ประกาศสำนักงานคณะกรรมการอาหารและยา
เรื่อง การยกเว้นการศึกษาชีวสมมูลในมนุษย์สำหรับผลิตภัณฑ์ยาตามหลักการของ
Biopharmaceutics Classification System (BCS)

ด้วยกระบวนการวิจัยและพัฒนาผลิตภัณฑ์ยามีขั้นตอนที่ซับซ้อนใช้เวลาและงบประมาณที่สูงในการพิสูจน์คุณภาพประสิทธิภาพและความปลอดภัยของยา การพัฒนาผลิตภัณฑ์ยาดังกล่าวมีความสำคัญต่อความมั่นคงทางระบบสาธารณสุขและการพึ่งพาตนเองของประเทศ สำนักงานคณะกรรมการอาหารและยาในฐานะหน่วยงานหลักที่มีพันธะกิจสำคัญในการกำกับดูแลผลิตภัณฑ์ยาของประเทศเล็งเห็นความสำคัญของการวิจัยและพัฒนาผลิตภัณฑ์ยา เห็นสมควรปรับปรุงข้อกำหนดหรือหลักเกณฑ์การปฏิบัติเพื่อลดงบประมาณและระยะเวลาในการพัฒนาผลิตภัณฑ์ยา รวมทั้งลดการศึกษาวิจัยในมนุษย์ด้วยหลักวิชาการที่ยอมรับได้เพื่อทำให้ผู้ป่วยเข้าถึงยาที่มีคุณภาพได้เร็วขึ้น รวมถึงเป็นการส่งเสริมการกำกับดูแลผลิตภัณฑ์ยาให้เป็นไปตามข้อมูลวิชาการที่ทันสมัย มีความชัดเจนในขั้นตอนการปฏิบัติ สอดคล้องกับมาตรฐานสากล โดยข้อ ๓ (๒) ของกฎกระทรวงว่าด้วยการขึ้นทะเบียนตำรับยา พ.ศ. ๒๕๕๕ ซึ่งออกตาม ความในพระราชบัญญัติยา พ.ศ. ๒๕๑๐ กำหนดให้ผู้รับอนุญาตที่ประสงค์จะขึ้นทะเบียนตำรับยาให้ยื่นคำขอขึ้นทะเบียนตำรับยาต่อพนักงานเจ้าหน้าที่พร้อมด้วยหลักฐานแสดงข้อมูลคุณภาพ ประสิทธิภาพ และความปลอดภัยของยา สำนักงานคณะกรรมการอาหารและยาจึงออกประกาศ ดังต่อไปนี้

ข้อ ๑ ให้ยกเลิกระเบียบสำนักงานคณะกรรมการอาหารและยา ว่าด้วยการยกเว้นการศึกษาชีวสมมูลในมนุษย์ สำหรับผลิตภัณฑ์ยารูปแบบของแข็งชนิดรับประทานที่ปลดปล่อยยาทันที พ.ศ. ๒๕๕๐ ประกาศ ณ วันที่ ๑๕ สิงหาคม ๒๕๕๐

ข้อ ๒ ให้ผู้รับอนุญาตผลิตยาหรือนำหรือสั่งยาเข้ามาในราชอาณาจักรที่ประสงค์จะยื่นรายงานการยกเว้นการศึกษาชีวสมมูลในมนุษย์ ตามหลักการ Biopharmaceutics Classification System (BCS) เพื่อประกอบการขึ้นทะเบียนตำรับยา ดำเนินการตามหลักเกณฑ์ ICH M9 guideline on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018, 10 February 2020) ของหน่วยงานกำกับดูแลด้านยาสหภาพยุโรป (European Medicines Agency, EMA) ตามแนบท้ายประกาศนี้

ข้อ ๓ บรรดารายงานการยกเว้นการศึกษาชีวสมมูลในมนุษย์ ที่เริ่มดำเนินการศึกษาและยื่นมาก่อนประกาศฉบับนี้และอยู่ระหว่างการพิจารณาของผู้อนุญาต ให้ถือว่าเป็นคำขอตามประกาศฉบับนี้โดยอนุโลม และถ้ามีความแตกต่างจากหลักเกณฑ์ตามประกาศนี้ ให้เจ้าหน้าที่พิจารณาสั่งแก้ไขเพิ่มเติมและอาจให้ส่งเอกสารเพิ่มเติมตามความจำเป็นและเหมาะสม

ทั้งนี้ ตั้งแต่บัดนี้เป็นต้นไป

ประกาศ ณ วันที่ ๒๐ เมษายน พ.ศ. ๒๕๖๓

(นายไพศาล ดั่นคุ้ม)
เลขาธิการคณะกรรมการอาหารและยา

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ICH M9 guideline on biopharmaceutics classification system-based biowaivers

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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ICH M9 on biopharmaceutics classification system-based biowaivers

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1. Introduction

1.1. Background and objective

Two drug products containing the same drug substance(s) are considered bioequivalent if their bioavailabilities (rate and extent of drug absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e., similarity in terms of safety and efficacy. In *in vivo* bioequivalence studies, the pivotal pharmacokinetic parameters AUC (area under the concentration time curve) and C_{max} (maximum concentration), are generally used to assess the rate and extent of drug absorption.

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is intended to reduce the need for *in vivo* bioequivalence studies i.e., it can provide a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance(s). The BCS categorizes drug substances into one of four BCS classes as follows:

Class I: high solubility, high permeability

Class II: low solubility, high permeability

Class III: high solubility, low permeability

Class IV: low solubility, low permeability

This guidance provides recommendations to support the biopharmaceutics classification of drug substances and the BCS-based biowaiver of bioequivalence studies for drug products. The BCS-based biowaiver principles may be applied to bioequivalence purposes not explicitly specified in the guideline, provided they can be supported by a thorough scientific rationale.

1.2. Scope

BCS-based biowaivers may be used to substantiate *in vivo* bioequivalence. Examples include comparison between products used during clinical development through commercialization, post-approval changes, and applications for generic drug products in accordance with regional regulations.

The BCS-based biowaiver is only applicable to immediate release, solid orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation. Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver in this guidance. Fixed-dose combination (FDC) products are eligible for a BCS-based biowaiver when all drug substances contained in the combination drug product meet the criteria as defined in sections 2 and 3 of this guidance.

2. Biopharmaceutics classification of the drug substance

BCS-based biowaivers are applicable to drug products where the drug substance(s) exhibit high solubility and, either high permeability (BCS Class I) or low permeability (BCS Class III).

A biowaiver is applicable when the drug substance(s) in test and reference products are identical. A biowaiver may also be applicable if test and reference products contain different salts provided that both belong to BCS Class I (high solubility and high permeability). A biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of

a drug substance from that of the reference product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept. Pro-drugs may be considered for a BCS-based biowaiver when absorbed as the pro-drug.

2.1. Solubility

A drug substance is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37±1°C. In cases where the highest single therapeutic dose does not meet this criterion but the highest strength of the reference product is soluble under the aforementioned conditions, additional data should be submitted to justify the BCS-based biowaiver approach.

The sponsor is expected to establish experimentally the solubility of the drug substance over the pH range of 1.2–6.8 at 37±1ºC. At least three pHs within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated. In addition, solubility at the pH of lowest solubility of the drug substance should be evaluated if it is within the specified pH range. These experiments should demonstrate that solubility is maintained over relevant timeframes to accommodate the expected duration of absorption.

Solubility should be evaluated by a method appropriate to the properties of the drug substance.

Equilibrium solubility experiments may be performed, using a shake-flask technique or an alternative method, if justified. Small volumes of solubility media may be employed if the available experimental apparatus will permit it. The pH for each test solution should be measured after the addition of the drug substance and at the end of the equilibrium solubility study to ensure the solubility measurement is conducted under the specified pH. The pH should be adjusted if necessary. The experiment should be conducted over a suitable timeframe to reach equilibrium.

