE) testing, has been established as a way to reduce costs in industrial drug development while assuring products of high quality to the patients. The primary saving comes from the difference in costs between performing an *in vitro* dissolution study and a human bioequivalence trial. The typical cost for one bioequivalence study is between 300,000 and 1,000,000 US dollar[1] whereas a comparative *in vitro* dissolution study is only a few per cent of this cost. However, there are a couple of additional indirect cost savings that in the long run are even more important in relation to shortening the time to market.

First, the time required to perform a human BE trial - including development of the protocol, gathering necessary regulatory approvals, performing the study, sample and statistical analysis and preparing the report - typically requires at least 4 - 6 months. By contrast, an *in vitro* dissolution study can be completed in a matter of days. If such a bridging activity is on the critical path to obtaining market approval, the time gained could well be transformed into increased revenues and in some cases a more favorable position in relation to competitors.

Second, the risk of random BE failures of products which are in fact bioequivalent to the comparator is minimal for *in vitro* dissolution testing whereas an *in vivo* study always carries a certain risk in this respect. For example, if the number of subjects included in a BE study is set to reach a statistical power of 0.90, which is a reasonably high level, probability theory implies that one out of ten studies will fail on a purely statistical basis. This is of special concern for drugs with highly variable intra-individual pharmacokinetics[2] for which it is practically speaking almost impossible to include enough study subjects to reach a power of 0.90 and the risk of failure is thereby even higher. The consequence of such a random failure occurring in an *in vivo* BE study include the costs for additional clinical trials and a significant delay in the market approval.

A more comprehensive analysis of cost savings that can be generated by BCS based biowaivers compared to performing *in vivo* BE studies has been performed by Cook et al.[1] In that work both direct and indirect cost savings were estimated based on BE

studies in US. The economical benefit of applying biowaivers to Class I and III drugs was estimated to be in order of more than 100 million US dollars. Thus, there is a great incentive for companies to apply biowaivers wherever feasible.

The BCS based biowaiver approach also offers advantages beyond cost and time reductions in the product development. One interesting aspect is that the quality of the product that has passed the biowaiver approval procedure may actually be higher than those that have passed human BE studies in some cases, since it is based on multiple pH *in vitro* dissolution testing. Human BE studies are considered to be the "gold standard" but here it has to be remembered that such studies are also only a model of the real situation as they are performed in healthy volunteers under very controlled conditions. In the practice setting, administration to patients could easily lead to other results due to different GI physiology or variations in the dosing conditions. In that context, dissolution testing under different pH conditions may better represent the range of conditions occurring in the practice setting and thereby provide a more discriminating test for drug products with pH dependent dissolution performance[3]. This argument is especially valid for highly soluble drugs, since apart from the pH, other variations in GI physiology would not be so important to product performance. For poorly soluble drugs, other factors would also have to be considered, but at present there is still insufficient validation and confidence in biorelevant dissolution media to fully replace *in vivo* studies for such drugs.

Last but not least, there is also an ethical advantage of using the BCS biowaiver procedure where applicable, since unnecessary drug exposure to human healthy volunteers can be eliminated in these cases while maintaining the same or even higher level quality standards to the patient. Polli even suggested that sponsors should provide a rationale for doing *in vivo* BE studies rather than *in vitro* based equivalence testing[3].

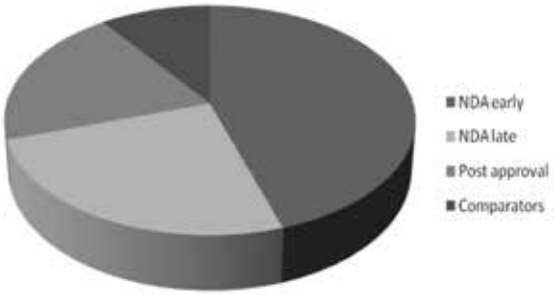
Application of BCS based biowaivers within the industry

BCS based biowaivers are primarily associated with approval of new multi-source products which is also the focus of biowaiver guidelines as well as the Biowaiver Monograph series. However, biowaivers are also of great relevance within the New Chemical Entity (NCE) based industry. An estimate of the fraction of bridging studies required for different purposes, based on experience in AstraZeneca, is provided in figure 1. The development of a commercial product and its manufacturing process is

an extensive effort going on in parallel with different stages of clinical trials. Therefore BE bridging studies are required between the clinical trial formulations and the final commercial product to ascertain whether efficacy and safety data obtained in clinical trials are also valid for the commercial product. Such bridging studies may occur on several occasions during clinical development and the number of studies may be further increased if several dosage strengths are used in the clinical trials and/or are to be marketed. The bridging approach to be used, i.e. *in vitro* dissolution vs. *in vivo* BE, is selected during early clinical development and this is a business decision driven by science and risk-based considerations, including assessments of the biopharmaceutics impact of formulation changes and clinical significance of differences in exposure.
In later clinical development, the requirements on bridging between clinical trial formulations in pivotal clinical studies and the "to be marketed formulation" are steered by regulatory BE guidelines. Such bridging documentation may be required not only at the time of launch but also afterwards, since there is continuous need during the life-time of a product to improve the efficiency of manufacturing and since sometimes manufacturing issues may lead to reformulations which require renewed BE documentation. Finally, a special area that may require BE bridging within NCE development is the need for blinded comparator products in some clinical trials. In order to achieve blinding in clinical studies the comparator product sometimes has to be modified and sometimes this modification will necessitate BE bridging between the original and modified product in order to make sure that clinical results obtained with the comparator are representative for the commercial product. In summary, BE bridging studies are an integral part of modern drug development for NCE products.

Figure 1.

Relative frequency of BE studies for different reasons including studies in a NDA for early bridging between clinical trial formulations (NDA early) and late bridging between clinical trial and market formulation (NDA late), post NDA approval manufacturing changes (SUPAC) and testing between blinded and original comparator products in clinical trials (comparator).



Which levels of biowaivers are possible?

Biowaivers have long been an acceptable approach for pivotal BE bridging in the following situations.

First, when a formulation or manufacturing change is implemented, this can be at one of several levels. If the change is likely to not have any impact on *in vivo* exposure, dissolution testing is deemed to be sufficient to demonstrate BE. Levels of acceptable formulation changes which would qualify for such an *in vitro* approach are defined in detail for example in European, US and Japanese guidelines[4-6]. Although these guidelines are primarily targeted towards post approval changes, they also give some hint regarding the level of changes acceptable for *in vitro* dissolution testing in NDAs.

A second situation where biowaivers are acceptable based on formulation similarity is for the introduction of new dosage strengths. All major regulatory guidances accept an *in vitro* approach if "dose proportional" formulations are used i.e. if the same percentage of all components are used for the different strength or if the active is only a very small percentage, typically less than 10 %, of the total weight of the formulation and the amount of inactive ingredients remain constant between different strengths.

