

**BCS-based biowaivers in the context of
ICH M9 and its implications
on the pharmaceutical industry**

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List of Abbreviations

ANVISA	Agência Nacional de Vigilância Sanitária
APEC	Asia-Pacific Economic Cooperation
API	active pharmaceutical ingredient
ASEAN	Association of Southeast Asian Nations
AUC	area under the curve
BA	bioavailability
BCS	biopharmaceutical classification system
BE	bioequivalence
C_{\max}	maximum plasma concentration
CFR	Code of Federal Regulations
EAC	East African Community
e.g.	exempli gratia, for example
EMA	European Medicines Agency
EML	Essential Medicines List
EU	European Union
f_2	similarity factor
FDA	Food and Drug Administration
FIP	Fédération Internationale Pharmaceutique
GHC	Gulf Health Council
h	hour
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
i.e.	id est, that is to say
IR	immediate-release
IVIVC	<i>in vitro</i> – <i>in vivo</i> correlation
min	minute
N	normal; equivalent concentration
PANDRH	Pan American Network for Drug Regulatory Harmonization
PK	pharmacokinetic
rpm	revolutions per minute

SADC	Southern African Development Community
SGF	simulated gastric fluid
<i>t</i>	time
US	United States (of America)
USP	United States Pharmacopeia
WHO	World Health Organization

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1 Introduction

1.1 Role of bioequivalence in drug development

For the efficacy and safety of a medicinal product, bioavailability of the active substance from the pharmaceutical form is of crucial importance. Bioavailability represents a pharmacokinetic tool describing the “rate and extent to which an active substance (resp. the active moiety) is absorbed from a pharmaceutical form and becomes available at the site of action” [1]. Based on the assumption of an intended systemic action, bioavailability of an active substance following intravenous administration is set to 100 %. While bioavailability of an active substance from a pharmaceutical form compared to that after intravenous administration is referred to as “absolute bioavailability”, “relative bioavailability” represents bioavailability in relation to a different non-intravenous dosage form.

Bioavailability is determined via measuring concentrations of the analyte in blood or plasma samples which are relatively easily available. Bioavailability depends on the properties of the active substance itself (solubility, molecular weight, polarity, ability to use active and passive transport systems in the body and resulting site and mechanism of absorption), and to a great extent on the route of administration and the properties of the pharmaceutical form.

Formulation effects including the manufacturing process are particularly relevant for the bioavailability of oral pharmaceutical forms, making use of the most wide-spread route of application.

Generic medicines play an important role in the pharmacotherapy worldwide. They enable high cost-savings, by referring to preclinical and clinical data already generated for the reference product, their development costs are significantly lower. Thus, pressure is applied on price, which is further lowered by the competition created between pharmaceutical companies. As a result, pharmacotherapy, for important indications, can be made accessible for more people, particularly in developing countries. An important example of this is antiretroviral therapy, an indication for which one-year therapy costs

have dropped from approximately 10,000 US\$ to less than 100 US\$ after generic medicines have been introduced to the market. Consequently the number of people having access to antiretroviral therapy has risen from 0.5 million in 2003 to 15.8 million in 2015 [2].

As the exact quantitative formulation of the reference product is normally subject to intellectual property, bioavailability of the active substance from the generic medicinal product is considered non-identical unless the opposite is demonstrated. Sub-bioavailability bears an inherent risk of reduced efficacy, while suprabioavailability increases the risk of toxicity so both must be avoided.

Bioequivalence (BE) is a term used for comparing different medicinal products (or different batches of the same medicinal product) which are considered bioequivalent if the rate and extent of their bioavailabilities are comparable following administration of the same molar dose, [3]. In this case their effects with regard to both safety and efficacy are expected to be the same and the medicinal products are considered pharmaceutical equivalents (i.e. same amount of same active substance, same dosage form) respectively pharmaceutical alternatives (same active moiety, but different salts, esters, or complexes, or difference in dosage form).

In practice, this means that bioavailability (Area under the Curve, AUC; maximum concentration, C_{max}) of the test product compared to that of the reference product lies within predefined intervals. Bioequivalence studies are not investigating safety or efficacy, but represent an *in vivo* comparison between different formulations under standardized conditions using representative batches (biobatches).

In vivo bioequivalence studies are most widely used in order to demonstrate comparable bioavailability between test and reference product.. As a result, therapeutic equivalence, i.e. safety and efficacy of the test product, can be concluded. In case of generic medicinal products, this means that the inherent risk of extrapolation of the preclinical and clinical data from the innovator can be deemed acceptable. The crucial importance of bioequivalence is reflected in the definition of a generic medicinal product by the European Union (EU): A generic medicinal product is “a medicinal product which has the same qualitative and quantitative composition in active substances and the same

pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies” [4].

Despite the fact that bioequivalence studies and biowaiver approaches are strongly connected to the development of generic medicinal products, it is very important to bear in mind that they are equally essential for the development of medicinal products in general. They also serve as proof of equivalence between differing formulations and/or batches during development as well as a drug’s entire lifecycle: Examples being formulation changes during the development phase, in the context of early and pivotal clinical trials, stability studies or in conjunction with post-approval changes.

1.2 Biowaiver concepts

According to the Declaration of Helsinki, “Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects” [5]. This also includes BE studies, which are mostly conducted on healthy volunteers.

In accordance to these principles, it is acceptable to waive *in vivo* BE studies under certain circumstances (biowaiver). This does, however, not imply that the demonstration of BE as such is waived, but that evidence of BE is generated by means of reliable *in vitro* instead of *in vivo* data.

As a general prerequisite to using *in vitro* data, the active substance must be stable under the test conditions (e.g. dissolution media) over the required test period. The *in vitro* method used has to be capable of discriminating between batches to a sufficient extent, meaning that the method has to be developed and validated depending on the purpose of the biowaiver application. This may include differentiation between formulations with different *in vivo* characteristics that should be displayed *in vitro* (establishment of *in vivo* – *in vitro* correlation) or differentiation between batches with regard to changes of critical parameters in the manufacturing process.

Several types of biowaiver concepts exist. They may be employed to support marketing authorization applications as well as line extensions or post-approval changes that would normally require *in vivo* BE tests:

- formulation-related biowaivers;
- proportionality waivers;
- biowaivers based on *in vitro* - *in vivo* correlation (IVIVC);
- BCS-based biowaivers.

For some pharmaceutical forms, e.g. simple aqueous solutions for intravenous or oral administration, BE is evident and a waiver may be granted.

Proportionality waivers are used for additional strengths of the same pharmaceutical form, i.e. only one *in vivo* BE study (usually applying the highest strength) is used in support of one or more additional strengths.

Biowaivers may also be based on meaningful IVIVCs, which is particularly relevant for modified-release formulations. The establishment of sound IVIVC is possible in case dissolution of the pharmaceutical form and/or solubility of the active substance, but not the process of absorption, represent the controlling steps for bioavailability [6].

The concept of BCS-based biowaivers is described in the following section.

1.3 BCS-based biowaivers

At the instigation of the United States (US) Food and Drug Administration (FDA) in 1995, Amidon *et al.* proposed a theoretical model describing the correlation of *in vitro* dissolution data and *in vivo* bioavailability of orally administered, systemically acting drugs [7] aiming at the prediction of oral drug absorption based on dissolution [8]. It had been found that the solubility of the active substance and its intestinal permeability were decisive parameters to classify a compound as a prerequisite to use a BCS-based biowaiver approach

Under this assumption, it was concluded that medicinal products with an identical dissolution profile under a series of conditions more or less referring to the environment

in the gastrointestinal lumen should also exhibit an identical bioavailability. As a result, four classes of substances were proposed (see also Figure 1.1):

- class I (high solubility, high intestinal permeability),
- class II (low solubility, high intestinal permeability),
- class III (high solubility, low intestinal permeability),
- class IV (low solubility, low intestinal permeability) [7].

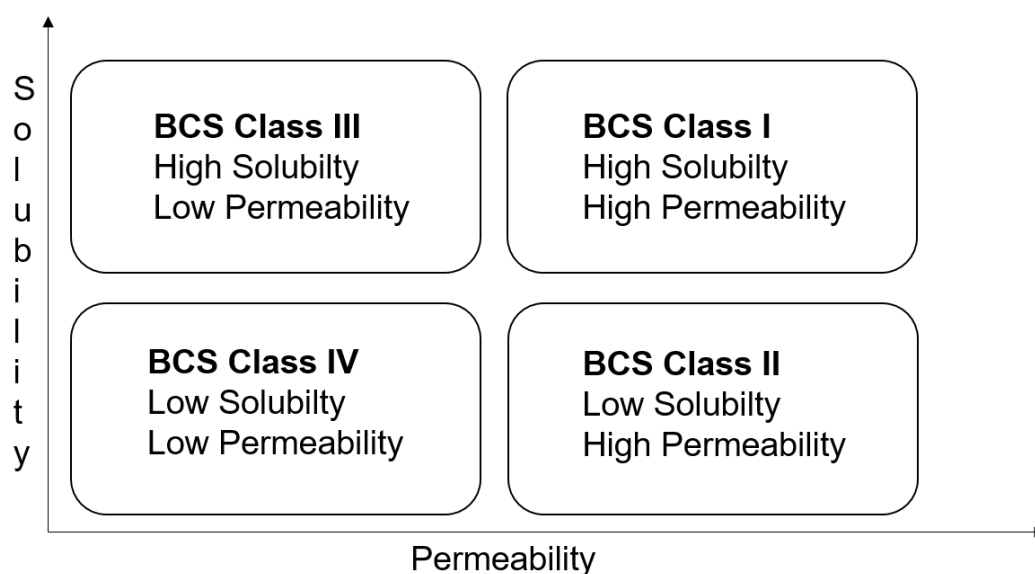


Figure 1.1: Substance classification according to the Biopharmaceutical Classification System (BCS)

In the following period, a further subdivision of the substance classes was propagated. Such a subdivision might be relevant for class II substances in terms of pH-dependent solubility, which exhibit good permeability. Class II substances representing weak acids with a pK_a of approximately 4 – 5 (referred to as Class IIa, including e.g. many non-steroidal anti-inflammatory drugs) should show low solubility in the stomach and prior to the small intestine, however with an increasing pH, their solubility increases rapidly so that dissolution is the controlling step. If the latter is rapid, respective pharmaceutical forms would, like BCS class I, behave like an oral solution in the gastrointestinal tract and be sufficiently absorbed in lower intestinal sections. In contrast, weakly basic class II substances (referred to as class IIb) should be well soluble in the stomach and might precipitate in lower intestinal sections. For neutral compounds (referred to as class IIc),

it was assumed that the *in vivo* conditions, such as presence of lipids and surfactant, would influence dissolution [9]. Another approach proposed the subdivision of class II substances into dissolution rate-limited and solubility-limited substances [10]. However, at least in a regulatory context, these further subdivisions were not accepted.