Alternatively, solubility experiments where the highest therapeutic single dose is examined in a 250 ml volume, or a proportionally smaller amount examined in a proportionally smaller volume of buffer, can be considered.

The lowest measured solubility over the pH range of 1.2–6.8 will be used to classify the drug substance.

A minimum of three replicate determinations at each solubility condition/pH using appropriate compendial media is necessary to demonstrate solubility using a suitably validated method.

In addition, adequate stability of the drug substance in the solubility media should be demonstrated. In cases where the drug substance is not stable with >10% degradation over the extent of the solubility assessment, solubility cannot be adequately determined and thus the drug substance cannot be classified. In addition to experimental data, literature data may be provided to substantiate and support solubility determinations, keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the studies.

2.2. Permeability

The assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies, e.g., absolute bioavailability or mass balance.

High permeability can be concluded when the absolute bioavailability is ≥85%. High permeability can also be concluded if ≥85% of the administered dose is recovered in urine as unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites. Regarding metabolites in feces, only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included, unless it can be demonstrated that

they are not produced prior to absorption, e.g., by microbial action within the gastrointestinal tract. Unchanged drug in feces cannot be counted toward the extent of absorption, unless appropriate data supports that the amount of parent drug in feces to be accounted for absorbed drug material is from biliary excretion, intestinal secretion or originates from an unstable metabolite, e.g., glucuronide, sulphate, N-oxide, that has been converted back to the parent by the action of microbial organisms.

Human *in vivo* data derived from published literature (e.g., product knowledge and bioavailability studies) may be acceptable, keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the results.

Permeability can be also assessed by validated and standardized *in vitro* methods using Caco-2 cells (see Annex I). The results from Caco-2 permeability assays should be discussed in the context of available data on human pharmacokinetics. If high permeability is inferred by means of an *in vitro* cell system, permeability independent of active transport should be proven as outlined in Annex I, "Caco-2 cell permeability assay method considerations".

If high permeability is not demonstrated, the drug substance is considered to have low permeability for BCS classification purposes.

Drug Substance Stability in the Gastrointestinal Tract

Additional data to document the drug's stability in the gastrointestinal tract should be provided if mass balance studies are used to demonstrate high permeability, unless ≥85% of the dose is recovered as unchanged drug in urine. Demonstration of stability in the gastrointestinal tract is required if *in vitro* Caco-2 studies are used to support high permeability. Stability in the gastrointestinal tract may be documented using compendial or simulated gastric and intestinal fluids. Other relevant methods may be used with suitable justification. Drug solutions should be incubated at 37ºC for a period that is representative of the *in vivo* contact of the drug substance with these fluids, i.e., one hour in gastric fluid and three hours in intestinal fluid. Drug concentrations should then be determined using a suitably validated method. Significant degradation (>10%) of a drug precludes BCS high permeability classification.

3. Eligibility of a drug product for a BCS-based biowaiver

A drug product is eligible for a BCS-based biowaiver provided that the drug substance(s) satisfy the criteria regarding solubility and permeability (BCS Class I and III), the drug product is an immediate-release oral dosage form with systemic action, and the drug product is the same dosage form and strength as the reference product. In cases where the highest single therapeutic dose does not meet the high solubility criterion but the highest strength of the reference product is soluble under the required conditions, BCS-based biowaivers can be supported based on demonstration of dose proportional pharmacokinetics (i.e., AUC and C_{max}) over a dose range that includes the highest single therapeutic dose.

Drug products with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application. Furthermore, the BCS-based biowaiver approach is applicable only when the mode of administration includes water. If administration without water is also intended (e.g., orodispersible products), a bioequivalence study in which the product is dosed without water should be conducted.

In order for a drug product to qualify for a BCS-based biowaiver, criteria with respect to the composition (excipients) and *in vitro* dissolution performance of the drug product should be satisfied. The drug product acceptance criteria are described in sections 3.1 and 3.2 below.

3.1. Excipients

Ideally, the composition of the test product should mimic that of the reference product. However, where excipient differences exist, they should be assessed for their potential to affect *in vivo* absorption. This should include consideration of the drug substance properties as well as excipient effects. To be eligible for a BCS-based biowaiver, the sponsor should justify why the proposed excipient differences will not affect the absorption profile of the drug substance under consideration, i.e., rate and extent of absorption, using a mechanistic and risk-based approach. The decision tree for performing such an assessment is outlined in Figures 1 and 2 in Annex II.

The possible effects of excipients on aspects of *in vivo* absorption such as solubility, gastrointestinal motility, transit time and intestinal permeability including transporter mechanisms, should be considered. Excipients that may affect absorption include sugar-alcohols, e.g., mannitol, sorbitol, and surfactants, e.g., sodium lauryl sulfate. The risk that a given excipient will affect the absorption of a drug substance should be assessed mechanistically by considering:

- the amount of excipient used,
- the mechanism by which the excipient may affect absorption,
- absorption properties (rate, extent and mechanism of absorption) of the drug substance.

The amount of excipients that may affect absorption in the test and reference formulations should be addressed during product development, such that excipient changes are kept to a minimum. Small amounts included in the tablet coating, or levels below documented thresholds of effect for the specific drug substance, are of less concern.

By definition, BCS Class I drugs are highly absorbed, and have neither solubility nor permeability limited absorption. Therefore they generally represent a low risk group of compounds in terms of the potential for excipients to affect absorption, compared to other BCS classes. Consideration of excipient effects for BCS Class I drug products should focus on potential changes in the rate or extent of absorption. For example, if it is known that the drug has high permeability due to active uptake, excipients that can inhibit uptake transporters are likely to be of concern. For BCS Class I drugs that exhibit slow absorption, the potential for a given excipient to increase absorption rate should also be considered.

For BCS Class I drugs, qualitative and quantitative differences in excipients are permitted, except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, i.e., within ± 10% of the amount of excipient in the reference product. Additionally, the cumulative difference for excipients that may affect absorption should be within ± 10%.

BCS Class III drug substances are considered to be more susceptible to the effects of excipients. These drugs are not considered highly permeable and may have site-specific absorption, so there are a greater number of mechanisms through which excipients can affect their absorption than for BCS Class I drugs. For BCS Class III drugs, all of the excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients). Excipients that may affect absorption should be qualitatively the same and quantitatively similar, i.e., within ± 10% of the amount of excipient in the reference product, and the cumulative difference for these excipients should be within ± 10%. This is defined in Table 1. Examples of acceptable differences in excipients are shown in Annex II. Differences in colorants and flavoring may be permitted when these constitute very small amounts of the formulation.

It is recognized that there are limitations to the application of Table 1, e.g., difficulty in determining the film coat weight for the reference product. Table 1 is provided as a target to give clarity to

sponsors. Deviations from this will require appropriate justification, based on the principles described above.

Table 1: Criteria expected to demonstrate quantitative similarity for products containing BCS Class III drugs.

Within the context of quantitative similarity, differences in excipients for drug products containing BCS Class III drugs should not exceed the following targets:	
Excipient class	**Percent of the amount of excipient in the reference**
Excipients which may affect absorption	
Per excipient:	**10%**
Sum of differences:	**10%**
	Percent difference relative to core weight* (w/w)
All excipients:	
Filler	**10%**
Disintegrant	
Starch	**6%**
Other	**2%**
Binder	**1%**
Lubricant	
Stearates	**0.5%**
Other	**2%**
Glidant	
Talc	**2%**
Other	**0.2%**
Total % change permitted for all excipients (including excipients which may affect absorption):	**10%**

*Note: Core does not include tablet film coat or capsule shell

BCS-based biowaivers are applicable to FDCs which are the same dosage form and strength. FDC formulations containing only BCS Class I drugs should meet criteria regarding excipients for a BCS Class I drug. FDC formulations containing only BCS Class III drugs, or BCS Class I and BCS Class III drugs, should meet criteria regarding excipients for a BCS Class III drug.