Third, in cases where "pharmaceutical similarity" cannot be claimed biowaivers are still possible when an *in vitro-in vivo* correlation (IVIVC) has been established. An IVIVC is obtained by testing several formulations with varying dissolution performance and then identifying a dissolution test that reflects these results. An example of such an approach is illustrated for metoprolol controlled release formulations in figure 2, showing the *in vitro* and *in vivo* dissolution time profiles for three different variants of the formulations, each having different release profiles. The *in vivo* dissolution profiles were calculated from the plasma drug concentrations by use of deconvolution[7]. This IVIVC was one of the first to be approved as a basis for a biowaiver and was later applied successfully to optimization of the manufacturing process e.g. by changes in the composition, as well as to prove BE after a change in manufacturing site. For the metoprolol example provided, the *in vitro* and *in vivo* profiles were almost superimposable but in some other cases the *in vitro* and *in vivo* processes may operate on different time-scales and in such cases a mathematical relationship would need to be established to obtain an IVIVC. The regulatory guidances also prescribe how to assess the predictability of the *in vitro* test based on comparisions of predicted and observed C_{max} and AUC values. Here the predictions are obtained from the *in vitro*

data, by applying the IVIVC relationship to transform the *in vitro* dissolution data into an *in vivo* dissolution profile and this is then convoluted to estimate the plasma drug concentration time profile. In order to get acceptance for biowaivers based on an IVIVC, a "level A correlation" which corresponds to an average difference in real and predicted average bioavailability data of not more than 10% must be obtained. The establishment and evaluation of IVIVCs are described in more detail, for example, in the FDA "IVIVC guidance"[8].

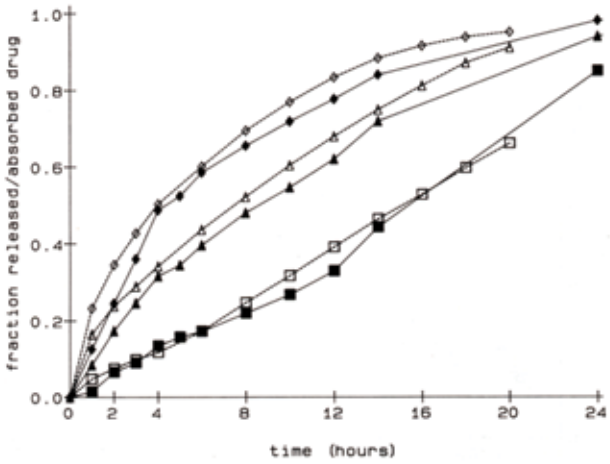


Figure 2

Mean *in vitro* dissolution profiles (open symbols, n=6) and absorption time profiles (filled symbols) in healthy volunteers (n=10) for three different metoprolol CR formulations7.

Interestingly, it has been pointed out that for immediate release tablets a linear relationship between dissolution *in vitro* and *in vivo* should not always be expected[9]. This is because other factors than dissolution, usually gastric emptying or permeability, become the rate limiting step to absorption. In this situation there will be a "safe space" where changes in dissolution will not affect *in vivo* performance, as illustrated in figure 3[10]. This was actually the basis for introduction of biowaivers for BCS Class I drugs[11] where it was recognized that for drugs having a fast enough dissolution profile, i.e. virtually complete dissolution within 30 minutes, gastric emptying rather than dissolution will control the drug absorption rate. It has also been shown that

this phenomenon of a "safe space" where dissolution is not affecting absorption is not limited to BCS Class I drugs but is also valid for BCS Class III drugs[12-14]. This "safe space" concept is further supported by biowaiver monograph publications for BCS Class III drugs like aciclovir, atenolol, cimetidine, lamuvidine and ranitidine, in which the suitability of the BCS based biowaiver has been affirmed[15]. In fact, there are also examples for Class II drugs where a "safe space" situation has been demonstrated[10]. The "safe space" type of IVIVC does not fully comply with the classical IVIVC requirements expressed in regulatory guidelines but should nevertheless be a useful approach in validating *in vitro* methods for biowaiver usage, especially in the context of Quality by Design. In such a case the critical composition and manufacturing variables are identified. These are then incorporated in several formulation variants which are subsequently tested in an *in vivo* study to establish an *in vitro-in vivo* relationship of some type[10]. Thus, such an IVIVC would be product-specific and not generally applicable to multi-source products.

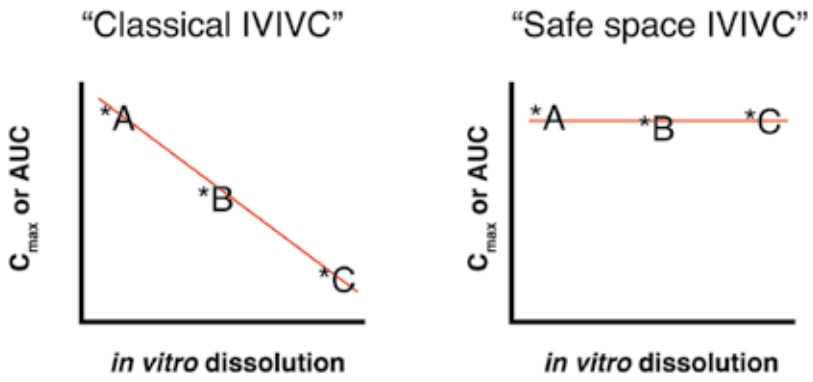


Figure 3

Schematic representation of different types of IVIVICs where A, B and C represents data for different formulations with different dissolution performance. "Classical IVIVC" represents the situation when dissolution is rate limiting and "safe space IVIVC" when other factors are rate limiting.

The most recent development in the biowaiver area implemented in regulatory guidelines are the BCS based biowaivers which were introduced in 2000[16]. This was a revolutionary step forward, since for the first time *in vitro* dissolution data were accepted as a replacement for *in vivo* data without prior establishment of an IVIVC or strict restrictions regarding pharmaceutical differences between the test and reference formulation. The BCS based biowaiver was originally introduced for BCS Class I drugs with a "complete" product dissolution within 30 minutes[17]. More recently this has been expanded in Europe to also include BCS Class III drugs with very rapid product dissolution (complete dissolution within 15 minutes)[17].