The classification system proposed by Amidon *et al.* [7] became known as “biopharmaceutical classification system (BCS)” and was subsequently taken up by different regulatory authorities in order to grant waivers for bioequivalence studies (BCS-based biowaivers) for immediate-release solid pharmaceutical forms under certain circumstances [8]. In practice, the acceptability of a BCS-based biowaiver depends on three aspects: the pharmacological profile (therapeutic range), the physicochemical characteristics of the active substance (influencing solubility and permeability), and characteristics of the pharmaceutical form (*in vitro* dissolution profile, excipients).

In the early 2000s, the concept of BCS-based biowaiver was taken up by the International Pharmaceutical Federation (FIP) and the World Health Organization (WHO) who started a joint project and formed a working group, the FIP Special Interest Group on Biopharmaceutics Classification System (BCS) and Biowaiver [11]. The aim was to collect published information on active substances prioritizing the WHO Essentials Medicines List [12] in order to create monographs in support of regulatory agencies [13]. To date, approximately 50 monographs have been published [14].

The BCS-based biowaiver approach has been implemented and developed in various regions of the world. While the underlying concept is the same, the general acceptance, interpretation, application, prerequisites and conditions so far differ due to the different regional regulations and guidance documents.

1.4 Aim

In the context of global merging of markets and economies, a harmonisation of the requirements in drug development is generally desirable. The International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) aims at establishing consensus between the regions and developing harmonized standards which are subsequently implemented by ICH members and often also by ICH observers.

As the concept of BCS-based biowaivers is of great relevance for both the pharmaceutical industry as well as the regulatory bodies and a need for harmonization was identified, ICH decided to work on a new multidisciplinary guideline, “M9: Biopharmaceutics Classification System-based Biowaivers”, in 2016 [15]. A respective draft has been published in June 2018 [16], while the final Step 4 document has been announced for May 2019 [17], but has not been published so far.

The aim of this thesis is to summarize the development and the current status of the BCS-based biowaiver approach as reflected by the US FDA, the EMA and the WHO regarding eligibility and requirements for testing. Within the ICH, these represent important member and observer institutions that have been chosen as they have significantly contributed to the development of the BCS-based biowaiver approach and have set milestones by publishing comprehensive guidance documents. For the sake of completeness, a brief overview of the current status in other ICH countries and regions shall be provided. Subsequently, the regulatory framework envisaged by the upcoming implementation of ICH guideline M9 shall be described and finally evaluated in the context of harmonization efforts, focusing on the implications on the pharmaceutical industry.

2 Development and current positioning of regulatory authorities towards BCS-based biowaivers in important ICH regions

2.1 United States of America

US FDA first mentioned the BCS in its Guidance to Industry on dissolution testing of immediate-release oral dosage forms come into force in 1997 in the context of *in vitro* - *in vivo* correlation and as an additional tool for setting specification for dissolution tests [18]. FDA was also the first regulatory authority to implement specific guidance on the application of BCS-based biowaivers in 2000 (Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System [19]). Unlike the EU, where the subject was - and still is - incorporated within a general guidance document on bioequivalence testing (a fact that is also reflected in the legally binding document of the EU [4]), FDA issued a separate Guidance for Industry which remained valid until 2017. The possibility of biowaivers is explicitly laid down in Title 21 of the Code of Federal Regulations (CFR) [20], section 320.22.

In 2015, the Guidance for Industry described in the previous section was significantly revised; the updated version finally came into effect at the end of 2017 [21].

The most striking change is the eligibility of BCS Class III substances for biowaiver.

Furthermore, it has been made clear that BCS-based biowaiver may also be applied for fixed combination products: If all active substances are considered BCS Class I, the provisions for BCS Class I apply, unless PK interactions are to be expected; in this case, drug product requirements for BCS Class III have to be applied. If the active substances belong to BCS Class III respectively Class I and III, the drug product provisions for Class III apply.

For BCS Class I substances, the prerequisites have basically remained the same (high solubility and high permeability of the active substance, rapid dissolution and similar

dissolution profiles compared to reference product or very rapid dissolution of both test and reference product). However the requirements regarding the formulation are clarified in a way that no excipients with an influence on intestinal absorption are allowed unless more extensive data are provided.

For BCS Class III substances, besides high solubility a very rapid dissolution of the pharmaceutical form is required (≥ 85 % of active substance dissolved within 15 min), and the basic test product formulation (except for colorants) is qualitatively the same and quantitatively very similar. The latter is specified with regard to permitted ranges for single excipient classes as well as the permitted overall amount of excipient changes.

Regarding the formulation, very few provisions are made, however the FDA clearly expresses that the use of common and widely used excipients in amounts consistent to comparable products are favourable. In case of excipients with a possible influence on PK, applicants are encouraged to seek FDA advice prior to application for a BCS-based biowaiver.

Regarding solubility testing, the expected pH range over which solubility has to be shown has been reduced to 1 – 6.8, representing an approximative harmonisation with EU and WHO requirements (presented in the following sections). As the highest dose strength is used for solubility testing, it is made clear that additional information will be required if the highest administered dose is higher than the highest dose strength.

The cut-off value for high permeability has similarly been harmonised with EU and WHO requirements as it has been decreased from ≥ 90 % to ≥ 85 %. Consequently, limit values in the required testing methods have also been adjusted. Considerable changes have been made with regards to methods used for absorption testing: It is made clear that human PK studies (mass balance or absolute BA) are the preferred methods, while *in vivo* or *in situ* animal models as well as *in vitro* methods may be used alternatively. Further guidance is provided regarding cases when one method of determination is sufficient. In addition, the attachment including model substances for membrane permeability testing has been extended and refined.

For dissolution criteria, a further category (“very rapidly dissolving”, i.e. ≥ 85 % dissolved within 15 min) is introduced in harmonization with EU and WHO requirements.

Different agitation speeds other than 100 rpm for USP Apparatus I and 50 rpm for USP Apparatus II are meanwhile accepted with justification. In contrast, a higher number of testing points is generally expected compared to the former guidance document.

Furthermore, the amount of dissolution medium has been reduced to 500 mL. An amount of 900 mL is only accepted with justification. The reduction is again explained to be based on real-life conditions: The volume of the stomach is estimated to be 250 mL after ingestion of an oral pharmaceutical form with a standard glass of water, as suggested. As this volume is too small for dissolution testing, 500 mL have been agreed on as “commonly used” [22]. This reduction in volume becomes relevant in case the active substance in question exhibits borderline solubility and the required dose is high.

In order to illustrate the differences between the former and current guidance document, the most important requirements are listed in Table 2.1: Comparison of recent and current FDA guidance documents on BCS-based biowaiver Table 2.1.

Table 2.1: Comparison of recent and current FDA guidance documents on BCS-based biowaiver

		Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2000) [19]	Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2017) [21]
BCS classes eligible for biowaiver		I	I and III
Narrow therapeutic index drugs		No	No
Fixed dose combinations			Yes
Pharmaceutical forms		IR solid oral	IR solid oral
	Pharmaceutical equivalents	Yes	Yes
	Pharmaceutical alternatives	No	No

		Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2000) [19]	Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2017) [21]
Solubility	Cut-off criterion	Highest dose strength soluble in 250 mL of medium at at 37±1 °C and pH 1 – 7.5 and pK _a , pK _a -1 and pK _a +1	Highest dose strength soluble in 250 mL of medium at 37±1 °C and pH 1 – 6.8 and pK _a , pK _a -1 and pK _a +1
	Method	Shake-flask or similar	Shake-flask or similar
	Conditions	Replicate determination, verification of pH prior and after addition of buffer	Replicate determination, verification of pH prior and after addition of buffer
Permeability/Absorption	Cut-off criterion	Complete (≥90 %)	Complete (≥85 %)
	Method	Absolute BV, human mass-balance studies, human intestinal perfusion studies, <i>in vivo</i> or <i>in situ</i> animal models, <i>in vitro</i> permeation studies	Absolute BV, human mass-balance studies, human intestinal perfusion studies, <i>in vivo</i> or <i>in situ</i> animal models, <i>in vitro</i> permeation studies
Dissolution	Cut-off criterion	<u>Class I</u> : rapid (≥85 % within 30 min) plus similarity of dissolution profiles or very rapid (≥85 % within 30 min)	<u>Class I</u> : rapid (≥85 % within 30 min) plus similarity of dissolution profiles or very rapid (≥85 % within 30 min) <u>Class III</u> : very rapid (≥85 % within 15 min)
	Sampling intervals	Sufficient number of intervals	Sufficient number of intervals

		Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2000) [19]	Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2017) [21]
	Conditions	<p><u>Apparatus:</u> USP Apparatus I respectively II <u>Volume:</u> ≤900 mL</p> <p><u>Agitation:</u> 100 rpm (USP Apparatus I); 50 rpm (Apparatus II)</p> <p><u>Sampling schedule:</u> e.g. 10, 15, 20, 30 min</p> <p><u>Buffer:</u> 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; pH 4.5 buffer; pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes</p> <p><u>Other conditions:</u> no surfactant; addition of enzymes acceptable in case of gelatine coatings</p>	<p><u>Apparatus:</u> USP Apparatus I respectively II <u>Volume:</u> ≤500 mL, ≤900 mL with justification</p> <p><u>Agitation:</u> 100 rpm (USP Apparatus I); 50 rpm (or 75 rpm with justification) (Apparatus II)</p> <p><u>Sampling schedule:</u> e.g. 5, 10, 15, 20, 30 min</p> <p><u>Buffer:</u> 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; pH 4.5 buffer; pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes</p> <p><u>Other conditions:</u> no surfactant; addition of enzymes acceptable in case of gelatine coatings</p>
Excipients		<p><u>Class I:</u> preferably widely used, approved within IR oral pharmaceutical forms</p>	<p>preferably widely used, approved within IR oral pharmaceutical forms</p> <p><u>Class I:</u> no excipients influencing PK</p> <p><u>Class III:</u> qualitatively the same</p>

		Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2000) [19]	Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2017) [21]
			and quantitatively very similar

Overall it can be stated that the FDA provided a very comprehensive guidance with regards to testing methodology already within their first guidance document. Significant changes were proposed in 2015, leaving the very conservative approach of application of BCS-based biowaiver approach merely to BCS Class I substances and adjusting the requirements for solubility and adsorption testing. These changes resulted in a harmonisation with EU and WHO requirements.