3.2. In vitro *dissolution*

When applying the BCS based biowaiver approach, comparative *in vitro* dissolution tests should be conducted using one batch representative of the proposed commercial manufacturing process for the test product relative to the reference product. The test product should originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified. During a (clinical) development phase, smaller batch sizes may be acceptable, if justified. The comparative *in vitro* dissolution experiments should use compendial apparatus and suitably validated analytical method(s).

The following conditions should be employed in the comparative dissolution studies to characterize the dissolution profile of the product:

- Apparatus: paddle or basket
- Volume of dissolution medium: 900 ml or less (it is recommended to use the volume selected for the quality control (QC) test).
- Temperature of the dissolution medium: 37±1°C.
- Agitation:
  - paddle apparatus - 50 rpm.
  - basket apparatus - 100 rpm.
- At least 12 units of reference and test product should be used for each dissolution profile determination.
- Three buffers: pH 1.2, pH 4.5, and pH 6.8. Pharmacopoeial buffers should be employed. Additional investigation may be required at the pH of minimum solubility (if different from the buffers above).
- Organic solvents are not acceptable and no surfactants should be added.
- Samples should be filtered during collection, unless *in-situ* detection methods are used.
- For gelatin capsules or tablets with gelatin coatings where cross-linking has been demonstrated, the use of enzymes may be acceptable, if appropriately justified.

When high variability or coning is observed in the paddle apparatus at 50 rpm for both reference and test products, the use of the basket apparatus at 100 rpm is recommended. Additionally, alternative methods (e.g., the use of sinkers or other appropriately justified approaches) may be considered to overcome issues such as coning, if scientifically substantiated. All experimental results should be provided.

To qualify for a BCS-based biowaiver for BCS Class I drug substances both the test product and reference product should display either very rapid (≥85% for the mean percent dissolved in ≤ 15 minutes) *in vitro* dissolution characteristics, or rapid (≥85% for the mean percent dissolved in ≤ 30 minutes) and similar *in vitro* dissolution characteristics (i.e., based on f2 comparison), under all of the defined conditions. In cases where one product has rapid dissolution and the other has very rapid dissolution, similarity of the profiles should be demonstrated as below.

For the comparison of dissolution profiles, where applicable, the similarity factor f2 should be estimated by using the following formula:

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

In this equation f2 is the similarity factor, n is the number of time points, R(t) is the mean percent reference drug dissolved at time t after initiation of the study and T(t) is the mean percent test drug dissolved at time t after initiation of the study.

The evaluation of the similarity factor is based on the following conditions:

- A minimum of three time points (zero excluded).
- The time points should be the same for the two products.
- Mean of the individual values for every time point for each product.
- Not more than one mean value of ≥85% dissolved for either of the products.
- To allow the use of mean data, the coefficient of variation should not be more than 20% at early time-points (up to 10 minutes), and should not be more than 10% at other time points.

Two dissolution profiles are considered similar when the f2 value is ≥50. When both test and reference products demonstrate that ≥85% of the labelled amount of the drug is dissolved in 15 minutes, comparison with an f2 test is unnecessary and the dissolution profiles are considered similar. When the coefficient of variation is too high, f2 calculation is considered inaccurate and a conclusion on similarity in dissolution cannot be made.

To qualify for a BCS-based biowaiver for BCS Class III drug substances both the test product and reference product should display very rapid (≥85% for the mean percent dissolved in ≤15 minutes) *in vitro* dissolution characteristics under the defined conditions.

For FDC formulations, dissolution profiles should meet the criteria for all drug substances in the FDC to be considered. FDC formulations containing only BCS Class I drugs should meet dissolution criteria for a BCS Class I drug. FDC formulations containing only BCS Class III drugs should meet dissolution criteria for a BCS Class III drug. For FDCs containing both BCS Class I and BCS Class III drugs the dissolution criteria for the applicable BCS class for each component should be applied.

For products with more than one strength, the BCS approach should be applied for each strength, i.e., it is expected that test and reference product dissolution profiles are compared at each strength.

4. Documentation

The sponsor should provide complete information on the critical quality attributes of the test drug substance(s) and drug product and as much information as possible for the reference product, including, but not limited to: polymorphic form and enantiomeric purity; and any information on bioavailability or bioequivalence problems with the drug substance(s) or drug product, including literature surveys and sponsor derived studies. All study protocols and reports should be provided. Information on validated test methods should be appropriately detailed according to current regulatory guidances and policies.

The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics.

The report should include all excipients, their qualitative and, where appropriate, quantitative differences between the test and reference products.

A full description of the analytical methods employed, including validation and qualification of the analytical parameters, should be provided. A detailed description of all test methods and media, including test and reference batch information [unit dose (strength and assay), batch number, manufacturing date and batch size where known, expiry date] should also be provided. The dissolution

report should include a thorough description of experimental settings and analytical methods, including information on the dissolution conditions such as apparatus, de-aeration, filtration during sampling, volume, etc.

In addition, complete information with full description of the methods applied should be provided for the Caco-2 cell permeability assay method, if applicable (see Annex I).

5. Glossary

AUC: Area under the concentration versus time curve

BCS: Biopharmaceutics Classification System

C_{max}: Maximum concentration

FDC: Fixed-dose combination

QC: Quality control

rpm: rotation per minute

Annex I: Caco-2 cell permeability assay method considerations

Permeability assays employing cultured Caco-2 epithelial cell monolayers derived from a human colon adenocarcinoma cell line are widely used to estimate intestinal drug absorption in humans. Caco-2 cells undergo spontaneous morphological and biochemical enterocytic differentiation, and express cell polarity with an apical brush border, tight intercellular junctions, and several active transporters as in the small intestine. Due to a potential for low or absent expression of efflux (e.g., P-gp, BCRP, MRP2) and uptake (e.g., PepT1, OATP2B1, MCT1) transporters, the use of Caco-2 cell assays as the sole data in support of high permeability for BCS classification is limited to passively transported drugs (see below Assay Considerations).

Method validation

The suitability of the Caco-2 cell assays for BCS permeability determination should be demonstrated by establishing a rank-order relationship between experimental permeability values and the extent of drug absorption in human subjects using zero, low (<50%), moderate (50–84%), and high (≥85%) permeability model drugs. A sufficient number of model drugs are recommended for the validation to characterize high, moderate and low permeability (a minimum 5 for each), plus a zero permeability marker; examples are provided in Table 2. Further, a sufficient number (minimum of 3) of cell assay replicates should be employed to provide a reliable estimate of drug permeability. The established relationship should permit differentiation between low, moderate and high permeability drugs.

Caco-2 cell monolayer integrity should be confirmed by comparing transepithelial electrical resistance (TEER) measures and/or other suitable indicators, prior to and after an experiment.

In addition, cell monolayer integrity should be demonstrated by means of compounds with proven zero permeability (refer to Table 2).

Reporting of the method validation should include a list of the selected model drugs along with data on extent of absorption in humans (mean, standard deviation, coefficient of variation) used to establish suitability of the method, permeability values for each model drug (mean, standard deviation, coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean ± standard deviation or 95% confidence interval) with identification of the high permeability class boundary and selected high permeability model drug used to classify the test drug substance.

In addition, a description of the study method, drug concentrations in the donor fluid, description of the analytical method and equation used to calculate permeability should be provided. Additionally, information on efflux potential, e.g., bidirectional transport data should be provided for a known substrate.