Relevance of Biowaiver Monographs to the industry

The Biowaiver Monographs available through peer reviewed scientific papers and at the FIP website http://www.fip.org/bcs_monographs provide reviews of published relevant data and assessments of suitability of biowaivers for a number of WHO listed essential drugs. Although these Monographs may primarily have their benefit as a means of drug approval of multi-source products, especially in developing countries, this work also could bring some benefit in context of development of NCEs. First of all the Biowaiver Monographs could be directly applied where these drugs are included as blinded comparators in pivotal clinical trials of NCEs. Another potential application is the development of fixed dose combinations with a more novel drug combined together with a WHO listed drug. The recommendations regarding biowaiving cannot always be directly applied because of some discrepancies between Biowaiver Monograph recommendations and specific regulatory guidance recommendations in some regions. However, the information provided give important insight regarding limiting steps in drug absorption, suitability of different dissolution approaches to predict *in vivo* behavior and the history of published success and failures in the BE area. This is critical information guiding development of such products in terms of minimizing the risk of BE failures in required *in vivo* studies.

More generally, the combined information of all Biowaiver Monographs provides a powerful database which can be useful to the NCE industry in several ways. First, it helps to risk-assess novel compounds with similar biopharmaceutical properties to those already monographed and second, the data can be used to establish a broader validation of different predictive methods. Biowaiver Monograph publications should therefore be followed by great interest by biopharmaceutical scientists with the industry.

Potential future developments of biowaiver concepts

Although there are a number of scientific opportunities to expand the use of biowaivers in the future, which will be discussed in more detail below, one of the greatest advances would probably be an international harmonization of possibilities to apply biowaivers. Especially the criteria for accepting biowaivers would benefit from further harmonization, preferably as an ICH initiative, thereby also encompassing regulations in novel major markets. The benefit of harmonization in this area is obvious, in that if there is only one single country that demands an *in vivo* BE study rather than accepting a biowaiver approach, an *in vivo* study will still have to be performed and much of the biowaiver benefits are thereby lost on a global basis. One outstanding topic that differs among regions is that there is a general acceptance of BCS Class I biowaivers, but the concept of BCS Class III based biowaivers are not fully implemented everywhere.

The possibility to expand biowaivers based on the BCS has been debated in the scientific community since the original publication of the BCS. For example, it has been suggested that the requirement of highest pH for the solubility measurements could be changed from 7.5 to 6.8 since the latter is more relevant for the pH in the upper GI tract ref[18] and this revision has actually been implemented in the most recent "biowaiver guidance" released by EMA[17]. It has also been suggested that for acidic drugs the boundaries for solubility are too restrictive (pH 1.0–7.5) and might be narrowed down to pH 5.0–7.4[19]. Yet another proposal has been to lower the high-permeability definition from 90% to 85% fraction absorbed[18]. This, too, has been implemented in the most recent EMA guidance.

There may also be additional possibililities in the future for more radical extensions of biowaiver applications. First of all, further refinement and *in vivo* validation of *in vivo*-relevant dissolution media holds the promise for including some Class II drugs in consideration for a biowaiver. In the first instance, this is likely to apply to drugs with dissolution rather than solubility limited absorption. For drugs with dissolution rate limited absorption, the absorption is directly related to dissolution. By contrast, for drugs with solubility limited absorption, the rate and extent of absorption is a complex interplay between permeability and solubility, also including potential for phenomena such as supersaturation and precipitation to play a role, neither of which are very well captured by today's methodologies. *In vitro* methodologies developed to capture more of the complexity and dynamics in the GI tract by means of fluid composition and removal of drug by permeation over the intestinal wall have been introduced

in the pharmaceutical development in recent years[20,21]. Initial studies published in pharmaceutics area where *in vitro* results from such methods have been compared to *in vivo* data have provided promising results[22,23]. Such advanced methods may thus find a role in context of biowaivers without prior product specific IVIVC even in more challenging cases, but this will require not only extensive *in vivo* validation but probably also a better understanding and control of variation sources in these highly complex methods.

Another important area of progress within the oral biopharmaceutics area that may play a role in the future in the biowaiver arena is the continuous improvement of software aimed at predicting oral drug absorption and plasma drug concentration profiles. These softwares are based on a combination of physiological, first principle physicochemical and empirical factors, including determination of key variables such as drug solubility and permeability[24,25]. These tools have been successfully applied to early research work but applications in context of biowaivers are sparse. The great opportunity with these tools in applications to support biowaivers is that drug specific models can be established, based on all relevant developmental data, that relate dissolution performance to bioavailability variables in a quantitative, mechanism-based manner rather than as pure mathematical exercise, as is the case for current IVIVCs. On the one hand, this could be applied to define "safe space" areas where dissolution will not affect bioavailability, in analogy with BCS Class I drugs. This would allow to define "BCS Class I behavior" among drugs of all BCS Classes. On the other hand, based on such modeling, product dissolution criteria may be relaxed beyond current criteria for some drugs while still not putting dissolution as a rate limiting step in the absorption process. For example, some work on BCS Class III drugs have shown that as long as the product can release the drug within 60 min, the dissolution does not seem to affect bioavailability[12]. A few examples have been published that further exemplify how such modeling can be applied in context of biowaiver work[26-28].

One important aspect in relying on BCS based biowaivers to establish bioequivalence between different formulations is the potential risk that different excipients used in the test and reference influence absorption beyond dissolution and solubility effects. For example, significant amounts of surfactants and certain lipids have been shown to influence the intestinal permeability, both for passive and carrier-mediated transport[29,30]. Effects on intestinal transit, which could influence absorption especially for low permeability drugs, have been reported for high amounts of certain sugar

alcohols or PEG[31]. Furthermore, there could also be a risk for formation of soluble complexes between the drug and an excipient, which if strong enough, would reduce driving force for absorption. This has been shown in some model studies e.g. for cyclodextrins[32]. Potentially, excipients could also interact with enzymes influencing first-pass metabolism. However, this seems less likely as no clear reports of such events based on *in vivo* data have come to light. Today this is handled for example in the FDA biowaiver guidance by only allowing biowaivers when well known excipients have been used in normal amounts, consistent with the intended function of the excipient, and also recognizing the potential issues with high dose surfactants and sweeteners[16]. The Biowaiver Monographs have taken a similar but slightly more narrow approach, recommending acceptance of biowaivers only if the same excipients are used as for products already marketed in regions with stringent regulatory requirements. In the future, it may be possible to relax these requirements, based both on better understanding of critical excipients as well as implementation of *in vivo*-predictive *in vitro* methods for some of these excipient effects. Refined use of modeling, as discussed above, will also help identifying anomalies in absorption due to excipient effects, at least for reference formulations.

Finally, a great opportunity to expand the usage of biowaivers would be to distinguish between testing for regulatory approval of generic products and approval of changes within a given product. In the former case there are two completely different products and approval has to be entirely based on dissolution testing on a stand-alone basis. In the latter case, especially now with the introduction of Quality by Design concepts[32], both in the NCE and generic industry, a significant knowledge is built up around the product during development. This includes elucidation of which factors are most critical for bioavailability performance. This is clearly a much more knowledge-rich situation, which should open up the possibility of greater flexibility in the application of biowaivers. If the totality of relevant *in vivo* data also can be appropriately modeled by oral absorption prediction software (as discussed above) in combination with *in vitro* product dissolution data, a situation can emerge where wide extensions of biowaivers should be possible without endangering the clinical quality of products to patients.