It provides guidance on testing conditions and acceptance criteria for dissolution testing in the context of quality control of batches used e.g. within clinical trials or stability studies used for registration purposes. Criteria for eligibility for dissolution testing according to this guidance with regards to the required pharmaceutical form, solubility, and therapeutic index are the same as for the eligibility for a BCS-based biowaiver. It is additionally stated that the active substance must be stable over the entire test and that products with claims stressing an importance of the time to C_{max} , such as rapid-onset product or rescue medications, are excluded.

The proposed testing conditions (USP Apparatus I or II, agitation: 100 respectively 50 rpm with possible justified exceptions, 37 ± 0.5 °C, 0.1N aqueous HCl, no use of surfactant) represent a facilitation compared to the general guidance on dissolution testing for immediate-release oral dosage forms [18]: Instead of a dissolution profile, a one-point determination is also deemed acceptable for other purposes than routine control. However the possibility to replace dissolution test by the test on disintegration initially proposed in the draft guidance document [23] for medicinal products a dissolution of ≥ 80 % within

15 min was not finally not implemented, same as for the initial proposal of 0.01 N HCl as an alternative for the higher concentration.

In addition to the general guidance documents, FDA maintains an extensive database currently containing approximately 1,700 product-specific guidance documents on generic drug development [24] including information on bioequivalence studies, however so far, little or no information on BCS classes and specific requirements for BCS-based biowaivers is included.

2.2 European Union

The first regulatory guidance taking into account BCS-based biowaiver was published by the European Medicines Agency (EMA) in 2001, where the possibility of BCS-based biowaivers is briefly described in section 5.1.1 of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence [1].

Subsequently shortcomings were noticed by the EMA, which lead to applicants following the more detailed FDA guidance and conducting tests not required in the European Union, low overall numbers and low quality of applications for BCS-based biowaivers or denial of such applications by regulatory authorities due to uncertainties. These were addressed in a concept paper published in 2007: unspecific data requirements regarding inherent risks of the active substances and lack of guidance regarding absorption properties as well as dissolution testing and evaluation of excipients [25].

The Guideline on the Investigation of Bioavailability and Bioequivalence came into effect in 2010 [3], replacing the former Note for Guidance. It has to be noted that the updated guideline focuses on immediate-release dosage forms with systemic action, while other pharmaceutical forms are discussed in separate guidance documents.

A separate appendix (Appendix III) referring to BCS-based Biowaiver is included in the guideline. Generally, sound peer-reviewed literature is accepted in support of classification and characterization of active substances. In contrast, data on the specific pharmaceutical form normally has to be generated by the applicant.

The most important change in comparison with the previous guidance document, and also with the FDA guidance valid at the time of publishing, is the eligibility of BCS class III substances for a biowaiver and clear cut-off criteria are defined with regard to dissolution profile and formulation.

In the question and answers section on the EMA website it is clarified that a biowaiver of strengths cannot be based on evidence of bioequivalence based on BCS, so that the requirements for BCS-based biowaiver must be fulfilled for each single strength [26].

Further clarification is provided on the active substance: generally, BCS-based biowaiver approach applies to pharmaceutical equivalents (i.e. same amount of exactly the same active substance and same dosage form [1]). With regard to pharmaceutically equivalent substances (same active moiety but difference in chemical form (salt, ester, etc.) of that moiety or in pharmaceutical form or strength, [1]) it is stated that only different salts may be eligible if both salt belong to BCS class I. In contrast, different different esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance, as an influence on bioavailability cannot be excluded.

While for pharmaceutical forms containing BCS class I substances either a very rapid (>85 % within 15 min) or a similarly rapid dissolution compared to the reference product (85 % within 30 min) is sufficient, both test and reference product of pharmaceutical forms containing BCS class III substances must exhibit a very rapid dissolution. Furthermore, in case of class III substances, excipients that might affect bioavailability have to be qualitatively and quantitatively the same and other excipients have to be qualitatively the same and quantitatively very similar. For class I substances, only the former applies, although the highest possible similarity with regard to the qualitative and quantitative composition of the formulation should be aimed for.

The Appendix also provides examples of excipients with a possible effect on bioavailability and advice on aspects that should be considered in this context.

An important change with regard to solubility is the fact that the EMA now requires solubility testing with the highest administered single dose instead of the highest dose strength. This stricter requirement is in contrast to FDA, however, in line with WHO guidance and better reflects therapeutic reality. Nevertheless this question is crucial for

the classification of active substances as “low solubility” or “high solubility” and the resulting BCS class, which is the reason for a critical discussion of this change regarding the solubility requirement [27].

Otherwise the definition of “high solubility” remains almost the same, except for one of the preferred pH values, which is adjusted from 4.6 to 4.5 and additional testing at pK_a if it is within the tested range, which represents an accordance to FDA requirements. Guidance is complemented by a brief description of methodology to be used for the test.

Regarding permeability, the guideline states that demonstration of complete absorption should preferably be used as an indicator of high permeability. A cut-off value for “complete absorption” is provided ($\geq 85\%$), being slightly less strict compared to the cut-off value previously set by FDA. This should preferably be demonstrated by means of *in vivo* data (which may possibly be derived from the literature). Compared to FDA guidance, the inclusion of metabolites into the sum of recovered active substance is more extensively described.

A significant difference in contrast to FDA is that fact that *in vitro* methods are only of a supportive nature but cannot be used as stand-alone method in order to determine permeability.

In case of of BCS class III substances, but also class I substances for which complete absorption could not be unequivocally demonstrated, the stricter criteria regarding dissolution and formulation as described above have to be applied.

In summary, methodology descriptions in order to determine solubility and in particular permeability are significantly less extensive compared to FDA guidance, leaving more freedom, but also more responsibility to the applicant.

The guidance on *in vitro* dissolution testing is much more detailed compared to the former guidance and in large parts comparable to the requirements previously set by FDA (though with some existing differences):

- In case non-pharmacopeial methods are used, their discriminating properties have to be demonstrated.
- Test methods and software for analysis have to be validated.

- Preferably, more than one batch of test and reference product should be used.
- Sampling time points are specified:
 - intervals: at least every 15 min, more frequently during most rapid change of dissolution curve; 5- or 10-min intervals in case of rapid dissolution;
 - minimum number of determinations:
 - $t = 15$ min in case of rapid dissolution (>85 % of active substance dissolved within 15 min) in order to clarify if dissolution takes place before gastric emptying;
 - 85 % of the active substance dissolved within more than 15 and up to 30 minutes: minimum three determinations – $t < 15$ minutes, $t = 15$ min, t close to the timepoint when 85 % are dissolved.
- Similarity of dissolution profiles between test and reference product must be demonstrated, e.g. via similarity factor f_2 . This is not required if >85 % of the active substance are dissolved within 15 min (later referred to “very rapid dissolution”).
- Acceptance limits should be predefined and not exceed 10 %; variabilities between test and reference product should be similar.
- Detailed guidance is provided on testing conditions (apparatus, volume of dissolution medium, temperature, agitation, sampling schedule, buffers, other conditions).

A comparison of the different aspects between the Note for Guidance published in 2001 [1] and the Guideline that has come into effect in 2010 [3] is provided in Table 2.2.

Table 2.2: Comparison of recent and current EMA guidance documents on BCS-based biowaiver

		Note for Guidance on the Investigation of Bioavailability and Bioequivalence (2001) [1]	Guideline on the Investigation of Bioavailability and Bioequivalence (2010) [3]
BCS classes eligible for biowaiver		I	I and III
Narrow therapeutic index drugs		No	No
Fixed dose combinations		Yes	Yes

		Note for Guidance on the Investigation of Bioavailability and Bioequivalence (2001) [1]	Guideline on the Investigation of Bioavailability and Bioequivalence (2010) [3]
Pharmaceutical forms		IR oral with systemic action	IR solid oral with systemic action and same pharmaceutical form
	Pharmaceutical equivalents	Yes	Yes
	Pharmaceutical alternatives		Yes (only different salts of BCS class I)
Solubility	Cut-off criterion	Highest dose strength soluble in 250 mL of three buffers at pH 1 – 8 (e.g. pH 1.0, 4.6, 6.8) at 37 °C	Highest single dose soluble in 250 mL of three buffers at pH 1 – 8 (e.g. pH 1.0, 4.5, 6.8) at 37 °C and pK _a if within specified range
	Method		Shake-flask or similar
	Conditions		Replicate determination, verification of pH prior and after addition of buffer
Permeability/Absorption	Cut-off criterion	Linear and complete	Complete (≥85 %)
	Method		Absolute BV or human mass-balance studies
Dissolution	Cut-off criterion	<u>Class I</u> : very rapid (>85 % within 15 min) or similarly rapid (not further specified)	<u>Class I</u> : very rapid (>85 % within 15 min) or similarly rapid (85 %: >15 min, ≤30 min) <u>Class III</u> : very rapid (>85 % within 15 min)
	Sampling intervals		At least every 15 minutes <u>Very rapid dissolution</u> : after 15 min <u>Comparably rapid dissolution</u> : at least

		Note for Guidance on the Investigation of Bioavailability and Bioequivalence (2001) [1]	Guideline on the Investigation of Bioavailability and Bioequivalence (2010) [3]
	<p>Conditions</p>		<p><15 min, 15 min, close to 85 %</p> <p><u>Apparatus</u>: paddle or basket <u>Volume</u>: ≤900 mL <u>Temperature</u>: 37±1 °C <u>Agitation</u>: usually 50 rpm (paddle), 100 rpm (basket) <u>Sampling schedule</u>: e.g. 10, 15, 20, 30, 45 min <u>Buffer</u>: pH 1.0 – 1.2 pH 4.5 and pH 6.8 (Ph.Eur. buffers recommended); addition of enzymes acceptable in case of gelatine coatings <u>Other conditions</u>: no surfactant; addition of enzymes acceptable in case of gelatine coatings</p>
<p>Excipients</p>		<p><u>Class I</u>: well established, no PK interaction expected</p>	<p><u>Class I</u>: excipients that might affect bioavailability: qualitatively and quantitatively the same <u>Class III</u>: excipients that might affect bioavailability: qualitatively and quantitatively the same; other excipients: qualitatively the same and quantitatively very similar</p>

In summary, besides the eligibility of BCS class III substances for biowaiver, the requirements have become significantly more concrete and comprehensive compared to the former guidance document, which had left considerable room for interpretation. This is particularly relevant regarding the evaluation of and requirements in terms of excipients. Still, there are far fewer specifications with regard to testing methodology compared to FDA guidance.