Assay considerations

Passive transport of the test compound should be demonstrated. This may be verified using a suitable assay system that expresses known efflux transporters, e.g., by demonstrating independence of measured *in vitro* permeability on initial drug concentration, e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 ml, or on transport direction (efflux ratio, i.e., ratio of apparent permeability (P_{app}) between the basolateral-to-apical and apical-to-basolateral directions <2 for the selected drug concentrations).

Efflux ratio = $P_{appBL \rightarrow AP}/P_{appAP \rightarrow BL}$.

Functional expression of efflux transporters should be verified by using bidirectional transport studies demonstrating asymmetric permeability of selected efflux transporter substrates, e.g., digoxin, vinblastine, rhodamine 123, at non-saturating concentrations.

The test drug substance concentrations used in the permeability studies should be justified. A validated Caco-2 method used for drug permeability determinations should employ conditions established during the validation, and include a moderate and a high permeability model drug in the donor fluid along with the test drug as internal standards to demonstrate consistency of the method. The choice of internal standards should be based on compatibility with the test drug, i.e., they should not exhibit any significant physical, chemical, or permeation interactions. The permeability of the internal standards may be determined following evaluation of the test drug in the same monolayers or monolayers in the same plate, when it is not feasible to include internal standards in the same cell culture well as the test drug permeability evaluation. The permeability values of the internal standards should be consistent between different tests, including those conducted during method validation. Acceptance criteria should be set for the internal standards and model efflux drug. Mean drug and internal standards recovery at the end of the test should be assessed. For recoveries <80%, a mass balance evaluation should be conducted including measurement of the residual amount of drug in the cell monolayer and testing apparatus.

Evaluation of the test drug permeability for BCS classification may be facilitated by selection of a high permeability internal standard with permeability in close proximity to the moderate/high permeability class boundary. The test drug is considered highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

Information to support high permeability of a test drug substance (mean, standard deviation, coefficient of variation) should include permeability data on the test drug substance, the internal standards, *in vitro* gastrointestinal stability information, and data supporting passive transport mechanism.

Table 2. Examples of model drugs for permeability assay method validation

Group	Drug
High Permeability (f_a ≥85%)	Antipyrine Caffeine Ketoprofen Naproxen Theophylline Metoprolol Propranolol Carbamazepine Phenytoin Disopyramide Minoxidil
Moderate Permeability (f_a = 50-84%)	Chlorpheniramine Creatinine

Group	Drug
	Terbutaline Hydrochlorothiazide Enalapril Furosemide Metformin Amiloride Atenolol Ranitidine
Low Permeability (f_a < 50%)	Famotidine Nadolol Sulpiride Lisinopril Acyclovir Foscarnet Mannitol Chlorothiazide Polyethylene glycol 400 Enalaprilat
Zero Permeability	FITC-Dextran Polyethylene glycol 4000 Lucifer yellow Inulin Lactulose
Efflux Substrates	Digoxin Paclitaxel Quinidine Vinblastine

Annex II: Further information on the assessment of excipient differences

Figure 1. BCS Class I drug substances

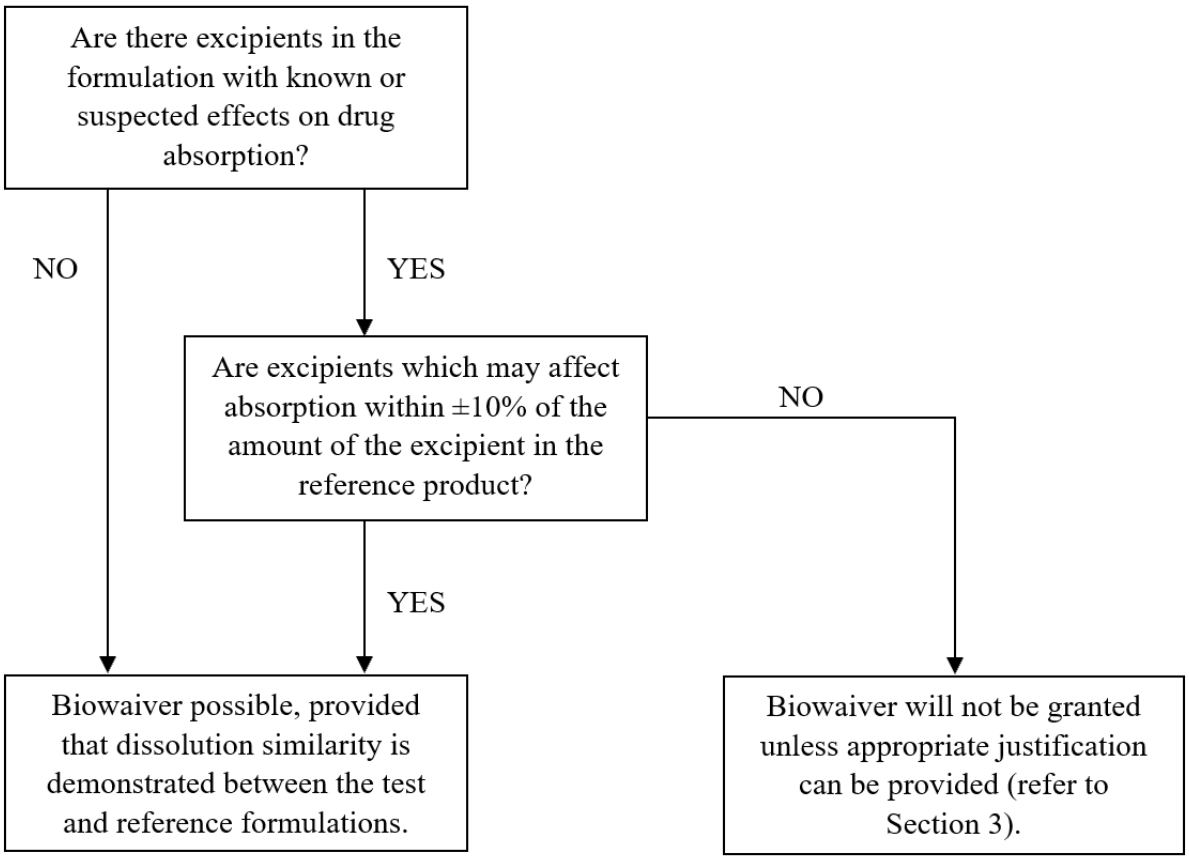
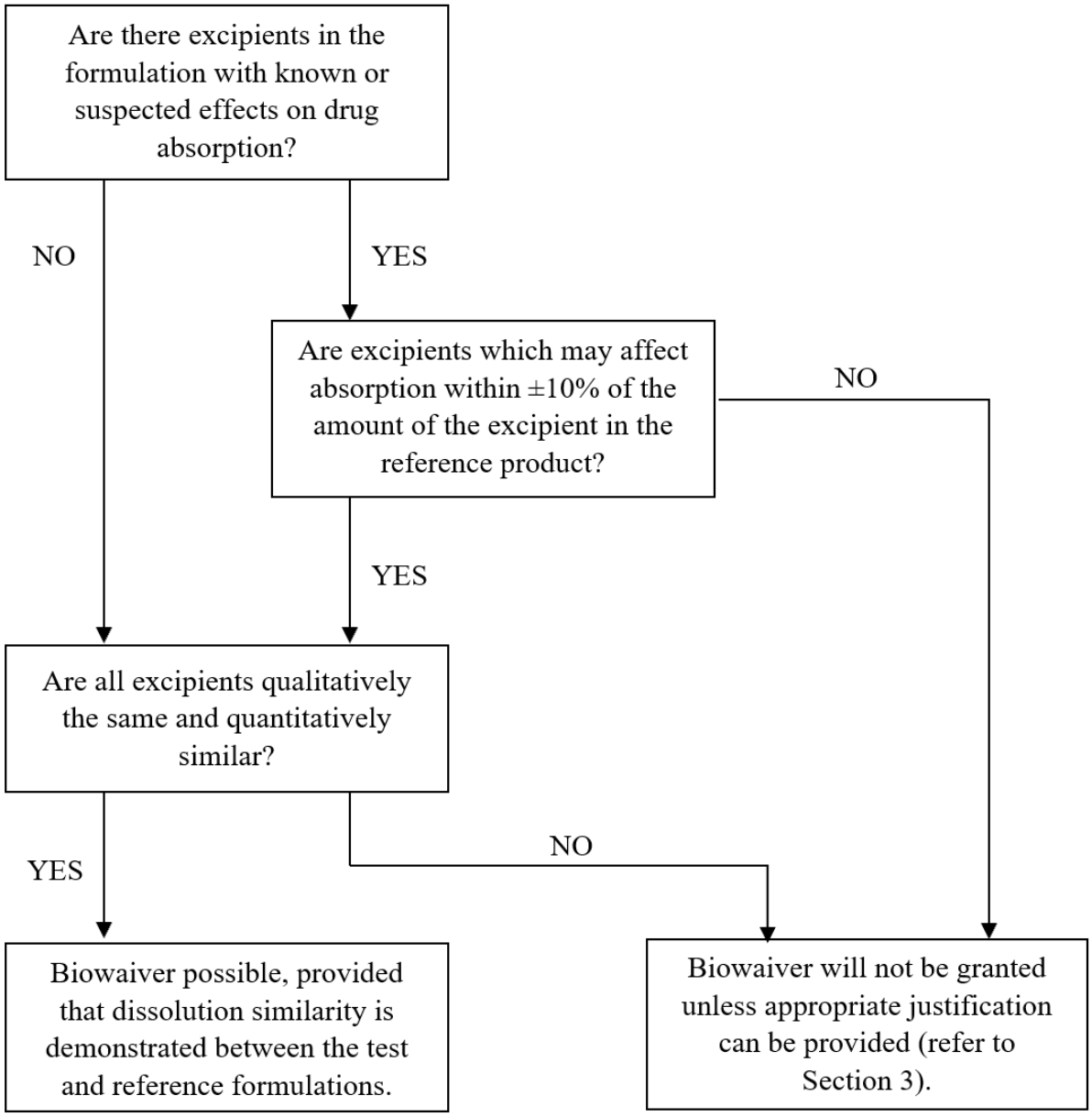