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BIOWAIVER IMPLEMENTATION FOR IMMEDIATE RELEASE ORAL FORMULATIONS IN THE WORLD HEALTH ORGANISATION.

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INTRODUCTION

New chemical entities or innovative new medicines are registered and marketed normally based upon a full dossier including extensive documentation on quality, preclinical and clinical safety and efficacy. When patent and other exclusive rights for these medicines expire, applicants may submit applications for generic or multisource versions of these medicines. The quality of the generic medicines should be similar to that of the innovator. Documentation to be submitted includes complete documentation on quality, but documentation on preclinical and safety and efficacy data can be waived normally with reference made to the innovator data. One of the basic concepts of generic medicines is that they can be used instead of the innovator drug without affecting efficacy and safety, i.e. they are therapeutically interchangeable. To substantiate this, it should be shown that after administration of the generic medicine and the innovator, the blood or plasma concentrations of the active substance are similar. This is confirmed by carrying out an *in vivo* bioequivalence study. This concept is recognized and accepted worldwide by regulatory authorities and strict criteria for these studies have been set by, for instance, the US Food and Drug Administration (FDA[1]) in the USA and by the European Medicines Agency (EMA[2]) in Europe. The FDA and EMA also recognize that instead of proof of similar quality via an *in vivo* bioequivalence study, *in vitro* dissolution data may be used to waive the requirement for a bioequivalence study in certain cases. This approach of biowaiving is based on the Biopharmaceutics Classification System (BCS) and was, for instance, incorporated by the FDA in their guidance in 2000[3].

Table 1. Drug substance classification according to the Biopharmaceutics Classification System (BCS).

BCS classification	Solubility	Permeability
BCS Class I	high	High
BCS Class II	low	High
BCS Class III	high	Low
BCS Class IV	low	Low

Within the BCS, based upon their solubility and permeability, active substances are categorized into four groups as shown in Table 1. At this time, the FDA only recognizes BCS Class I drugs as eligible for a BCS based biowaiver. In line with the FDA, the EMA[2,4] also incorporated the possibility of biowaiving in their guidance. At the moment the EMA recognizes BCS Class I and III drugs as eligible for a BCS based biowaiver.

BIOWAIVER IMPLEMENTATION IN THE WHO

Within the WHO, regulatory aspects and principles for medicines are overseen by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The WHO Expert Committee on Specifications for Pharmaceutical Preparations is the highest level advisory body to WHO's Director-General and its Member States in the area of quality assurance. This body gives support and puts forward standards to be applied in evaluation of bioequivalence studies, as published in the WHO Guidelines on registration requirements to establish interchangeability (WHO Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations; Technical Report series (TRS) No.937[5]). This document includes Quality Control and Quality Assurance aspects, Prequalification of priority medicines and Regulatory guidance. Elaborate guidance is given on registration requirements for multisource (generic) pharmaceutical products in order to establish interchangeability. In addition, a proposal is given to waive *in vivo* bioequivalence requirements for the WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. The guidance described in this report can be used by national authorities who do not have such guidance in place. Further, the information can be of support for procurement agencies and major international bodies, institutions, and organizations, like the Global Fund and UNICEF.

As mentioned before, TRS 937 offers guidance on requirements to establish interchangeability and to waive *in vivo* bioequivalence requirements. To do so, the WHO took the progressive step of adopting the concepts of the Biopharmaceutics Classification System[6] as a new concept for bioequivalence testing.

High solubility

In line with the BCS concepts, the WHO considers a drug or pharmaceutical ingredient highly soluble when the highest dose recommended by WHO (if the active pharmaceutical ingredient is on the WHO Model List of Essential Medicines) or highest dose strength available on the market as an oral solid dosage form (if the active pharmaceutical ingredient does not appear on the WHO Model List of Essential

Medicines) is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8. The solubility profile over this pH range should be determined at 37 ± 1 °C in the aqueous media. At least three replicate determinations at each pH is advised to evaluate the solubility.
An upper pH limit of 6.8 has been chosen to be sure that the drug has dissolved before it reaches the mid-jejunum where it is absorbed. This upper limit is also applied by the EMA[2], whereas the FDA[1] sets an upper pH limit of 7.5.

High permeability

The WHO considers a drug to be highly permeable when its extent of absorption in humans is at least 85%. The estimation of the extent of absorption should be based on data coming from a mass balance determination or from absolute bioavailability data, using an intravenous dose of the innovator or comparator. This criteria is in line with, for instance, what the EMA[2] requires, but is less stringent than the FDA[1] requirement of 90% absorption. Differences may be attributed to what the regulatory authorities consider a critical limit and to what extent such limits can be substantiated taking into account, for instance, mass balance studies showing variability in recovery values.
In addition, the WHO also accepts alternative test methods for permeability determination of the drug. However, in this case the suitability of the method must be proven and a positive control, i.e. a drug with known high permeability and which is absorbed *in vivo* for at least 85%, and a negative control, i.e. a drug with low permeability and having a low absorption *in vivo*, should be included.
Moreover, additional tests may provide supportive data to conclude whether a drug has a high permeability and is absorbed more than 85% *in vivo*. Such tests include *in vivo* or *in situ* intestinal perfusion studies using animal models and validated *in vitro* permeation across a monolayer of cultured epithelial cells (e.g. Caco-2) which includes control drugs with known permeability and *in vivo* absorption[7]. As mentioned, these tests are only considered supportive by the WHO and the test alone is not considered proof of high permeability.

Dissolution data to support the BCS based biowaiver

To establish interchangeability and to waive *in vivo* bioequivalence requirements, *in vitro* dissolution data of the immediate-release generic formulation and innovator or comparator formulation, should adhere to strict criteria. Based on the rate of dissolution of the drug, the formulation is considered to be either very rapidly dissolving, rapidly dissolving, or less than rapidly dissolving.

Very rapidly dissolving:
The WHO considers a formulation to be very rapidly dissolving when at least 85% of the labelled amount of the drug substance dissolves in 15 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the following media:

— a pH 1.2 HCl solution;
— a pH 4.5 acetate buffer; and
— a pH 6.8 phosphate buffer.

Rapidly dissolving:
The WHO considers a formulation to be rapidly dissolving when at least 85% of the labelled amount of the drug substance dissolves in 30 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the following media:

— a pH 1.2 HCl solution;
— a pH 4.5 acetate buffer; and
— a pH 6.8 phosphate buffer.