Since October 2013, EMA continuously publishes product-specific guidance regarding bioequivalence. So far, close to 60 individual guidance documents have been finalized, a comparatively small number in contrast to the number of FDA product-specific guidances. Mostly, the EMA guidance also includes the information whether the active substance is assigned to class I or III and in some cases gives further guidance on the possibility of BCS-based biowaivers [28].

2.3 World Health Organization (WHO)

The WHO holds an observer status within ICH. It does not represent a regulatory agency, however it takes a global role in creating international standards and guidance, mainly in order to assist middle and low income countries with limited capacities in terms of medicinal product regulation, e.g. including regulatory assessment of quality, safety and efficacy of medicinal products, quality of active substances and inspection activities. All adopted guidelines are annually published within the Technical Report Series issued by WHO Expert Committees. A large number of countries worldwide refer to the WHO guidelines, e.g. if no individual guidance is available. Furthermore, the guidelines are of relevance in context with the WHO Prequalification of Medicines Programme.

The first guidance on BCS-based biowaiver was drafted in 2005 and finalized in 2006. It was incorporated into revision of the guideline “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability” [29]. Furthermore, a new guideline “Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate release, solid oral dosage forms”

was published, where active substances from the WHO Essential Medicines List [12] were classified regarding their BCS class and their eligibility for biowaiver [30].

Unlike FDA and EMA, WHO considered, besides BCS class I and III substances, also BCS class II substances representing weak acids (often referred to as BCS class IIa) as eligible for a BCS-based biowaiver. The requirements were high solubility at pH 6.8, rapid dissolution of the dosage form and similarity of the dissolution profiles, an extended risk evaluation with particular focus on excipients and exclusion of products where C_{\max} was considered a critical parameter.

A revision of the guideline “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability” was carried out in 2014 and officially implemented in 2015 [31]. In contrast, the guideline “Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate release, solid oral dosage forms” is still under revision. It is intended to maintain the tables containing biowaiver-related information on single active substances as a living document; a respective draft was published in 2018 [32].

In contrast to the former version, the current version of the guideline “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability” does not consider BCS class IIa substances as eligible for a biowaiver anymore.

In all cases, solubility of the active substance is determined using the highest single therapeutic dose.

In terms of absorption testing, it is stated that literature data on mass balance studies or absolute bioavailability may be derived from the literature if it can be ensured that the design of the tests is appropriate.

For dissolution testing, the use of pharmacopeial buffers is recommended. Furthermore, it is clarified that that no surfactants should be used; in contrast, the use of enzymes, such as pepsin or pancreatin, may be appropriate, e.g. in case of capsules or caplets containing gelatin.

Guidance with regard to excipients is extended: For pharmaceutical forms containing BCS class I substances, it is recommended that the excipients should be used either in the reference product or in other formulations of the same active substance approved in ICH-associated countries.

For products containing BCS class III substances, the excipients should be qualitatively the same and quantitatively similar to that of the reference product.

In both cases, critical excipients with a possible effect on bioavailability, such as sugar alcohols or surfactants, should be qualitatively the same and quantitatively similar. The definition of “similar” is based on the allowable quantitative changes in excipients for a variation set by WHO [33], which permit only half of the range compared to the FDA [21].

In 2017, an appendix “Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the biopharmaceutics classification system” was added to the guideline [34]. While the general conditions remain the same, further guidance is provided on the methodology. In addition to the three standard pH values, testing is also required at any known solubility minima within the pH range. The shake-flask method is preferred, however other methods are possible if justified. The use of pharmacopeial buffers is recommended, taking into account factors such as common ion effects and ionic strength. pH should be verified with a calibrated pH meter; in order to ensure that the equilibrium has been reached (preferably after strong agitation followed by a period left for sedimentation), samples should be taken at different timepoints. For the assay, a validated, stability-indicating method should be used.

The changes between the guidelines dating from 2007 respectively 2015 are illustrated in Table 2.3.

Table 2.3: Comparison of recent and current WHO guidance documents on BCS-based biowaiver

		WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 937, Annexes 7 and 8 (2006) [29], [30]	WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 992, Annex 7 (2015) [34]
BCS classes eligible for biowaiver		I, III and IIa	I and III
Narrow therapeutic index drugs		No	No
Fixed dose combinations		Yes, if all APIs belong to class I	Yes, if all APIs belong to class I
Pharmaceutical forms		IR, solid, oral	IR, solid, oral
	Pharmaceutical equivalents	Yes	Yes
	Pharmaceutical alternatives		Yes (different salts only)
Solubility	Cut-off criterion	<p><u>Class I and III:</u> Highest dose according to EML or highest single dose soluble in ≤ 250 mL of three buffers at pH 1.2 – 6.8 at 37 ± 1 °C</p> <p>Class IIa: Highest dose according to EML or highest single dose soluble in ≤ 250 mL of buffer at pH 6.8 at 37 ± 1 °C</p>	<p><u>Class I and III:</u> Highest single dose soluble in ≤ 250 mL of three buffers at pH 1.2 – 6.8 at 37 ± 1 °C and known solubility minima if within specified range</p>
	Method		Shake-flask or similar
	Conditions		Replicate determination, verification of pH with calibrated pH meter
Permeability/Absorption	Cut-off criterion	Complete (≥ 85 %)	Complete (≥ 85 %)

		WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 937, Annexes 7 and 8 (2006) [29], [30]	WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 992, Annex 7 (2015) [34]
	Method	Absolute BV, human mass-balance studies, human intestinal perfusion studies	Absolute BV, human mass-balance studies, human intestinal perfusion studies
Dissolution	Cut-off criterion	<p><u>Class I:</u> very rapid (>85 % within 15 min) or rapid (85 %: ≤30 min) and similar to reference product</p> <p><u>Class III:</u> very rapid (>85 % within 15 min)</p> <p><u>Class IIa:</u> rapid (85 %: ≤30 min) and similar to reference product</p>	<p><u>Class I:</u> very rapid (>85 % within 15 min) or rapid (85 %: ≤30 min) and similar to reference product)</p> <p><u>Class III:</u> very rapid (>85 % within 15 min)</p>
	Sampling intervals	For evaluation of similarity of dissolution profiles: 10, 15, 20, 30, 45 and 60 minutes	For evaluation of similarity of dissolution profiles: 10, 15, 20, 30, 45 and 60 minutes
	Conditions	<p><u>Apparatus:</u> paddle or basket</p> <p><u>Volume:</u> ≤900 mL</p> <p><u>Temperature:</u> 37±1 °C</p> <p><u>Agitation:</u> 75 rpm (paddle), 100 rpm (basket)</p> <p><u>Buffer:</u> pH 1.0 – 1.2, pH 4.5 and pH 6.8</p> <p><u>Other conditions:</u> no surfactant; addition of enzymes acceptable</p>	<p><u>Apparatus:</u> paddle or basket</p> <p><u>Volume:</u> ≤900 mL</p> <p><u>Temperature:</u> 37±1 °C</p> <p><u>Agitation:</u> 75 rpm (paddle), 100 rpm (basket)</p> <p><u>Buffer:</u> pH 1.2 HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer (pharmacopeial buffers recommended)</p> <p><u>Other conditions:</u> no surfactant; addition of</p>

		WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 937, Annexes 7 and 8 (2006) [29], [30]	WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 992, Annex 7 (2015) [34]
		in case of gelatine coatings	enzymes acceptable in case of gelatine coatings
Excipients		Present in the reference or a comparable authorized finished product; similar quantities or quantity typically used for specific type of dosage form	<u>Class I:</u> critical excipients: qualitatively the same and quantitatively similar; all excipients: used either in the reference product or in other approved; formulations of the same active substance <u>Class III:</u> qualitatively the same and quantitatively similar

In summary, WHO guidance on BCS-based biowaivers is closer to EU than to FDA guidance, with a tendency to less strict requirements. Apart from the cessation of accepting weak acids of BCS-class II for a BCS-based biowaiver, no significant evolution has taken place over time.

3 Acceptance of BCS-based biowaivers in further ICH regions

3.1 Japan

In the current National Institute of Health Services „Guideline for Bioequivalence Studies of Generic Products“ [35], no possibility of using the BCS-based biowaiver approach is provided neither for marketing authorization applications nor variations to existing products. Despite the fact that the subject is under consideration [36], the BCS has not been mentioned in official documents so far. This is based on the position of the Japanese regulatory authority stating that solubility and permeability of an active substance are inconclusive with regard to bioavailability and bioequivalence, but differences in bioavailability are rather based on formulation effects and manufacturing process characteristics.[37].

3.2 Canada

Health Canada published a guidance document on BCS-based biowaiver in 2014 [38].

BCS class I as well as class III substances are eligible for a biowaiver for conventional, immediate-release solid dosage form with intended systemic action; the dosage form must be identical to that of the reference product. The guidance is applicable for pharmaceutical equivalents. According to the policy on interpretation of identical medicinal ingredients [39], this also includes the various hydrates and solvates (in case the solvate is within acceptable levels), but not complexes, esters, salts, isomers or mixtures of isomers. Narrow therapeutic index drugs are excluded; fixed-dose combinations are eligible if each substance complies with the requirements. It is furthermore stated that an application for a BCS-based biowaiver must be provided for each single strength.