Figure 2. BCS Class III drug substances



Examples of acceptable differences in excipients

Example 1: BCS Class I biowaiver

The formulation of the test product is qualitatively the same as that of the reference product. Additionally, it contains sorbitol, an excipient with known or suspected effects on drug absorption. The amount of sorbitol in the test formulation is within the permitted range of 45 mg to 55 mg based on the amount of sorbitol in the reference formulation (i.e., 50 mg ± 10%).

Component	**Amount (mg) reference**	**Amount (mg) test**
Drug substance	100	100
Microcrystalline cellulose (filler)	100	95
Sorbitol (filler)	50	55
HPMC (binder)	10	10
Talc (glidant)	5	5
Total	265	265

Example 2: BCS Class III biowaiver

The test formulation is qualitatively the same as the reference formulation. Additionally, it contains sorbitol, an excipient with known or suspected effects on drug absorption. The amount of sorbitol in the test formulation is within the permitted range of 9 mg to 11 mg based on the amount of sorbitol in the reference formulation (i.e., 10 mg ± 10%). Differences in the amount of other excipients are within the criteria outlined in Table 1, Section 3.1.

Component	**Reference Product**		**Test Product**		**Absolute % difference relative to core weights**
	Composition (mg)	**Proportion relative to core weight (%w/w)**	**Composition (mg)**	**Proportion relative to core weight (%w/w)**	
Drug substance	100	49.3%	100	46.5%	--
Lactose monohydrate (filler)	85	41.9%	97	45.1%	3.2%
Sorbitol (filler)	10	4.9%	9	4.2%	0.7%
Croscarmellose sodium (disintegrant)	6	3.0%	7	3.3%	0.3%
Magnesium stearate (lubricant)	2	1.0%	2	0.9%	0.1%
Total	203	100%	215	100%	
				Total change:	**4.3%**

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10 February 2020
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Committee for Medicinal Products for Human Use

ICH M9 guideline on biopharmaceutics classification system-based biowaivers - questions and answers

Step 5

Transmission to CHMP for adoption	30 January 2020
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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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Code	History	Date
M9 Q&As	Adoption by the Regulatory Members of the ICH Assembly under Step 4	20 November 2019
M9 Q&As	Endorsement by the ICH Assembly under *Step 2* and release for public consultation.	7 June 2018

ICH M9 guideline on biopharmaceutics classification system based biowaivers - questions and answers

Table of contents

1. Introduction – scope

#	Date of approval	Questions	Answers
1.1	**Nov. 2019**	Are drug substances that exhibit non-linear pharmacokinetics eligible for a BCS-based biowaiver?	Drug substances that exhibit non-linear pharmacokinetics are eligible for a BCS-based biowaiver if they meet the solubility and permeability criteria for BCS I or III classification.
1.2	**Nov. 2019**	Why does the guideline allow for regional differences in applications for BCS-based biowaivers for generic products?	The guideline focuses on BCS-based biowaiver principles to be applied for bioequivalence purposes provided they are supported by a sound scientific rationale. The provision in the guideline that accommodates exceptions to existing regulations that do not permit BCS-based biowaivers for generic product applications, at this time, does not disqualify implementation of these harmonized technical requirements to demonstrate BCS based biowaivers for other product applications unless explicitly stated.
1.3	**Nov. 2019**	For fixed-dose combination products, can one of the drug substances qualify for a BCS-based biowaiver, while the other does not?	All drug substances in a fixed-dose combination product must fulfill the criteria for either BCS Class I or III to qualify for a biowaiver. If one of the drug substances is not a BCS Class I or III drug substance, the possibility that the FDC formulation may influence in vivo performance cannot be excluded.
1.4	**Nov. 2019**	Why are drugs with a narrow therapeutic index excluded from eligibility for a BCS-based biowaiver, especially if rate and extent of absorption of BCS Class I and III drug substances are a directly attributed function of solubility and permeability?	Drugs with a narrow therapeutic index can be defined as those drugs where small differences in dose or blood concentration may lead to dose and blood concentration dependent, serious therapeutic failures or adverse drug reactions. They are characterized by a steep drug dose-response relationship within the usual dose range or a narrow span between effective drug concentrations and concentrations associated with serious toxicity. Thus, doses must be titrated and monitored carefully. Although there is no international list of NTI drugs, the demonstration of in vivo bioequivalence for these drugs is generally subject to specific requirements such as tightened

#	Date of approval	Questions	Answers
			acceptance criteria (e.g., Cmax and/or AUC: 90–111%) and particular study design features in some regions. BCS-based biowaiver principles are not designed to take into account more stringent criteria for a biowaiver. Therefore, the BCS-based biowaiver approach is not considered a suitable surrogate for the establishment of bioequivalence of narrow therapeutic index drugs.