For comparison of dissolution data between the generic product and the comparator formulation, the WHO requests comparative *in vitro* dissolution studies based on the generation of comparative dissolution profiles and not only on a single-point dissolution test. For obtaining dissolution profiles for the generic and comparator formulations, similar test conditions and an apparatus that conforms to the specifications in The International Pharmacopoeia, have to be applied, which is obvious, otherwise a good comparison of the dissolution profiles is not possible. The WHO accepts using the paddle method at 75 rpm or the basket method at 100 rpm at pH 1.2, 4.5 and 6.8. In addition, for the dissolution media International Pharmacopoeia buffers are recommended, but alternative compendial buffers with the same pH and buffer capacity are also accepted. The temperature of the dissolution medium should be 37°C. These conditions are generally accepted conditions although a paddle speed of 50 rpm may be preferred by some[2,3].
Furthermore, the WHO indicates that samples collected to analyse the concentration of the drug in the medium should be obtained at for instance, 10, 15, 20, 30, 45 and 60 minutes after start of the dissolution test, to obtain a characterisation of the

dissolution profile. Furthermore, the WHO requests a minimum of 12 dosage units of each product be evaluated, which makes a reliable comparison between generic and innovator/comparator possible, if necessary. These recommendations are in line with those described by Moore and Flanner[8] and Shah et al[9].

In the case that dissolution is rapid, i.e. less than 85% of the drug is dissolved within 15 min, WHO request further comparability testing of the dissolution profiles by using the similarity factor f2.
The similarity factor f2, i.e.,

$$f2 = 50 \times \log\{[1 + (1/n)\Sigma_{t=1} \times^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

is the general accepted and applied comparison calculation[2,3,8,9]. In line with this, the WHO also takes into account the variability in the first data point (less than 20% variance) and other data points (less than 10% variance), and that a maximum of one time-point should be considered after 85% dissolution of the comparator product has been reached.
Comparability in dissolution profiles is concluded in cases where the difference in profiles between generic and comparator is less than 10%, which reflects an f2 values between 50 – 100.

According to the WHO Guidelines on registration requirements to establish interchangeability[5], other appropriate statistical methods may be used for comparison of dissolution profiles, provided that the same criterion is used for acceptance (maximum 10% difference between the profiles). The use of alternative methods is accepted, as long as they are validated for the purpose of the intended use. However, the EMA[2] and FDA[3] do not accept such an alternative approach for full biowaivers and only f2 testing for dissolution profile comparison is applicable.

Excipients

Next to permeability and solubility of the active ingredient(s), the excipients used in the formulation should be taken into account. The WHO indicates that the excipients included in the formulation of a multisource product or generic product should be well-established for use in products containing that drug, and that the excipients used should not lead to differences between the comparator and generic product with respect to processes affecting absorption. This includes effects on gastrointestinal

motility or interactions with transport processes. In addition, the pharmacokinetics of the drug may not be altered by the excipients.
To support the contention that excipients do not affect absorption and/or the pharmacokinetics of the drug, a reference can be made to the excipients contained in the comparator product or to the excipients included in other formulations containing the same drug as the generic at issue, and those products should then have marketing authorizations in countries participating in the International Committee on Harmonisation (ICH; i.e. members European Union, Japan and USA; and the ICH observers Canada and Switzerland). Information on the qualitative composition of the formulation can, in many cases, be obtained from the web sites of national drug regulatory authorities, such as The Netherlands[10].
Surfactants, like sodium lauryl sulphate, and osmotically active substances like mannitol and sorbitol are generally well known excipients that may affect dissolution from the formulation and absorption of the drug from the gastro-intestinal tract. The WHO recognises that content differences of these excipients in the generic formulation and the comparator formulation may result in bioinequivalence. Therefore, the better the generic matches the comparator with regard to the excipients, the lower the risk is of an inappropriate decision on equivalence using a biowaiver based on the BCS.

Candidates for a full BCS based biowaiver

For the WHO Model List of Essential Medicines immediate-release, solid oral dosage forms[11], TRS 937 proposes that BCS Class I, II and III active ingredients be eligible for a biowaiver under certain conditions.
The WHO considers BCS Class I drugs, i.e. drugs with a high permeability and high solubility, candidates for a biowaiver. Generic formulations containing such a drug may be exempted from proving bioequivalence through an *in vivo* bioequivalence study.
In lieu of *in vivo* data, dissolution data should be provided for the generic formulation and the comparator formulation showing that dissolution at pH 1.2, pH 4.5 and 6.8 is comparable.
In cases where dissolution is very rapid, i.e. no less than 85% of the drug is dissolved within 15 min, no further comparability testing of the dissolution profiles has to be carried out and comparability is concluded as such. In cases where dissolution is rapid, i.e. less than 85% of the drug is dissolved within 15 min, the WHO requests further comparability testing of the dissolution profiles by using the similarity factor f2.
In addition, possible differences in content (qualitatively and if possible quantitatively)

of excipients should be taken into account, but this is considered less critical, as possible interactions are limited when the drug is highly soluble and quickly absorbed.

The WHO considers BCS Class III drugs, i.e. drugs with a low permeability and high solubility, also as candidates for a biowaiver. Generic formulations containing such a drug may be exempted from proving bioequivalence through an *in vivo* bioequivalence study. In lieu of *in vivo* data, dissolution data should be provided for the generic formulation and the comparator formulation, showing that dissolution at pH 1.2, pH 4.5 and 6.8 is very rapid, i.e. no less than 85% of the drug is dissolved within 15 min, no further comparability testing of the dissolution profiles has to be carried out and comparability is concluded as such.
For BCS Class III cases, possible differences in content of excipients are considered critical, especially in cases where the absorption of the drug is very low (i.e. below 50%) and in cases of absorption windows, i.e. absorption in the area of the proximal part of the gastrointestinal tract. Therefore, the generic should match the comparator with regard to the excipients (qualitatively and quantitatively) as much as possible, to lower the risk of an inappropriate decision on equivalence.
The EMA[2] also considers BCS Class III drugs eligible for a biowaiver and the criteria set are in line with those of the WHO. However, excipients that might affect bioavailability should be qualitatively and quantitatively the same, and other excipients should be qualitatively the same and quantitatively very similar.