The requirements for solubility (highest therapeutic dose approved in Canada or highest proposed single dose if currently not approved in Canada), permeability and dissolution are in line with those in the EU. In terms of dissolution testing, the guidance document

contains information on cases where commercial batches should be used for testing instead of pilot batches: These include low active substance dosages or low proportions of the active substance in the dosage form or variable, complex or new manufacturing processes.

Requirements regarding the formulation state that critical excipients must be the same and may not differ by more than 10 % in terms of their quantity compared to the reference products. While for pharmaceutical forms containing BCS class I substances it is only recommended that all excipients are identical and quantitatively very similar, this is mandatory in case of class III substances (except for non-functional coatings).

In summary, the requirements in Canada are very close to those in the EU, with few differences in terms of the eligibility of pharmaceutical alternatives.

3.3 Switzerland

The swissmedic guidance document for the approval of medicinal products for human use with known active substance [40] directly refers to the EU guidance.

3.4 Brazil

The current biowaiver guidance document published by the Agência Nacional de Vigilância Sanitária (ANVISA) [41] sets the following requirements: BCS-based biowaivers may be granted for immediate-release oral pharmaceutical forms. Also fixed combination products are eligible in case each active substance complies with the requirements.

One characteristic difference in contrast to other countries is that the eligibility of active substances for a BCS-based biowaiver is not automatically supported for specific BCS classes, but is directly defined by ANVISA in the form of a periodically updated positive list containing, so far, only BCS-class I substances [42]. All listed substances exhibit a permeability of ≥ 85 % so that no repective data have to be generated [43].

Well-established excipients should be used in appropriate amounts; it is recommended that the same excipients as in the reference product should be used. Critical excipients

should be identical and be used in an appropriate amount. Special provisions are given for isoniazide-containing pharmaceutical forms (no use of saccharides).

The testing requirements with regard to solubility, permeability and dissolution are in line with the EU requirements; it is explicitly stated that phase diagrams may be alternatively used for the determination of equilibrium solubility [41], [44].

3.5 South Korea

The Standard on Pharmaceutical Equivalence Test published by the Ministry of Food and Drug Safety in 2018 [45] dedicates an annex to BE study waivers for oral tablets, capsules, powders and granules. Only BCS-class I substances are eligible. In case an excipient that is not contained in the reference product or unusual amounts of excipients are used, justification is required; this is particularly relevant for critical excipients.

The guidance is in accordance with the FDA Guidance for Industry published in 2000 [19]. Remarkably, the South Korean standard has not yet been updated in line with the current FDA Guidance for Industry [21].

It is furthermore stated that if an active substance has been deemed highly soluble respectively highly permeable by the Ministry of Food and Drug Safety, the respective tests may be waived.

3.6 China

Based on the Guidelines on the Bioavailability and Bioequivalence Studies of Drug Products published in the Chinese Pharmacopeia, Chinese Food and Drug Administration presently grants Biowaivers for immediate-release formulations containing BCS class I substances with either very rapid or rapid dissolution with similar dissolution profile compared to the test product. Only pharmaceutical equivalents are eligible for BCS-based biowaivers [46], [47].

3.7 Taiwan

The Regulation of Bioavailability and Bioequivalence studies first published in 2009 and most recently amended in 2015 does not directly list the possibility of applying for BCS-based biowaivers, but states that apart from biowaiver possibilities listed in the regulation, other biowaivers that are approved by the central competent health authority according to information provided by the applicants“ may be possible [48]. According to a survey among representatives from regulatory bodies conducted by the International Generic Drug Regulators Programme Bioequivalence Working Group revealed that Taiwan is currently accepting BCS-based biowaivers for class I and III substances [42].

3.8 Association of Southeast Asian Nations (ASEAN)

The Association of Southeast Asian Nations (ASEAN) represents an association initially founded by Indonesia, Malaysia, the Philippines, Singapore and Thailand. Meanwhile Brunei Darussalam, Vietnam, Laos and Myanmar have joined. Among the member states, the regulatory authorities of Singapore and Malaysia hold an ICH observer status independent from ASEAN. One of ASEAN’s goals is the harmonization of standards and technical requirements.

The ASEAN Guideline for the Conduct of Bioequivalence studies was initially published in 2004 and revised several times, most recently in 2015 [49]. It represents an adoption of the EMA Guideline on the Investigation of Bioequivalence [3]. The only difference is that ASEAN accepts BCS-based biowaivers only for BCS class I substances and has thus eliminated the sections referring to class III substances.

In addition to the guidance provided by ASEAN, several member states have published their own guidance documents on bioequivalence testing and/or BCS-based biowaivers, which are referred to in the following sections 3.8.1 to 3.8.3.

3.8.1 Singapore

In accordance with ASEAN, Singapore used to accept BCS-based biowaiver for BCS class I substances only [42]. However the current version of the Guidance by Health Sciences Authority on Product Interchangeability and Biowaiver Request for Chemical

Generic Drug Applications published in 2018 [50], an appendix to the Guidance on Therapeutic Product Registration in Singapore, also allows BCS-based biowaivers for class III substances. The document does not provide any description on the methodology and is otherwise in complete accordance with to ASEAN (and thus EU) guidance.

3.8.2 Philippines

The Food and Drug Administration Philippines does not publish an own guidance document. Previously the authority used to refer to the WHO guidance [51], however it has to be assumed that meanwhile, ASEAN standards have to be applied.

3.8.3 Malaysia

The Ministry of Health published an own guidance document in 2013 [52], referring to the EMA and WHO guidance (the latter prior to revision). Only BCS-class I substances are considered acceptable for biowaiver, and the eligibility is restricted to a list of active substances included in the document. This list is published and maintained on the authority website [53]. It has to be assumed that the guidance issued by ASEAN is meanwhile followed.

3.9 India

The Guidelines for Bioavailability & Bioequivalence Studies published by the Central Drugs Standard Control Organization date back to 2005. Although the BCS is not explicitly mentioned, bioequivalence studies may be replaced by *in vitro* studies if solubility and absorption of the active substance as well as dissolution data for the finished product [54]. The requirements conform to the FDA Guidance for Industry published in 2000 [19]. In 2017, a notification published by the Ministry of Health and Family Welfare indicated that both BCS class I and III may be eligible for a biowaiver [55], however this new development has not yet been implemented into guidance documents.

3.10 Cuba

Despite the fact that the BCS is mentioned in the glossary of the guidance document on bioavailability and bioequivalence studies dating from 2007, it is not mentioned in the core guideline text, and no possibility for a biowaiver based on requirements in accordance with BCS is listed in the respective section [56]. The FDA Guidance for Industry published in 2000 [19] is listed in the bibliography, however no further reference is made.

3.11 Mexico

The current Mexican guideline for submission of research protocols to demonstrate the drug interchangeability [57] does not mention the BCS. This is in accordance with the results of the survey among representatives from regulatory bodies already mentioned above [42], stating that to date, no BCS-based biowaivers are accepted in Mexico.

3.12 Columbia

The Columbian Ministry for Health and Social Protection published a resolution dealing with bioavailability and bioequivalence studies in 2016 [58]. The Technical Annex 1 adopts the current WHO guidance and thus granting BCS-based biowaivers for immediate-release oral pharmaceutical forms containing BCS class I and III substances. Furthermore a supportive document has been published including the BCS classification of those active substances for which BE studies generally have to be provided [59].

3.13 Moldova

No information is available regarding requirements for bioequivalence studies and biowaivers from the side of the regulator authority Moldova. According to a review published in 2014, bioequivalence requirements have not yet been fully implemented [60]. Based on the content of its website [61], the Medicines and Medical Devices Agency tends to refer to European legislation.

3.14 Kazakhstan

According to a recent review [62], a guideline on bioequivalence testing dating from 2007 exists in Kazakhstan, however this could not be verified. In 2015, the Order On Approval of the Medical Agents, Medical Products and Medical Equipment Examination Procedures was amended, accepting biowaivers for BCS class I substances [63]. The requirements are only described briefly and conform to those in the US, the EU and the WHO guidance.

3.15 Iran

As the medicines section of the official website of the Iran Food & Drug Administration [64] is currently under construction, unfortunately no information on the acceptance of BCS-based biowaivers in Iran is available at present.

3.16 Russia

An English translation of the guidance document “Methodological recommendations for drug manufacturers on in vitro equivalence test for generic drug products according to biowaiver procedure” has been published by FIP [65]. The listed requirements are in accordance with EU requirements. However it has been stated that for initial marketing authorization applications, BCS-based biowaiver approaches for BCS class I and III substances are only accepted for further strengths, but evidence of bioequivalence cannot be entirely provided by means of *in vitro* studies [62].

3.17 South Africa

The guideline “Biostudies” [66] was implemented in 2015 and refers to current WHO guidance. BCS-based biowaivers are accepted for BCS class I and III substances.

3.18 Armenia

As the medicines section of the official website of the Scientific Centre of Drug and Medical Technology Expertise [64] does not provide the possibility to assess English legislative or guidance documents, unfortunately no information on the acceptance of BCS-based biowaivers in Armenia is presently available.

3.19 Australia

In its guidance on biopharmaceutical studies, Therapeutic Goods Administration adopts the European guidelines. Additional guidance is provided on the conduct of comparative dissolution testing and justifications for not submitting *in vivo* data [67].

3.20 Turkey

No English guidance documents are accessible via the website of the Turkish regulatory authority [64]. However, an evaluation published in 2013 revealed that decisions on BCS-based biowaiver applications have so far taken into account FDA, EU as well as WHO requirements. Generally, BCS-based biowaivers for class I and III substances are acceptable [68].

3.21 Guidance published by further regional harmonisation initiatives

In addition to guidance documents published by regulatory authorities holding a member or observer state within the ICH, guidance regarding the acceptance of BCS-based biowaivers is also available from national competent authorities which are not directly present, however represented by one or more of the regional harmonization initiatives holding an observer state within the ICH. Of these, only ASEAN has published its own guidance document on bioequivalence studies (see section 3.8).