2. Biopharmaceutics classification of the drug substance

#	Date of approval	Questions	Answers
2.1	**Nov. 2019**	Is a BCS-based biowaiver applicable if the test and reference products contain different salt forms of the same drug substance?	A BCS-based biowaiver may be applicable if the test and reference products contain different (simple) salts, provided that both belong to BCS Class I (high solubility and high permeability). This biowaiver approach is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of a drug substance from that of the reference product, since these differences may lead to differences in bioavailability that may not be deducible by means of experiments used to support a BCS-based biowaiver. In addition to the scientific aspects, the legal basis for submission and regulatory requirements should be considered.
2.2	**Nov. 2019**	How is weight change associated with a different salt accounted for when assessing solubility?	The BCS classifies a specific drug substance. The dose of the specific active moiety needs to be identical irrespective of the salt forms. Hence, there is no relevance for weight change.
2.3	**Nov. 2019**	Why is a BCS-based biowaiver applicable only when a pro-drug is absorbed as the pro-drug?	The BCS is based on solubility and permeability criteria for a specific drug substance. The classification cannot be conferred to different compounds, e.g., a parent drug and a metabolite. Moreover, the solubility criterion considers oral intake with a

#	Date of approval	Questions	Answers
			defined amount of aqueous liquid which is not relevant for a metabolite unless it is formed immediately following intake and prior to absorption. BCS classification should refer to the drug substance in the drug product since in vitro dissolution of the same moiety is utilized to demonstrate product similarity.

2.1. Solubility

#	Date of approval	Questions	Answers
2.1.1	**Nov. 2019**	How should the pH be adjusted during the solubility experiment?	There are various acceptable methods to adjust the pH of the solution. When a pH adjustment is necessary, the sponsor should justify the chosen method. A deviation in pH of ±0.1 is considered acceptable.
2.1.2	**Nov. 2019**	How is the duration of the solubility measurement determined?	For an equilibrium solubility assessment, the duration over which the solubility is established should be supported by sufficient scientific justification based on the time required to reach equilibrium. In cases where equilibrium solubility cannot be determined, the duration of the solubility experiment should be supported by sufficient scientific justification based on the expected time for absorption *in vivo*.
2.1.3	**Nov. 2019**	How are common ion effects associated with certain buffers accounted for when testing solubility?	Common ion effects are not expected to affect solubility.
2.1.4	**Nov. 2019**	If there is significant variability among individual results, should the lowest solubility be based on the mean of the replicates at a given pH, or the lowest result obtained for a single replicate?	Typically, significant variability should not be observed in individual replicates for highly soluble drug substances. The determination of the lowest solubility should be based on the mean of the replicates.

#	Date of approval	Questions	Answers
2.1.5	**Nov. 2019**	Can literature data or alternative scientific justification for solubility be used as pivotal data to qualify a drug substance for a BCS-based biowaiver?	Experimental solubility data should be provided to establish the solubility of the drug substance. Literature data may be submitted to further support the solubility data.
2.1.6	**Nov. 2019**	Why does the guideline set a limit for degradation of a drug substance to not more than 10% when assessing solubility?	The 10% cut-off is set to ensure that the determination of solubility is not over estimated due to degradation of the drug substance. This limit is considered well achievable experimentally.

2.2. Permeability

#	Date of approval	Questions	Answers
2.2.1	**Nov. 2019**	Why are permeability assessments restricted to Caco-2 cell lines? Can other fully validated cell-lines, e.g., MDCKII, LLC-PK1, be used to provide an estimate of permeability for BCS classification?	It is acknowledged that permeability can be estimated by other *in vitro* (other cell lines, such as MDCKII) or *in situ* (Loc-I-Gut)/*ex-vivo* (everted rat gut sac model) tools, however, as the assessment of permeability by *in vitro* approaches was not established at any other regulatory agency beyond the US FDA, it was agreed to rely initially on the method for which the most experience exists. In the future, when regulators have gained more experience with *in vitro* data, other cell-lines or animal *ex vivo* and *in situ* methods may be considered, but only with rigorous validation and standardization according to the principles as outlined in Annex I of the current draft guideline.
2.2.2	**Nov. 2019**	For certain drugs that demonstrate moderate permeability (50-84%) in validated Caco-2 cell line studies, but in practice are observed to be unstable in the GI tract and would otherwise be highly permeable, why are these drugs designated as low permeability?	As only highly permeable drugs will benefit from a BCS I classification (which gives additional flexibility for excipient changes and broader dissolution criteria (i.e., ≥85% within 30 minutes)), further differentiation of permeability classifications other than highly permeable (i.e., moderate or low permeability) is not relevant in the context of BCS-based biowaivers. For drugs with instability in the GI tract, it is not possible to demonstrate high

#	Date of approval	Questions	Answers
			permeability *in vivo*. In cases where high permeability cannot be conclusively demonstrated by one of the methods described in the guideline, a biowaiver can still be obtained by following the principles of a BCS III classification (i.e., restrictions on excipient changes and very rapid dissolution (i.e. ≥85% within 15 minutes).
2.2.3	**Nov. 2019**	Comment on the sample size required to provide a reliable estimate of drug permeability.	An estimated number of replicates needed to correctly delineate the permeability classification is difficult to define as it depends on the individual assay variability. Inter-lab variability is considered high and potential sources of variability have been described (Volpe, J Pharm Sci (97), 2008;(Lee et al, Eur J Pharm&Biopharm (114), 2017). However, inter-lab variability is substantially lower for BCS Class I compared to Class III drug substances (Lee et al.). For drug substances with a Papp > 10 x 10^{-6} cm/s, variability is reported to be moderate (5–20% ; Peng et al., Eur J Pharm Sci (56), 2014; Jin et al. J Pharmcol & Toxicol Methods (70), 2014). It is therefore unlikely that high variability would result in misclassification of high permeability. Therefore, the minimum number of 3 replicates defined for assays based on Caco-2 epithelial cell monolayers is considered justified.
2.2.4	**Nov. 2019**	If the Papp values obtained for low, moderate and high permeability drugs overlap, how are they statistically differentiated when comparing the individual values for drugs of each group?	In the context of this guidance a dichotomic outcome is the goal, i.e., the drug substance demonstrates high permeability or not. The in vivo permeability of the reference drug substances listed in Annex 1 has been confirmed in human studies, which demonstrate that the mean values are clearly differentiated into low, moderate and high permeability. Furthermore, numerous laboratories have successfully validated Caco-2 cell line systems for BCS classification using these reference drug substances, which necessitates differentiation between the high, moderate and low permeability drug substances *in vitro*. If the mean values for low, moderate and high drugs are overlapping

#	Date of approval	Questions	Answers
			when experimentally determined, this is likely an indication of an issue with the setup or performance of the Caco-2 cell line assay used. For demonstration of permeability classification of the test drug substance, the assay is standardized to these reference drug substances, and the test drug substance has to demonstrate an apparent permeability (Papp) equal or greater than the high permeability reference drug substance(s) to be classified as highly permeable. No further statistics need to be applied.

3. Eligibility of a drug product for a BCS based biowaiver

#	Date of approval	Questions	Answers
3.1	**Nov. 2019**	Why are different dosage forms of test and reference products not eligible for BCS-based biowaivers?	Differences in formulations of the same drug substance can influence *in vivo* performance. Specific recommendations regarding the dosage forms and excipients have been considered in the context of this BCS-based biowaiver guideline to accommodate the impact of formulation differences on *in vivo* performance in order to mitigate the risk associated with incorrect conclusions of bioequivalence. However, the principles of the guideline may be applied to bridge different dosage forms during product development, if sufficiently justified, e.g., based on previous *in vivo* data.
3.2	**Nov. 2019**	Why are orodispersible tablets (ODT) not eligible for a BCS-based biowaiver if they are administered without water?	As residual gastric volume is well below 250 ml, the estimation of solubility of the drug substance in 250 ml of liquid media is not applicable to products that are taken without water. Defining the volume of media required to establish the solubility classification would be challenging for ODTs that are taken without water. Furthermore, the current dissolution methodology is of limited value

#	Date of approval	Questions	Answers
			for a product that is to be dispersed in the mouth without the intake of a glass of water. For such products, a bioequivalence study with the ODT dosed without water should be conducted.