The WHO also considers BCS Class II drugs, i.e. drugs with a high permeability and a low solubility, as candidates for a biowaiver. This only applies to weak acids, i.e. having a low solubility at pH 1.2 or 4.5, but a high solubility at pH 6.8. The latter is defined as the highest dose which is soluble in 250 ml. Such drugs are more than 85% absorbed and as absorption does not take place in the stomach where the pH is low, solubility at low pH is considered less critical.
Generic formulations containing such a drug may be exempted from proving bioequivalence through an *in vivo* bioequivalence study. In lieu of *in vivo* data, dissolution data should be provided for the generic formulation and comparator formulation showing that dissolution at pH 6.8 is rapid, i.e. no less than 85% of the drug is dissolved within 30 min, and that dissolution at pH 1.2 and 4.5 is comparable, substantiated by comparability testing of the dissolution profiles using the similarity factor, f2.
In line with the criteria set for BCS Class III drugs, possible differences in content

of excipients are considered critical and therefore, the generic should match the comparator with regard to excipients (qualitatively and quantitatively) as much as possible, to lower the risk of an inappropriate decision on equivalence. It is reasonable to expect that BCS Class II formulations are more subject to differences in the release rate, as the transition from pH 1.2 and 4.5 to 6.8 and the rate of dissolution is more dependent on formulation effects. The latter becomes more critical in cases where Cmax is critical for the therapeutic effect and in such a situation, a biowaiver may not be considered applicable.
As indicated, it may be questionable whether it is appropriate to apply biowaivers to the BCS Class II weak acid drugs. FDA[3] and EMA[2] do not recognize them as eligible for a biowaiver. Biowaivers for this type of BCS Class II drugs may not be considered feasible as the major concern is that *in vitro* dissolution data may not be sensitive to detect differences *in vivo,* as shown by Álvarez et al[12]. for ibuprofen. Although dissolution tests showed similarity, *in vivo* bioequivalence was not shown in all cases for the Cmax, and thus *in vitro* dissolution tests may not detect differences in absorption rate.

In conclusion, the WHO proposes biowaiver criteria that are broader than those set presently by the FDA[1] and EMA[2], especially with regard to inclusion of the BCS Classes. This is, in short, reflected in the diagrams shown in Tables 2, 3 and 4.

Table 2. Eligibility for the biowaiver procedure based on solubility and permeability characteristics of the active pharmaceutical ingredient according to the FDA[1].

	CLASS I High permeability High solubility *Eligible*	**CLASS II** High permeability Low solubility *Not Eligible*	

	CLASS III Low permeability High solubility *Not Eligible*	**CLASS IV** Low permeability Low solubility *Not Eligible*	

Table 3. Eligibility for the biowaiver procedure based on solubility and permeability characteristics of the active pharmaceutical ingredient according to the EMA[2].

	CLASS I High permeability High solubility *Eligible*	**CLASS II** High permeability Low solubility *Not Eligible*	
	CLASS III Low permeability High solubility *Eligible*	**CLASS IV** Low permeability Low solubility *Not Eligible*	

Table 4. Eligibility for the biowaiver procedure based on solubility and permeability characteristics of the active pharmaceutical ingredient according to the WHO[11].

	CLASS I High permeability High solubility *Eligible*	**CLASS II** High permeability Low solubility *Eligible*	
	CLASS III Low permeability High solubility *Eligible*	**CLASS IV** Low permeability Low solubility *Not Eligible*	

Biowaivers for additional strengths

The WHO indicates that waivers for additional strengths may be possible, in cases where an application exists for more than one strength and for one of the strengths, bioequivalence has been shown. In such a case the following criteria are applied:

- the strength for which bioequivalence has been shown and the additional strengths products are manufactured by the same manufacturer at the same manufacturing site

- all the strengths are proportionally similar in formulation, which means:
  — all active and inactive ingredients are in exactly the same proportions in the different strengths
  — or in case of a high potency drug, where the amount of the drug in the formulation is less than 10 mg per dosage unit, and for which the total weight of the dosage form remains almost similar for all strengths (within ± 10% of the total weight) and the same inactive ingredients are used for all strengths, and the change in strength is

obtained by altering essentially only the amount of the drug.

- and appropriate dissolution data have been submitted to show comparable dissolution between the strength for which bioequivalence has been shown and the other strengths.

For the latter, dissolution conditions should be in line with those indicated for the BCS based biowaiver, i.e. testing at the 3 pHs (1.2, 4.5 and 6.8) and application of a model independent mathematical approach, like f2 testing, in cases where dissolution is less than 85% within 15 min.
The criteria set by the WHO are more or less in line with those requested by the FDA[3] and EMA[2]. However, for the FDA, the pharmacokinetics of the drug should be linear, while currently the EMA requests, for instance, that the strength used in the bioequivalence study is the most sensitive strength (dose) to detect possible differences between the generic and the comparator. In addition, the EMA considers a high potency drug to be in a formulation in cases where the amount of drug is less than 5% of the core weight of the formulation. Furthermore, although f2 testing is preferable, in cases where the f2 statistic is not suitable, similarity may be compared using model-dependent or model-independent methods e.g. by statistical multivariate comparison of the parameters of the Weibull function or the percentage dissolved at different time points. In such cases, alternative methods to the f2 statistic to demonstrate dissolution similarity are acceptable, but the method should be statistically valid and satisfactorily justified.

BIOWAIVER IMPLEMENTATION IN THE PREQUALIFICATION OF MEDICINES PROGRAMME

Introduction to the Prequalification of Medicines Programme

The WHO Prequalification of Medicines Programme[33] (PQP) began in 2001. This programme, initiated due to the HIV/AIDS pandemic, was introduced to assure that medicinal products in this area supplied for procurement meet WHO norms and standards with respect to quality, safety and efficacy. Moving forward, the programme expanded to also include the therapeutic areas of tuberculosis, malaria and reproductive health, as well as influenza and zinc sulphate for diarrhoea. The invited drug products are listed in the Invitations for Expression of Interest issued by the programme and updated frequently. Most applications to PQP are generics, however, innovator or generic product dossiers approved in the ICH region can be and are

submitted. In such cases an abbreviated prequalification procedure is followed relying on the Stringent Regulatory Authority (SRA) approval.
Generic applications not approved by an SRA however are assessed fully by experienced quality and pharmacokinetic/bioequivalence assessors from a range of regulatory authorities. Assessment is carried out during one-week long bimonthly assessment sessions in Copenhagen, Denmark. Assessment applies internationally accepted criteria to the data submitted and relies on guidance issued by FDA[3] and EMA[2] as well as WHO documents. Further in the past few years, PQP requirements have been harmonized with those of the ICH region. With expert assessors from various jurisdictions consistency in PQP assessment is monitored carefully. In addition, any updates of guidances are communicated on the PQP website[33]. Moreover, if requested, advice will be provided on study protocols, study design, analytical method validation and other related issues within the framework of existing guidance documents.
As PQP relies not only on guidance of the WHO[5], but also those set by stringent regulatory authorities such as the FDA and EMA, some criteria accepted in PQP may deviate from those mentioned in the WHO Guidelines on registration requirements to establish interchangeability (WHO Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations; Technical Report series No.937[5]). The latter can be used by, for instance, national authorities who do not have such guidance in place and those authorities can decide to which extent and how stringent criteria can be included in their national policy.
As indicated above, generics or multisource pharmaceutical products submitted to PQP need to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator's (comparator) product. In addition, reasonable assurance must be provided that the generic product has the same quality as the comparator and is therapeutically equivalent and interchangeable with the comparator product. To ensure this, the generic product should be bioequivalent to the comparator product.
Types of studies which can be submitted include *in vivo* pharmacokinetic bioequivalence studies, pharmacodynamic studies and comparative clinical trials, however, bioequivalence studies based on pharmacokinetics have become the standard study design. In PQP, pharmacodynamic studies and comparative clinical trials are considered acceptable only in exceptional cases, where proof of bioequivalence by a pharmacokinetic study is not feasible.
Although BCS based biowaiver applications had been theoretically possible for many years for applications submitted to the FDA, EMA and other European regulatory