3.21.1 Asia-Pacific Economic Cooperation (APEC)

The Asia-Pacific Economic Cooperation (APEC) currently counts 21 member states, among which the status in the US, Japan, Canada, Australia, Mexico, China, South Korea, Taiwan, Singapore, the Philippines, Malaysia, and Russia has already been described in previous sections. In addition, the national competent authorities of New Zealand and Chile have published guidance documents covering BCS-based biowaivers. While Medsafe, the New Zealand Medicines and Medical Devices Safety Authority, directly refers to EU guidance [69], the Chilean guidance document [70] dates from 2007 and refers to the WHO guidance published in 2006. BCS-based biowaiver is generally accepted for BCS class I; for classes III and certain substances of class II, the acceptance will be decided on a case-by-case basis.

3.21.2 East African Community (EAC)

The East African Community (EAC) comprises the member states Burundi, Kenya, Rwanda, South Sudan, Tanzania, and Uganda. Guidance regarding BCS-based biowaivers is available in Rwanda, Tanzania and Uganda. Rwanda is accepting BCS-based biowaivers for class I [71], Tanzania [72] and Uganda [73] for both classes I and III.

3.21.3 Gulf Health Council (GHC)

The Gulf Health Council (GHC) currently represents the nine countries. The national competent authorities of Saudi Arabia and Jordan have published respective guidance documents. In Saudi Arabia, only BCS class I substances are eligible for a biowaiver [74]; in Jordan, class III substances are also eligible [75].

3.21.4 Pan American Network for Drug Regulatory Harmonization (PANDRH)

The Pan American Network for Drug Regulatory Harmonization (PANDRH) comprises of almost fifty member states. The status regarding BCS-based biowaivers in Brazil, Canada, Chile, Mexico, Colombia, Cuba and the US has been described in previous sections. Further guidance on the issue is available from the national competent authorities of Argentina and Uruguay. In Argentina, BCS-based biowaivers are considered for a number of BCS class I and III substances with intermediate health risk

listed within the guidance document [76]. In Uruguay, BCS-based biowaivers are generally accepted for class I substances and in exceptional, justified cases for classes II and III [77].

3.21.5 Southern African Development Community

The Southern African Development Community currently comprises 16 member states. Guidance documents published by the national competent authorities of South Africa and Tanzania have already been mentioned in previous sections. In addition, guidance documents regarding BCS-based biowaivers are available in Zambia and Zimbabwe. In Zambia, BCS-based biowaivers are accepted for class I and III [78], whereas the guidance document from Zimbabwe dates from 2009 and refers to the WHO guidance published in 2006. BCS-based biowaiver is thus principally accepted for BCS class I, II and III [79].

4 Draft Guideline ICH M9

4.1 Current status

In case of entirely new ICH guidelines, a formal ICH procedure has to be followed [80]. In terms of BCS-based biowaivers, a need for harmonization has been identified, and the process has been initiated by the endorsement of a concept paper [15] and a business plan [17] in 2016. Following consenses building within the Expert Working Group, the draft guideline [16] has been adopted in 2018. Currently, step 3 is ongoing: Comments from public consultation have been submitted and are being evaluated and discussed by the Expert Working Group. Subsequently, the guideline text shall be finalized and adopted by the ICH assembly, which was initially planned for May 2019, but so far has not taken place. Finally, the guideline has to be implemented by all ICH members.

4.2 Prerequisites for BCS-based biowaivers

The scope of the draft ICH M9 draft guideline [16] includes immediate-release solid oral pharmaceutical forms with systemic action. Pharmaceutical forms intended for buccal or sublingual absorption are not eligible for BCS-based biowaivers; orodispersible pharmaceutical forms may be considered in case buccal or sublingual absorption can be excluded. Additionally, for this kind of pharmaceutical forms, the product information texts must state that it must be swallowed with water, as other liquids may have an impact on solubility, intestinal absorption and/or dissolution.

In accordance with the other guidance documents published so far, narrow therapeutic index drug products are excluded; BCS-based biowaivers for fixed-dose combinations are acceptable in case each single active substance complies with the requirements.

BCS class I as well as class III substances are eligible for a BCS-based biowaiver, while class II substances are not taken into account.

The active substances in the test and reference product have to be identical, i.e. the guideline is only applicable to pharmaceutical equivalents, not pharmaceutical alternatives.

In contrast to current EU guidance, also BCS-based biowaivers for different salts of the same active substance are not acceptable. Pharmaceutical forms containing prodrugs may be considered, however only if the active substance is absorbed as a prodrug, i.e. conversion to the active moiety does not occur prior to intestinal absorption.

Generally, peer-reviewed literature data may be used in order to provide information in terms of solubility and permeability of the active substance, provided it can be ensured that the results have been obtained from high-quality studies. In contrast, data on the specific pharmaceutical form normally has to be generated by the applicant.

The definition of “high solubility” is as follows: The highest single therapeutic dose must be completely soluble in ≤ 250 mL of aqueous media over a pH range of 1.2 – 6.8 at 37 ± 1 °C. Additional data will be required if the highest dose strength, however not the highest single therapeutic dose fulfils this requirement (e.g. demonstration of proportional PK, i.e. AUC and C_{\max} , over a dose range including the highest therapeutic dose).

In terms of permeability, assessed preferably by means of pharmacokinetic studies in humans determining the absorption, i.e. either determination of absolute bioavailability or mass balance studies, an active substance is deemed “highly permeable” when the absolute bioavailability is ≥ 85 % or if ≥ 85 % of the active substance are recovered. In line with FDA guidance, permeability may also be assessed by means of validated and standardized *in vitro* tests using Caco-2 cells in case of passively transported active substances. *In vivo* and *in situ* animal models are not taken into account. In case the requirements for “high permeability” cannot be fulfilled, the active substance is classified as exhibiting “low permeability”.

The specifications for *in vitro* dissolution testing are as follows: Pharmaceutical forms containing BCS class I substances must exhibit either very rapid dissolution (≥ 85 % of active substance dissolved within ≤ 15 minutes) or rapid dissolution (≥ 85 % within ≤ 30 min) and similar dissolution characteristics under all *in vitro* conditions (i.e. three buffers: pH 1.2, pH 4.5 and pH 6.8 and –in some regions- purified water) compared to the reference product. It is clarified that if one of the products exhibits rapid and the other one very rapid dissolution, dissolution profiles must be similar. No evaluation of similarity is required in case of very rapid dissolution of both products. For

pharmaceutical forms containing BCS class III substances, very rapid *in vitro* dissolution is required. The specifications for fixed dose combinations are set based on the active substances (BCS class I only: very rapid dissolution or rapid dissolution and similar dissolution profile; BCS class I and III or class III only: very rapid dissolution).

The discussion regarding assessment of formulation and excipients is more extensive compared to current guidance documents. Decision trees and tables demonstrating examples of acceptable differences in formulation between test and reference product are provided in the form of an appendix to the guideline.

In any case, the single excipients as well as the entire formulation have to be assessed with regard to their potential to alter intestinal absorption, whereby small amounts used for tablet coating or with documented evidence that absorption is not influenced are of less concern.

For pharmaceutical forms containing BCS class I substances, qualitative and quantitative differences in terms of excipients are generally permitted, as intestinal absorption of this group of substances is less prone to formulation effects. However critical excipients with regard to intestinal absorption may not differ by more than 10.0 % compared to the reference product. This permission does, however, not exempt the applicant from assessing each (potential) excipient with regard to its influence on rate and extent of absorption, taking into account the specific characteristics of the active substance, e.g. mechanism (active/passive) and location of absorption and consider the results during formulation development.

The risk of formulation effects is evidently higher in case of pharmaceutical forms containing BCS class III substances so that all excipients have to be qualitatively the same and quantitatively very similar. As for BCS class I substances, difference with regard to critical excipients in comparison to the reference product may not exceed ± 10.0 %. For all other excipients, a table listing allowable differences has been taken from FDA guidance (except that a film coat is not taken account and the differences are expressed relative to core weight and not to the total formulation). Notably, three decimal places are used instead of two as with the FDA guidance document.

For excipients used in fixed dose combinations, the requirements for BCS class I substances apply if all active substances belong to class I; otherwise, the requirements for class III substances apply.

4.3 Details on testing conditions

Compared to the current guidance documents, the description of methodology for the determination of solubility, permeability and *in vitro* dissolution has been further substantiated.

In accordance with current guidance documents, equilibrium solubility testing has to be carried out under the following test conditions:

- 250 mL of buffer over a pH range of 1.2 – 6.8 at 37 ± 1 °C;
- shake-flask technique or alternative method, if justified;
- use of validated, stability-indicating assay method.

In addition, it is emphasized that stability of the active substance in the solubility media over the duration of the test has to be demonstrated (degradation: ≤ 10 %). Furthermore, it is clarified that the lowest measured solubility over the specified pH range is relevant for the classification of solubility.

Regarding the guidance on methodology for the determination of permeability, guidance on the inclusion of recovered metabolites is further refined: Parent compound as well as metabolites occur in the urine only if absorption has taken place and thus may be included into the sum of recovered active substance. In case of compounds recovered from feces, unchanged parent compound may not be due to lack of evidence of absorption. The latter also applies for metabolites resulting from reduction or hydrolysis as these may be generated by intestinal microbiota, so that only oxidative and conjugative metabolites may be considered (unless unequivocal evidence for formation after absorption exists for other metabolites).

Unless high permeability is demonstrated by determination of absolute bioavailability, stability in the gastrointestinal tract has to be demonstrated using a validated, stability-

indicating assay method (degradation: $\leq 10\%$). The conditions for the respective stability study the same as described in the FDA guidance document.

An annex has been dedicated to the use of Caco-2 cell permeability assay methodology. The description includes all considerations provided in the FDA guidance document but is more extensive. A minimum of five compounds each exhibiting low, moderate and high permeability (examples for each class are provided in the form of a table) should be used for validation in order to ensure that the assay method is able to discriminate between substances with different permeability. A minimum of three cell assay replicates is required. Furthermore, cell monolayer identity has to be demonstrated prior to and after the test by means of transepithelial electrical resistance measures and/or other suitable indicators, as well as using compounds exhibiting zero permeability. Internal standards have to be used.