3.1. Excipients

#	Date of approval	Questions	Answers
3.1.1	**Nov. 2019**	*In silico* PBPK absorption modelling is widely used in industry to assess the risk of changes in formulation performance. Can a robust risk assessment be used to assess the potential impact (inclusion/ exclusion) of an excipient change beyond the recommended ranges?	Although it is recognized that *in silico* PBPK absorption modelling is used to assess the risk in product performance due to formulation changes, currently such models cannot comprehensively predict all potential differences in absorption due to critical excipients. Validation of *in silico* models for such purposes is further limited by a lack of mechanistic understanding for some observed excipient effects, including a lack of high quality *in vivo* data for some excipient classes. Therefore, a risk assessment based on model predicted effects would not support a change in excipient beyond the recommended range. However, in some circumstances *in silico* PBPK modelling may provide useful supporting evidence as part of a wider excipient risk assessment, for example sensitivity analysis using an appropriately validated PBPK absorption model for excipients where the mechanism of effect is well understood.
3.1.2	**Nov. 2019**	Please clarify if the excipients listed under the heading "All excipients" in Table 1, are expected to affect absorption?	Table 1 provides criteria to demonstrate quantitative similarity for products containing BCS Class III drug substances. The excipient classes listed in the table are functional classes; however, within such a class an excipient can be an excipient which may affect absorption. In that case the difference in the % of the amount of this excipient compared to the reference should be within 10%.

#	Date of approval	Questions	Answers
3.1.3	**Nov. 2019**	What may be an 'appropriate justification' for a deviation of an acceptable difference in excipients as listed in Table 1?	Typically, a lot of data on the *in vivo* performance of a formulation is obtained during a product development program. Such data, e.g. formulations with different ranges of excipients showing no effect on drug absorption, including a thorough mechanistic assessment, may support changes in excipients beyond those mentioned in Table 1.
3.1.4	**Nov. 2019**	For BCS Class III drug substances, excipients are required to be qualitatively the same and quantitatively similar. What is the consideration on an excipient with the same type but different grade? Is this excipient considered as "qualitatively the same"?	If appropriate, a difference in grade of excipient should be assessed relative to the functional properties of the excipient in the formulation. For some excipient types, a change in excipient grade would not be expected to impact product performance. For others, a modification in grade can potentially impact drug product dissolution (e.g., changes in HPMC particle size distribution, viscosity and substitution; changes in specific surface area of stearate lubricants). The assessment of excipient comparability requires a case-by-case decision to conclusively demonstrate "qualitative similarity".
3.1.5	**Nov. 2019**	Why are limits not defined for allowable differences for sugar alcohol excipients?	Currently, sufficient data is not available to qualify thresholds of effect for these excipients. Furthermore, the impact of the changes caused by these excipients will vary depending on the properties of the drug substance (i.e., sensitivity of the pharmacokinetic profile to alterations in intestinal transit). Changes in the level of these excipients are therefore subject to the same restriction as other excipients that may affect absorption, i.e., within ± 10% of the amount of excipient in the reference product.
3.1.6	**Nov. 2019**	For BCS Class III drugs, all excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients, colorant, flavor agent, or preservatives) Can representative	Examples demonstrating excipient quantitative similarity can be found in Annex II of the guidance. Additionally, many of the recommendations for allowable excipient differences in Table 1, Section 3.1, of the guidance are expressed as percent difference

#	Date of approval	Questions	Answers
		examples be provided that meet and do not meet these criteria?	relative to core weight (w/w). If a test product meets these recommendations, but there are large differences in absolute amounts of excipients (for example, if core weight is not similar between the test and reference products), additional justification may be requested.

3.2. In vitro *Dissolution*

#	Date of approval	Questions	Answers
3.2.1	**Nov. 2019**	Can the use of sinkers be justified for situations other than for coning, i.e., sticking, floating etc.?	Yes, if appropriately justified, sinkers may be used to overcome issues noted during dissolution experiments. The same experimental conditions should be applied for the reference and test formulations.
3.2.2	**Nov. 2019**	What is the approach to compare dissolution profiles for BCS Class I products, where one meets the criteria for very rapid (≥85% for the mean percent dissolved in ≤15 minutes) and the other for rapid (≥85% for the mean percent dissolved in ≤30 minutes) *in vitro* characteristics?	If one product exhibits dissolution at greater than 85% at 15 minutes but the other does not, sufficient sampling points should be taken to calculate f2 to demonstrate similarity.
3.2.3	**Nov. 2019**	For dissolution profile comparisons not enough sampling points may be valid for the calculation of f2 due to a high variability at the earlier time points. How can this be addressed?	For BCS Class I drug substances, high variability in dissolution is not expected and alternate statistical methodologies, e.g., boot strapping, to demonstrate similarity is therefore not considered applicable. In cases where high variability occurs due to coning, alternative methods (e.g., the use of sinkers or other appropriately justified approaches) may be considered to overcome issues such as coning, if scientifically justified.
3.2.4	**Nov. 2019**	For dissolution profile comparisons, in some cases, different time-points may result in different f2 values,	This situation should only occur in exceptional cases. The time points for the calculation of the f2 value have to be pre-specified. In

#	Date of approval	Questions	Answers
		although the time-points may meet the criteria and conditions listed in the guideline. For example, time-points of 10, 20, 30min result in a f2<50, whereas time-points of 8, 20, 30min yield a f2>50. How can this situation be reconciled?	general, all pre-specified sampling points should be used and justified.
3.2.5	**Nov. 2019**	When the dissolution profiles are different (rapid and very rapid) between test and reference products, do the same dissolution time points have to be used for a f2 calculation to demonstrate comparability?	The same time points should be used for the f2 calculation. See also response to 3.2.4.
3.2.6	**Nov. 2019**	Can a BCS-based biowaiver for one product strength be extended to other strengths in the product series?	No; a BCS-based biowaiver requires supporting data for each strength in a product series. *In vitro* comparison of the test product strengths to respective strengths of the reference product excludes possible drift that may occur when an additional waiver is made without comparison to the respective reference strength.
3.2.7	**Nov. 2019**	Are comparisons between the following dosage forms eligible for a BCS-based biowaiver? - Uncoated tablets versus film-coated tablets? - Tablets versus capsules?	- Uncoated tablets and non-functional film-coated tablets are considered to be the same dosage form; a comparison between these dosage forms would be eligible for a BCS-based biowaiver. - Tablets and capsules are not considered to be the same dosage form and in principle a BCS-based biowaiver may not be acceptable (see also response to 3.1).
3.2.8	**Nov. 2019**	What is the recommended agitation requirement for comparative dissolution assessments for suspension dosage forms?	For suspensions, a rotational speed of 50 rpm is recommended with the paddle apparatus. A lower rotation speed may be used but is not required.