authorities, the number of approved submissions was low. It was against this background of limited regulatory experience, that PQP started its implementation of BCS based biowaivers in 2008. Importantly, PQP has a wealth of experience of assessment of data in support of generic product dossiers, which supported the pilot implementation of BCS based biowaivers in PQP in 2008 for certain selected APIs.

Biowaivers in the Prequalification of Medicines Programme

The basis for biowaivers is the Biopharmaceutics Classification System, i.e. classification of categories of drug substances based upon their solubility and permeability, and are in line with those mentioned for the WHO, in which four classes are identified, i.e. having high solubility and high permeability (Class I), low solubility and high permeability (Class II), high solubility and low permeability (Class III) and low solubility and low permeability (Class IV).

Regarding solubility, the PQP considers a drug to be highly soluble when the highest dose recommended or highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1.2 – 6.8, in line with the criteria of the WHO.
Regarding permeability, the PQP considers a drug to be highly permeable when the extent of absorption in humans is 85% or more, in line with the criteria of the WHO.

For a waiver of a bioequivalence study, normally the drug should belong to BCS Class I, however, as indicated before, BCS Class III drug substances have been recognized as eligible for a waiver by regulatory authorities like the EMA[2]. Also within PQP, BCS Class III drug substances are considered acceptable for a BCS based biowaiver. Further to the criteria for solubility and permeability of the active ingredient, the immediate-release generic product should exhibit very rapid or rapid *in vitro* dissolution characteristics in order to be considered for a biowaiver.
Within PQP, an immediate-release generic product is considered very rapidly dissolving when more than 85% of the labelled amount of the drug substance dissolves within 15 min (using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm, volume 900 ml or less), in each of the following media:

- a pH 1.2 HCl solution
- a pH 4.5 acetate buffer, and
- a pH 6.8 phosphate buffer

In case of a rapidly dissolving drug substance, more than 85% of the labelled amount of the drug substance dissolves within 30 min in the 3 media mentioned above.
In addition, similarity in dissolution profiles should also be demonstrated with the comparator product for the immediate-release multisource product. Moreover, the excipients used in the immediate-release generic product should be well established and should not affect the gastrointestinal motility or other processes affecting absorption. Also here the general rule applies that the closer the composition of the generic product is to that of the comparator product with regard to excipients, the lower the risk of an inappropriate decision on equivalence using a biowaiver based on the BCS.

For Class I drug substances, within the PQP, the substance should exhibit high solubility and complete absorption, the product should show very rapid (not less than 85% within 15 min) or rapid dissolution (not less than 85% within 30 min) comparable to the innovator comparator product, and the formulation should be comparable with regard to excipients that might affect bioavailability (qualitatively and quantitatively the same).
For Class III drug substances, within PQP, the substance should exhibit high solubility and limited absorption, the product should show very rapid (not less than 85% within 15 min) dissolution comparable to the innovator comparator product, and the generic formulation should contain comparable excipients that might affect bioavailability (qualitatively and quantitatively the same) and other excipients should be qualitatively the same and quantitatively very similar. This is in line with the EMA criteria.
In general, drug substance properties, like solubility and absorption, can be substantiated by literature data. Drug product properties, i.e. dissolution, should be substantiated by *in vitro* dissolution data, in which the generic product is compared with the innovator comparator product. *In vitro* dissolution should be investigated within the range of pH 1 – 6.8 (at least pH 1.2, 4.5, and 6.8). Additional investigations may be required at pH values in which the drug substance has minimum solubility. Furthermore, within PQP, the use of any surfactant is not considered acceptable.
In cases where dissolution is more than 85% within 15 min for both products, no additional comparability testing is necessary and mathematical calculation is not needed. In cases where dissolution is less than 85% within 15 min and not less than 85% within 30 min, f2-testing should be used to demonstrate profile similarity of generic and comparator, i.e. the f2 value should be between 50 and 100.

The criteria set in PQP for BCS Class I and III drugs may trigger applicants to submit a BCS based biowaiver application, for which the applicant should normally gather all the necessary data to substantiate permeability and solubility. However, to facilitate for the applicants, based on the scientific principles outlined in the guidelines of FDA[3], EMA[2] and WHO[5,11], WHO PQP has reviewed the available data related regarding safety, solubility, absorption, and dissolution characteristics of the medicinal products invited to PQP, and has identified the following drugs to be eligible for BCS based biowaiver applications, as shown in table 5.

Table 5. Drugs currently eligible for BCS based biowaiver applications in the Prequalification of Medicines Programme.

Active Pharmaceutical Ingredient (API)	Therapeutic Group	Highest oral dose [mg]	BCS Class
Abacavir sulfate	Antiretroviral	600	III
Emtricitabine	Antiretroviral	200	I
Lamivudine	Antiretroviral	300	III
Stavudine	Antiretroviral	40	I
Zidovudine	Antiretroviral	300	I
Ethambutol	Anti-tuberculosis	300	III
Isoniazid	Anti-tuberculosis	400	III
Levofloxacin	Anti-tuberculosis	300	I
Ofloxacin	Anti-tuberculosis	750	I
Pyrazinamide	Anti-tuberculosis	400	III

This means that at the moment, only the drugs identified in Table 5 are eligible for a biowaiver in PQP. Applicants do not have to submit a complete dossier supporting solubility, absorption, and dissolution characteristics of these medicinal products, only dissolution characteristics, i.e. comparable dissolution between the generic product and the comparator product, as specified in the following sections. Furthermore, the qualitative and quantitative composition of the generic and the comparator should be compared in order to exclude possible bioavailability differences after intake.

The BCS Class category, i.e. Class I or III, identified for lamivudine, stavudine, ethambutol, isoniazid, levofloxacin and pyrazinamide are in line with those indicated in the FIP monographs[14,15,16,17,18,19] however it should be noted that for WHO PQP, the more conservative approach has been chosen, i.e. in cases where the monograph indicated the drug as borderline BCS Class I and III, BCS Class III has been chosen.