As stated earlier, *in vitro* models for the determination of permeability are only representative for purely passive transport mechanisms. It is extensively described how this can be demonstrated (demonstration of dose-proportional PK or use of a suitable efflux transporter model).

In terms of *in vitro* dissolution testing, the following test conditions are specified:

- use of at least pilot batch size
- paddle (agitation: 50 rpm) or basket (agitation: 100 rpm) apparatus;
- volume of dissolution medium: ≤ 900 mL (preferably the same amount as used for QC test)
- temperature: 37 ± 1 °C;
- minimum of 12 units for both test and reference product;
- three buffers (pH 1.2, pH 4.5, pH 6.8) plus pH of minimum solubility, if applicable; purified water as additional medium may be requested by some regions;
- no use of organic solvents or surfactant;
- use of enzymes is acceptable with justification if gelatin is included in the formulation and cross-linking has been demonstrated;
- samples should be filtered during collection to avoid continuation of dissolution;

-
- use of basket apparatus or use of sinkers is permitted with justification (e.g. in case of high variability or coning);
 - if similarity of dissolution profiles has to be evaluated, the similarity factor f_2 should be used.

Overall, the use of a larger volume of dissolution medium in contrast to the FDA guidance document has prevailed; in contrast, specifications for agitation in conjunction with the paddle apparatus have been set to 50 rpm, with no exceptions intended.

5 Discussion and Conclusion

5.1 BCS-based biowaivers - acceptance and harmonization status prior to ICH M9

As already mentioned before, the acceptance of BCS-based biowaivers is currently broadly diversified and ranges from complete non-acceptance of the concept to acceptance for BCS classes I and III.

Regardless of the identical concept which has not significantly changed over time and that there are many parallels regarding the basic principles, it has to be concluded that the three most important guidance documents published by institutions associated with ICH (FDA, EMA, WHO) still differ in detail.

Before 2015, major differences existed between FDA on the one side and EMA and WHO requirements - which were already harmonized to a large extent at this timepoint - on the other: , ,

- While FDA accepted BCS-based biowaivers only for class I substances, both WHO and EMA were also accepting class III substances from 2006 respectively 2010.
- While EMA and WHO required the solubility requirements to be fulfilled for the highest single administered dose, fulfilment for the highest dose strength was sufficient for FDA.
- The criterion for “high permeability” was stricter ($\geq 90\%$) compared to EMA and WHO ($\geq 85\%$).
- No exceptions were accepted regarding agitation speeds in the context of dissolution testing.

Overall, it can be observed that over time, the clarity of structure, stringency and level of detail of guidance documents has improved and new insights have been included. A certain step towards harmonization of requirements was induced in 2015 by means of revision of the FDA guidance for industry.

To date, FDA guidance still exhibits significant differences in contrast to EMA and WHO guidance (a comparative table of the current guidance documents is provided in section 5.2).

The most important difference refers to the dose to be tested for the classification of solubility: while EMA and WHO require the highest single administered dose to be used, FDA so far holds on to testing of the highest dose strength. This difference may change the classification of an active substance as “high” or “low solubility” and thus also the assignment to BCS classes and is thus of crucial importance for the interpretation of data on active substance derived from the literature of public assessment reports. It can be concluded that this kind of data can only be reliably referenced in conjunction with the dose used for solubility testing.

FDA requires a dissolution media volume of ≤ 500 mL; a volume of ≤ 900 mL is only accepted with justification. In terms of harmonization, this was a step back compared to the previous version of the guidance document. In practice, if the active substance is applied at low doses and/or is can be unambiguously classified as “high” or “low solubility”, this difference might not be of high relevance. However additional testing might still be required in some cases.

Based on the guidance documents, *in vivo* and *in situ* animal models as well as *in vitro* methods are accepted as stand-alone methods by the FDA for determination of permeability, whereas they are considered merely supportive by EMA and WHO. With regard to this aspect, EMA has the strictest requirements, accepting only absolute bioavailability or *in vivo* human mass balance studies; WHO additionally accepts *in vivo* intestinal permeability tests in humans. Nevertheless, based on practical experience, the acceptance of permeability data based on alternative methods is often possible provided they are meaningful and consistent.

Additional differences exist being of less importance:

- Only pharmaceutical equivalents are eligible for BCS-based biowaivers. This difference is also not harmonized between EU and WHO guidance.
- Higher agitation speeds in case of paddle apparatus need to be justified to the FDA (and also EMA), whereas for WHO, they are considered standard.

- As statistical method for the demonstration of similar dissolution profiles, FDA only accepts the similarity factor. This difference is negligible as the other institutions evenly prefer this method.
- The allowable differences regarding the formulation in comparison with the reference products are not harmonized. In this regard, WHO has published the most detailed requirements. It can, however, be assumed that in practice the assessment is handled very similarly by all major regulatory bodies.

A surprisingly high number of regulatory authorities in other ICH regions have published their own guidance documents covering BCS-based biowaivers. The vast majority of them follow the guidance provided by WHO or EMA. Table 5.1 provides an overview of the acceptance of BCS-based biowaivers in single countries associated with ICH (BCS-class II has not been taken into account as among experts, this class is not considered eligible anymore).

In summary, despite the described differences a global approach for generic drug development for immediate-release oral pharmaceutical forms based on a BCS-based biowaiver concept is already deemed feasible to date, provided the applicant is able to fulfil the strictest requirement in place where differences still exist. Furthermore, it is recommended to choose a formulation as close as possible to the reference product. Generally, only pharmaceutical equivalents should be considered.

A global development approach appears feasible particularly for BCS class I active substances, as BCS-based biowaivers for these compounds are generally considered low-risk and are accepted in most regions.

For BCS class III active substances, a more conservative evaluation is required. BCS class II substances are generally not considered eligible anymore.

There is consensus that BCS-based biowaivers should not be considered for narrow therapeutic range drugs, medicinal products with particular claims related to PK properties (e.g. fast onset) or rescue medications. These terms are not harmonized and it also has to be mentioned that there is no explicit therapeutic or physiological reason why the BCS concept should not be applied in such cases. While the latter has been established for bioequivalence acceptance limits of 80 – 125 %, the reason for restraint

rather seems to be a lack of data justifying use of the concept for the more strict bioequivalence limits established for narrow therapeutic index drugs (90 – 111 %). In summary respective decisions have to be taken on a case-by-case basis.

BCS-based biowaivers for non-solid pharmaceutical forms are not widely accepted and should be evaluated with care.

Nevertheless, a further harmonization is desirable, as a large number of guidance documents have to be considered in the context of the evaluation of development approaches. Furthermore Japan, representing one of the large pharmaceutical markets, to date is not accessible for products developed based on a BCS-based biowaiver, as the concept as such is not been accepted to date. The need for further harmonization was also affirmed by ICH, leading to the development of ICH M9 as a universal guidance document.

Table 5.1: Acceptance of BCS-based biowaivers in the ICH regions

Country Code	US	EU	WHO	JP	CA	CH	BR	KR	CN	TW	ASEAN	SG	PH	MY	IN	CU	MX	CO	MD
BCS class I	+	+	+	-	+	+	+*	+	+	+	+	+	+	+	+?	-	-	+	-?
BCS class III	+	+	+	-	+	+	-	-	-	+	+	+	+	-?	+?	-	-	+	-?

Country Code	KZ	IR	RU	ZA	AM	AU	TR	NZ	CL	RW	TZ	UG	SA	JO	AR	UY	ZM	ZW
BCS class I	+	?	-?	+	?	+	+	+	+	+	+	+	+	+	+	+	+	+
BCS class III	-	?	-?	+	?	+	+	+	(+)	-	+	+	-	+	+	(+)	+	+

*only for listed active substances

5.2 ICH M9: further harmonization efforts

In the beginning of the consensus process for the development of ICH M9, the following issues represented potential points for discussion:

- It was not entirely clear if pharmaceutical alternatives were eligible for BCS-based biowaivers under certain circumstances.
- The view on whether the highest therapeutic dose or the highest dose strength should be used for the determination of solubility was controversial, the former reflecting therapeutic reality, the latter being in line with the set-up in the framework of *in vivo* bioequivalence studies.
- *In vitro* methods for the determination of permeability based on intestinal cell monolayers are widely used, however their acceptance for justifying a BCS-based biowaiver was not harmonized.
- The methodology for dissolution testing currently differs between the ICH regions: The volume of dissolution media was considerably lower in the US; there were differences regarding the specific test conditions to be used. A harmonization would be desirable and facilitate drug development.

The outcome of the consensus process in comparison with currently valid US, EU and WHO guidance documents is presented in Table 5.2.

In terms of the controversial issues described above, consensus could be reached with regard to almost all points.

It was decided that pharmaceutical alternatives were not no longer eligible for BCS-based biowaivers.

For solubility testing, the highest single therapeutic dose should be used. However there is an exception for active substances with borderline solubility, i.e. if the high solubility criterion cannot be met with the highest single dose but the highest strength of the reference product is soluble under the required conditions. This possibility of exception can be interpreted as a compromise between the stricter EMA (highest therapeutic dose) versus the less strict FDA position (highest dose strength). In such

cases, eligibility for BCS-based biowaiver may be substantiated by further data, e.g. by demonstrating dose proportional pharmacokinetics. This means that AUC and c_{\max} have to be linear over a dose range including the highest therapeutic dose and thus often represents a major obstacle.

As an alternative to *in vivo* PK studies, *in vitro* methods for the determination of permeability based on Caco-2 cells are now considered acceptable as stand-alone methods, as suggested by the current FDA guidance.

Testing methodology for *in vitro* dissolution testing was harmonized to a large extent, however the use of purified water as an additional medium may still be required regionally. The use of the similarity factor for statistical evaluation was agreed.

Furthermore, harmonized allowable differences in excipient amounts were established.