ANNEX I: Caco-2 cell permeability assay method considerations

#	Date of approval	Questions	Answers
A.1	**Nov. 2019**	The guideline states that the BCS classification through *in vitro* permeability demonstration is limited to passively transported drugs. However 12 of the 40 model drugs (see Table 2) for method validation of Caco-2 cells are transported actively: Four of these 12 are efflux markers (digoxin, paclitaxel, quinidine and vinblastine), the other 8 are transported actively (Furosemide = OAT3; Metformin OCT1 and OCT2; Amiloride=OCT2; Famotidine= OCT2; Acyclovir =OAT1 and OCT1, Theophylline =OAT2; and Enalapril = PepT1 and 2). Can the apparent contradiction be explained?	In a comparison between 24 human jejunal permeabilities and Caco-2 permeabilities the *in vivo* and *in vitro* drug permeability measurements correlated well for passively absorbed drugs but less well for actively transported drugs (Sun et al. Pharm Res (19) 2002). Caco-2 monolayers can be, thus, used to predict passive drug transport in humans, whereas prediction of transport by carrier mediated systems might be inaccurate, owing to an altered expression of carriers in this cell line (Di et al., Drug Discover Today (17) 2012). Accordingly, the reference drugs defining high permeability are rapidly (passively) permeating drugs such as naproxen, antipyrine and metoprolol with comparable permeability coefficients in Caco-2 cells and in human jejunum. Although some of the example model drugs may in some part undergo active transport, the permeabilities of these drug substances in Caco-2 monolayers have been shown to reliably correlate with *in vivo* permeability. Because carrier expression in cell lines may be different from *in vivo* conditions, this correlation is not universally observed for all actively transported drugs. Therefore, without meaningful *in vivo* data, *in vitro* data cannot be the sole means to determine the permeability classification of actively transported drugs. The final conclusion of a drug substance being classified as highly permeable by means of the Caco-2 cell monolayer assay would be feasible only for drug substances devoid of any active transport.
A.2	**Nov. 2019**	In situations where a drug substance is subject to efflux in Caco-2, but the apparent Km value is much lower than the relevant intestinal concentrations, efflux activity can be saturated at all concentrations and permeability is	Lack of efflux or saturation of efflux transporters cannot be differentiated if the applied physiologically-relevant concentrations (see Annex I e.g., 0.01, 0.1 and 1x highest strength dissolved in 250 ml medium) exceed a drug's Km value. In that case, a drug substance

#	Date of approval	Questions	Answers
		then only driven by passive diffusion. *In vitro* data could be used in such cases, especially if human clinically observed pharmacokinetics is linear. Can products with low Km qualify for a BCS-based biowaiver based on supportive data, e.g. human pharmacokinetics, Absorption-Distribution-Metabolism-Elimination (ADME) data?	may qualify for high permeability if the apparent permeability, Papp, is ≥ the high permeability reference standard. Additionally, the Caco-2 assay must be validated demonstrating the bi-directional transport of known probes (Table 2) proving functional activity of efflux transporter(s). If *in vivo* data can be presented that demonstrate high permeability according to the guidance (i.e., ADME or absolute bioavailability), a high permeability classification may still be granted. For drug substances that do not qualify for a high permeability designation, it needs to be emphasized that a BCS Class III waiver option is also available if all other conditions according to the guidance are fulfilled.
A.3	**Nov.2019**	Since Caco-2 cells predict permeability of actively transported drugs why are these drugs excluded from qualification for a BCS-based biowaiver?	See response A1; actively transported drugs are not excluded if the human *in vivo* data support the classification as highly permeable. The use of the Caco-2 cell assay only would be not adequate for this purpose (as transporter expression in Caco-2 systems may differ from *in vivo* expression).
A.4	**Nov.2019**	For some validated Caco-2 cell monolayer models, an efflux ratio greater than 2 might be more appropriate as the threshold for observed efflux. Can an efflux ratio threshold of greater than 2 be justified based on the model compounds/data set from validation results?	In the of absence of any active transport whether uptake or efflux, the ratio between Papp apical (A) to basolateral (B) –absorptive- and B to A is expected to be 1 or close to 1. Any deviation from 1 would indicate some contribution of an active transport. An efflux ratio of greater than 2 has been adopted as indicative of the drug being a substrate for efflux transporter (Giacomini, et al. Nat Rev Drug Discov. 2010; 9:215-236).
A.5	**Nov. 2019**	Provide examples of references for the model drugs for permeability assay method validation.	Please refer to: • Volpe DA. Application of Method Suitability for Drug Permeability Classification. AAPS J. 2010;12(4):670-8.”

#	Date of approval	Questions	Answers
			• Li C. et al. Development of *In Vitro* Pharmacokinetic Screens Using Caco-2, Human Hepatocyte, and Caco-2/Human Hepatocyte Hybrid Systems for the Prediction of Oral Bioavailability in Humans. Journal of Biomolecular Screening 2007; 12(8):1084-1091 • Peng Y. et al. Applications of a 7-day Caco-2 cell model in drug discovery and development. European Journal of Pharmaceutical Sciences 2014; 56: 120-130 • Kasim NA et al. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. Molecular Pharmaceutics 2004; 1(1): 85-96 • Lennernäs, H. 'Intestinal permeability and its relevance for absorption and elimination', Xenobiotica 2007; 37(10): 1015 – 1051 • Thiel-Demby VE. Biopharmaceutics Classification System: Validation and Learnings of an *In Vitro* Permeability Assay. Molecular Pharmaceutics 2009; 6(1): 11-18 • Giacomini, et al. Nat Rev Drug Discov. 2010; 9:215-236 • FDA, United States *In Vitro* Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies Guidance for Industry (October 2017)

4. ANNEX: Q&As linked to the respective Sections of ICH M9 Guideline

Sections of ICH M9 Guideline	1: Introduction-Scope	2.0: BIOPHARMACEUTICS	2.1: Solubility	2.2: Permeability	3.0: ELIGIBILITY OF A DRUG	3.1: Excipients	7: Title	AnnexI: CACO-2 CELL	Other ICH Guidelines
1. Introduction – Scope									
1	1.1								
2	1.2								
3	1.3								
4	1.4								
2.0 BIOPHARMACEUTICS CLASSIFICATION OF THE DRUG SUBSTANCE									
1		2.1							
2		2.2							
3		2.3							
2.1. Solubility									

Sections of ICH M9 Guideline	1: Introduction-Scope	2.0: BIOPHARMACEUTICS	2.1: Solubility	2.2: Permeability	3.0: ELIGIBILITY OF A DRUG	3.1: Excipients	7: Title	AnnexI: CACO-2 CELL	Other ICH Guidelines
1			2.1.1						
2			2.1.2						
3			2.1.3						
4			2.1.4						
5			2.1.5						
6			2.1.6						
2.2. Permeability									
1				2.2.1					

Sections of ICH M9 Guideline	1: Introduction-Scope	2.0: BIOPHARMACEUTICS	2.1: Solubility	2.2: Permeability	3.0: ELIGIBILITY OF A DRUG	3.1: Excipients	7: Title	AnnexI: CACO-2 CELL	Other ICH Guidelines
2				2.2.2					
3				2.2.3					
4				2.2.4					
3.0 ELIGIBILITY OF A DRUG PRODUCT FOR A BCS-BASED BIOWAIVER Title									
1					3.1				
2					3.2				
3.1. Excipients									
1						3.1.1			

Sections of ICH M9 Guideline	1: Introduction-Scope	2.0: BIOPHARMACEUTICS	2.1: Solubility	2.2: Permeability	3.0: ELIGIBILITY OF A DRUG	3.1: Excipients	7: Title	AnnexI: CACO-2 CELL	Other ICH Guidelines
2						3.1.2			
3						3.1.3			
4						3.1.4			
5						3.1.5			
6						3.1.6			
3.2. *In Vitro* Dissolution									
1							3.2.1		
2							3.2.2		

Sections of ICH M9 Guideline	1: Introduction-Scope	2.0: BIOPHARMACEUTICS	2.1: Solubility	2.2: Permeability	3.0: ELIGIBILITY OF A DRUG	3.1: Excipients	7: Title	AnnexI: CACO-2 CELL	Other ICH Guidelines
3							3.2.3		
4							3.2.4		
5							3.2.5		
6							3.2.6		
7							3.2.7		
8							3.2.8		
Annex I. CACO-2 CELL PERMEABILITY ASSAY METHOD CONSIDERATIONS									
1								A.1	

Sections of ICH M9 Guideline	1: Introduction-Scope	2.0: BIOPHARMACEUTICS	2.1: Solubility	2.2: Permeability	3.0: ELIGIBILITY OF A DRUG	3.1: Excipients	7: Title	AnnexI: CACO-2 CELL	Other ICH Guidelines
2								A.2	
3								A.3	
4								A.4	
5								A.5	