BCS Class I drugs

For BCS Class I drugs, within PQP, dissolution data should be provided for the generic formulation and comparator using the paddle apparatus at 75 rpm or less, or the basket apparatus at 100 rpm. In addition, surfactants should not be used. The rotation speed required for the paddle apparatus is less critical than that required by, for instance, the EMA[2] which requests a rotation speed at 50 rpm for the paddle apparatus. Based on the experience of assessment of data in support of generic product dossiers and the available data regarding safety, solubility, absorption, and dissolution characteristics of the medicinal products it was concluded that for the drugs listed in table 5, the dissolution speed of 75 rpm for the paddle apparatus is sufficiently discriminatory to detect differences in dissolution which may lead to differences in the rate and extent of absorption.

The dissolution data provided should show comparable dissolution. In cases where dissolution is very rapid, i.e. no less than 85% of the drug is dissolved within 15 min, no further comparability testing of the dissolution profiles has to be carried out and comparability is concluded as such. In cases where dissolution is rapid, i.e. less than 85% of the drug is dissolved within 15 min, WHO PQP requests further comparability testing of the dissolution profiles by using the similarity factor f2 and comparability is concluded in cases where the f2 lies between 50 – 100.

In order to minimize the possible impact of excipients on the bioavailability of the drug, PQP also considers it to be a significant asset to a biowaiver application if the proposed generic product contains similar amounts of the same excipients as the comparator product. Regarding the latter, information may be obtained from public sources of stringent regulatory authorities. For BCS Class I drugs, at a minimum, well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be discussed. Excipients that may affect the bioavailability of the drugs, like mannitol, sorbitol, and surfactants, should not differ qualitatively and quantitatively between the proposed product and the comparator product.

BCS Class III drugs

For BCS Class III drugs in PQP, dissolution data should be provided for the generic formulation and comparator using the paddle apparatus at 75 rpm or less, or the basket apparatus at 100 rpm. As with BCS Class I drugs, surfactants should not be used in these dissolution studies. The dissolution data provided between the generic formulation and comparator should show that dissolution is very rapid, i.e. no less than 85% of the drug is dissolved within 15 min.

For BCS Class III drugs, excipients in the proposed product formulation must be qualitatively the same and quantitatively very similar to that of the comparator product, except excipients that may affect the bioavailability of the drug (e.g., mannitol, sorbitol, surfactants) which should not differ qualitatively or quantitatively between the proposed product and the comparator product. The term 'very similar' is defined as per 'Level 1 Changes' according to the SUPAC (Scale-Up and Post-approval Changes, US FDA) guidance[20].

These strict criteria set in the PQP, i.e. very rapid dissolution and quantitatively and qualitatively similar composition, are set to lower the risk of an inappropriate decision on equivalence, due to the low absorption of the drug which may be more affected by excipients and the possibility of absorption windows, and hence may be more affected by slower dissolution and excipients.

In addition, specifically for isoniazid, lactose and/or other 'reducing sugars' may interact with isoniazid and can affect its bioavailability[17,21,22,23]. Therefore lactose and/or other 'reducing sugars' should not be included in the formulation of the proposed product unless present in the same amount in the comparator product.

Fixed dose combinations

Several invited products in PQP are fixed dose combinations. Biowaivers may also be applicable for fixed dose combinations, as long as all active substances in the fixed dose combination belong to BCS Class I or III and the excipients fulfil the requirements as mentioned above.

WHO comparator product

The comparator product used in a bioequivalence study or a biowaiver is normally the innovator pharmaceutical product available on the (local) market, since for the innovator product, quality, safety and efficacy have been established. National authorities can set their own criteria to select innovator products to be used as

comparator in bioequivalence studies for generic or multisource products.
For applications to WHO PQP, the WHO has selected comparator products which should be used in bioequivalence studies and/or in biowaiver applications[24]. Recommended comparator products are listed for anti-tuberculosis medicines, anti-malarial medicines, influenza-specific antiviral medicines, medicines for HIV/AIDS and related diseases and reproductive health products. A selected comparator product should be purchased from a well regulated market with stringent regulatory authority, i.e. from countries participating in the International Conference on Harmonization (ICH).

Identification by WHO of a drug to be eligible for a BCS based biowaiver application is made purely on the solubility, absorption, safety and related properties of the drug (BCS Class I or Class III). It does not imply that the recommended comparator product(s) will be rapidly dissolving in the case of BCS Class I drug or very rapidly dissolving in the case of BCS Class III drug, which is the requirement for BCS based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the PQP website is indeed suitable for a BCS based biowaiver application before product development. Thus, though a listed comparator product may not be suitable for BCS based biowaiver purposes, it may still be suitable for *in vivo* bioequivalence studies.

This is also applicable for fixed dose combinations. However, in some cases no fixed dose combination comparator product is available and as such, a BCS based biowaiver cannot be applied. In such cases, *in vivo* bioequivalence studies should be submitted using the individual comparator products.

Biowaivers for additional strengths

In PQP, a waiver for additional strengths may be possible, in cases where an application exists for more than one strength and for which one of the strengths bioequivalence has been shown. In line with the criteria listed for the WHO (see above), the strength for which bioequivalence has been shown and the additional strength products should be manufactured by the same manufacturer at the same manufacturing site, all the strengths should be proportionally similar in formulation, and comparable dissolution by appropriate dissolution testing should show comparable dissolution between the strength for which bioequivalence has been shown and the other strengths. For the latter, dissolution conditions should be in line with those indicated for the BCS based biowaiver, i.e. testing at three pHs (1.2, 4.5 and 6.8) and applying a model independent mathematical approach, like f2 testing in case dissolution is less than 85% within 15 min.

CONCLUSION

The approach of waiving bioequivalence studies in certain cases using *in vitro* dissolution data based on the Biopharmaceutics Classification System is recognized by the WHO and its Prequalification of Medicines Programme (PQP). Compared to the FDA, which recognizes BCS Class I drugs as eligible for biowaivers and the EMA which recognizes BCS Class I and III drugs as eligible for biowaivers, the WHO suggests that for BCS Class I, II (weak acids) and III biowaivers may be possible, whereas the Prequalification of Medicines Programme only allows biowaivers for BCS Class I and III drugs. With regard to the latter, based on the scientific principles outlined in the guidelines of the FDA, EMA and WHO, WHO PQP has reviewed its available data regarding safety, solubility, absorption, and dissolution characteristics of the medicinal products invited to PQP, and has identified abacavir sulfate, emtricitabine, lamivudine, stavudine, zidovudine, ethambutol, isoniazid, levofloxacin, ofloxacin and pyrazinamide as being eligible for a BCS based biowaiver in PQP.

The criteria to be applied for a biowaiver related to permeability, solubility, formulations aspects and dissolution are generally comparable between the FDA, EMA, WHO and the WHO Prequalification of Medicines Programme.

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