Currently comments from the consultation phase are being discussed. In the comments submitted to EMA by the pharmaceutical industry [81], the following main points were identified, apart from those already described above:

- It is not entirely clear how to deal with contradictory data on BCS classification of active substances. (This problem is most probably also based on different doses used for solubility testing (highest strength versus highest single dose)).
- Stability requirements for solubility testing over the entire pH range are considered to be too strict.
- The description of *in vitro* methods for the determination of permeability currently only refers to Caco-2 cell-based models; alternative models are not taken into account.
- It was criticized that some regional requirements will possibly remain.
- Higher agitation speeds and alternative methods for statistical evaluation of similarity of dissolution profiles should be acceptable.
- Formulation changes during early phases of clinical development should be less restrictive in order to allow for early formulation changes.

- The term “pharmaceutical equivalent” requires further classification as otherwise switches from e.g. capsule to tablet are not possible.
- A definition for “narrow therapeutic index” is missing.

It will be interesting if these comments will influence the harmonized guideline text.

Table 5.2: Comparison of current regional guidance compared to draft guideline ICH M9

		FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2017) [21]	EMA Guideline on the Investigation of Bioavailability and Bioequivalence (2010) [3]	WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 992, Annex 7 (2015) [34]	Draft guideline ICH M9: Biopharmaceutics Classification System-based Biowaivers [16]
BCS classes eligible for biowaiver		I and III	I and III	I and III	I and III
Narrow therapeutic index drugs		No	No	No	No
Fixed dose combinations		Yes	Yes	Yes, if all APIs belong to class I	Yes
Pharmaceutical forms		IR solid oral	IR solid oral with systemic action and same pharmaceutical form	IR, solid, oral	IR solid oral with systemic action
	Pharmaceutical equivalents	Yes	Yes	Yes	Yes
	Pharmaceutical alternatives	No	Yes (only different salts of BCS class I)	Yes (different salts only)	No

		FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2017) [21]	EMA Guideline on the Investigation of Bioavailability and Bioequivalence (2010) [3]	WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 992, Annex 7 (2015) [34]	Draft guideline ICH M9: Biopharmaceutics Classification System-based Biowaivers [16]
Solubility	Cut-off criterion	Highest dose strength soluble in 250 mL of medium at 37±1 °C and pH 1 – 6.8 and pK _a , pK _a -1 and pK _a +1	Highest single dose soluble in 250 mL of three buffers at pH 1 – 8 (e.g. pH 1.0, 4.5, 6.8) at 37 °C and pK _a if within specified range	Highest single dose soluble in ≤250 mL of three buffers at pH 1.2 – 6.8 at 37±1 °C and known solubility minima if within specified range	Highest single dose soluble in ≤250 mL of aqueous media at pH 1.2 – 6.8 at 37±1 °C and pK _a if within specified range
	Method	Shake-flask or similar	Shake-flask or similar	Shake-flask or similar	Shake-flask or similar
	Conditions	Replicate determination, verification of pH prior and after addition of buffer	Replicate determination, verification of pH prior and after addition of buffer	Replicate determination, verification of pH with calibrated pH meter	Replicate determination, verification of pH prior and after addition of buffer
Permeability/Absorption	Cut-off criterion	Complete (≥85 %)	Complete (≥85 %)	Complete (≥85 %)	Complete (≥85 %)
	Method	Absolute BV, human mass-balance studies, human intestinal	Absolute BV or human mass-balance studies	Absolute BV, human mass-balance studies,	Human PK studies, e.g. absolute BV mass-balance,

		FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2017) [21]	EMA Guideline on the Investigation of Bioavailability and Bioequivalence (2010) [3]	WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 992, Annex 7 (2015) [34]	Draft guideline ICH M9: Biopharmaceutics Classification System-based Biowaivers [16]
		perfusion studies, <i>in vivo</i> or <i>in situ</i> animal models, <i>in vitro</i> permeation studies		human intestinal perfusion studies	validated and standardized <i>in vitro</i> methods using Caco-2 cells
Dissolution	Cut-off criterion	<u>Class I</u> : rapid ($\geq 85\%$ within 30 min) plus similarity of dissolution profiles or very rapid ($\geq 85\%$ within 30 min) <u>Class III</u> : very rapid ($\geq 85\%$ within 15 min)	<u>Class I</u> : very rapid ($> 85\%$ within 15 min) or similarly rapid (85%: > 15 min, ≤ 30 min) <u>Class III</u> : very rapid ($> 85\%$ within 15 min)	<u>Class I</u> : very rapid ($> 85\%$ within 15 min) or rapid (85%: ≤ 30 min) and similar to reference product) <u>Class III</u> : very rapid ($> 85\%$ within 15 min)	<u>Class I</u> : rapid (85% within ≤ 30 min) and plus similarity of dissolution profiles or very rapid ($\geq 85\%$ within ≤ 15 min) <u>Class III</u> : very rapid ($> 85\%$ within 15 min)
	Sampling intervals	Sufficient number of intervals	At least every 15 minutes	For evaluation of similarity of dissolution profiles: 10, 15, 20, 30, 45 and 60 minutes	At least every 15 minutes

		FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2017) [21]	EMA Guideline on the Investigation of Bioavailability and Bioequivalence (2010) [3]	WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 992, Annex 7 (2015) [34]	Draft guideline ICH M9: Biopharmaceutics Classification System-based Biowaivers [16]
			<p><u>Very rapid dissolution</u>: after 15 min</p> <p><u>Comparably rapid dissolution</u>: at least <15 min, 15 min, close to 85 %</p>		<p><u>Very rapid dissolution</u>: after 15 min</p> <p><u>Comparably rapid dissolution</u>: at least <15 min, 15 min, close to 85 %</p>
	Conditions	<p><u>Apparatus</u>: USP Apparatus I respectively II</p> <p><u>Volume</u>: ≤500 mL, ≤900 mL with justification</p> <p><u>Agitation</u>: 100 rpm (USP Apparatus I); 50 rpm (or 75 rpm with justification) (Apparatus II)</p>	<p><u>Apparatus</u>: paddle or basket</p> <p><u>Volume</u>: ≤900 mL</p> <p><u>Temperature</u>: 37±1 °C</p> <p><u>Agitation</u>: usually 50 rpm (paddle), 100 rpm (basket)</p>	<p><u>Apparatus</u>: paddle or basket</p> <p><u>Volume</u>: ≤900 mL</p> <p><u>Temperature</u>: 37±1 °C</p> <p><u>Agitation</u>: 75 rpm (paddle), 100 rpm (basket)</p>	<p><u>Apparatus</u>: paddle or basket</p> <p><u>Volume</u>: ≤900 mL</p> <p><u>Temperature</u>: 37±1 °C</p> <p><u>Agitation</u>: 50 rpm (paddle), 100 rpm (basket)</p>

		FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2017) [21]	EMA Guideline on the Investigation of Bioavailability and Bioequivalence (2010) [3]	WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 992, Annex 7 (2015) [34]	Draft guideline ICH M9: Biopharmaceutics Classification System-based Biowaivers [16]
		<p><u>Sampling schedule:</u> e.g. 5, 10, 15, 20, 30 min</p> <p><u>Buffer:</u> 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; pH 4.5 buffer; pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes</p> <p><u>Other conditions:</u> no surfactant; addition of enzymes acceptable in case of gelatin coatings</p>	<p><u>Sampling schedule:</u> e.g. 10, 15, 20, 30, 45 min</p> <p><u>Buffer:</u> pH 1.0 – 1.2, pH 4.5 and pH 6.8 (Ph.Eur. buffers recommended)</p> <p><u>Other conditions:</u> no surfactant; addition of enzymes acceptable in case of gelatin coatings</p>	<p><u>Buffer:</u> pH 1.2 HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer (pharmacoepial buffers recommended)</p> <p><u>Other conditions:</u> no surfactant; addition of enzymes acceptable in case of gelatin coatings</p>	<p><u>Buffer:</u> pH 1.2, pH 4.5 and pH 6.8 (pharmacoepial buffers); purified water in some regions</p> <p><u>Other conditions:</u> no surfactant or organic solvents; addition of enzymes acceptable in case of gelatin shells and coatings in case of crosslinking</p>
Excipients		preferably widely used, approved within	<u>Class I:</u> excipients that might affect	<u>Class I:</u> critical excipients:	<u>Class I:</u> excipients that might affect

		FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2017) [21]	EMA Guideline on the Investigation of Bioavailability and Bioequivalence (2010) [3]	WHO Expert Committee on Specifications for Pharmaceutical Preparations Technical Report Series 992, Annex 7 (2015) [34]	Draft guideline ICH M9: Biopharmaceutics Classification System-based Biowaivers [16]
		<p>IR oral pharmaceutical forms</p> <p><u>Class I</u>: no excipients influencing PK</p> <p><u>Class III</u>: qualitatively the same and quantitatively very similar</p>	<p>bioavailability: qualitatively and quantitatively the same</p> <p><u>Class III</u>: excipients that might affect bioavailability: qualitatively and quantitatively the same;</p> <p>other excipients: qualitatively the same and quantitatively very similar</p>	<p>qualitatively the same and quantitatively similar; all excipients: used either in the reference product or in other approved; formulations of the same active substance</p> <p><u>Class III</u>: qualitatively the same and quantitatively similar;</p>	<p>bioavailability: qualitatively the same and quantitatively similar ($\pm 10\%$ compared to reference)</p> <p><u>Class III</u>: excipients that might affect bioavailability: qualitatively and quantitatively the same;</p> <p>other excipients: qualitatively the same and quantitatively similar</p>

Overall it is concluded that ICH M9 will represent a milestone of harmonization with regard to BCS-based biowaivers as it provides more detailed guidance on general eligibility and testing requirements.

This will further facilitate global approaches in drug development for the pharmaceutical industry. On the other hand, clear requirements will also be beneficial in terms of assessment by regulatory authorities.

Nevertheless, it should be taken into account that the draft guideline neither explicitly states nor guarantees a general acceptance of BCS-based biowaivers. This question will be of particular interest for applications in Japan, as an ICH region that up to this timpoint completely rejected the BCS concept as such.

If doubts remain with regard to acceptance or testing details, it is always recommended to choose a more conservative approach and/or to liaise with the competent regulatory authority in the framework of a scientific advice procedure.

As a conclusion, an adoption of ICH M9 will most certainly have a positive impact for the pharmaceutical industry as well as for regulatory authorities.

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Eidesstattliche Versicherung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Ort, Datum

Unterschrift