15 February 2019
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Overview of comments received on ICH guideline M9 on biopharmaceutics classification system based biowavers (EMA/CHMP/ICH/493213/2018)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Morningside Healthcare
2	LEO Pharma A/S
3	HELM AG
4	EFPIA
5	Medicines for Europe
6	SciencePharma
7	BioBridges
8	AESGP - Association of the European Self-Medication Industry
9	Gedeon Richter Plc.

Please note that comments will be sent to the **ICH M9 EWG** for consideration in the context of Step 3 of the ICH process.

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1. General comments – overview

Stakeholder no.	General comment (if any)
2	LEO Pharma A/S appreciates the possibility to comment on this important guidance document. Over all we are in agreement with the proposal; detailed comments can be found below.
3	For the scope of this guideline, does the EMA encourage to refer to BCS classifications of APIs previously pubished by authorities?
	The use of the Caco II concept is clearly defined in this guideline. However, a clarification on the use of alternative models should be included in the text.
4	The guideline is well written and a useful step towards providing a harmonised approach to reduce the need for in vivo bioequivalence studies across the regions.
	Regional Regulations: The draft guideline allows for regional regulatory interpretations in several areas (the term 'region/regional' is mentioned twice). There is a real risk of divergence across countries/regions, for example in terms of the scope and applicability, the requirement to use purified water as an additional dissolution medium. The original goal to harmonize and facilitate biowaivers across regions will be compromised if the guideline allows a disharmonized approach on technical and regulatory considerations of biowaivers.
	Specific considerations during development: Some of the exclusions in the guidance around progressing a change (e.g. of salt form or product type – e.g. capsule to tablet) without conducting an in vivo PK study should be reconsidered for change management in early development. In early development, such changes may be common and should be capable of being progressed on the basis of scientific evaluation and in vitro evaluation (without need for in vivo PK evaluation), as is currently accepted. It would not be useful if this guidance made it more difficult to progress changes in early development.
	Permeability: Use of other cell lines Caco-2 cell lines are most preferred due to historic precedence but limiting use to Caco-2 only is scientifically restrictive as new advances mean other, improved methods with better predictions may become possible. With appropriate justification and validation, there should be no restriction on the use of alternative cell lines.
	Pharmaceutical equivalent: This draft guideline does not allow a biowaiver option for changes in dosage form for a BCS Class I product (example: capsule to tablet). The suggestion is that a BCS Class I based biowaiver should be allowed for a dosage form change.
	Excipients:

Stakeholder no.	General comment (if any)
	The proposed criteria for excipient change for BCS 3 drug products are very restrictive. Propose that a risk-based approach is adopted where the potential of an excipient change to impact absorption is mechanistically assessed on a case-by-case basis.
	In-vitro-dissolution: Higher agitation speed than 50 rpm in the paddle apparatus should be acceptable. F2 test for BCS 1 drugs (rapid dissolving) should be not required, or at least other suitable statistical method accounting for inherent higher dissolution data variability can be used. Purified water should be not required as additional dissolution medium.
	Products with more than one strength: We recommend allowing the application of BCS based biowaiver to other strengths using either the dissolution comparison of the highest strength,if strengths are compositionally similar and PK is linear across the rangeand / or using bracketed based approaches (test highest and lowest strengths).
5	Medicines for Europe welcomes the opportunity to comment on the 'ICH guideline M9 on biopharmaceutics classification system based biowaivers' (EMA/CHMP/ICH/493213/2018)" and appreciates the initiative on the harmonization of BCS based biowaivers at the ICH level.
	We would like to highlight that the line numbers in the draft guideline are not the same in all versions of the draft published (EMA, FDA, ICH, etc.). The line numbers in this document refer to the line numbers indicated in the draft version of the document released by EMA as available at https://www.ema.europa.eu/documents/scientific-guideline/ich-m9-biopharmaceutics-classification-system-based-biowaivers-step-2b-first-version_en.pdf (accessed on 2019-01-25).
7	We appreciate very much the initiative on the harmonized approach towards BCS-based biowaivers. However, many specific recommendations proposed by the current draft of "ICH guideline M9 on biopharmaceutics classification system based biowaivers" appear very strict leaving almost no space for the case-by-case justification. We are of the opinion that the common principle of "No unnecessary human testing should be performed" should be always supported when convincing justification is provided despite of the fact that the particular approach may not be fully in line with the guideline. Therefore, it should be emphasized in the final text of the guideline that the recommendations provided are generally applicable however appropriate justification will be always considered.
8	ICH Guideline M9 on biopharmaceutics classification system based biowaivers is well appreciated as a specific guideline has been expected for a long time in this field in order to support streamlined global drug development.
9	In section **2. Biopharmaceutics classification of the drug substance** in *line 66* the current texts says: *"A biowaiver is only applicable when the drug substance(s) in test and reference*

Stakeholder no.	General comment (if any)
	products are identical. For example, a biowaiver is not applicable when the drug substance in the test product is a different salt, ester, isomer, or mixture of isomers from that in the reference product." The current definition for generic medicinal products is found in Directive 2001/83/EC, Article 10(2)(b), which states that a generic medicinal product is a 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. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. However, when the active substance in both test and reference products is identical and contain salts with similar properties then *in vivo* bioequivalence studies may in some situations not be required. For example Biowaiver may be applicable if test and reference contain different salts provided that both belong to BCS-class I (high solubility and complete absorption) since in this case the different salt has no clinical relevance or any effect on the bioequivalence due to the rapid dissociation. **Proposed change:** *"A biowaiver is only applicable when the drug substance(s) in test and reference products are identical. For example, a biowaiver is not applicable when the drug substance in the test product is a different salt (Biowaiver may be applicable in some exceptional cases, if test and reference contain different salts provided that both belong to BCS-class I high solubility and complete absorption), ester, isomer, or mixture of isomers from that in the reference product."*

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
52-56	4	**Comment:** To harmonize across the regions "in accordance with regional regulations" should be deleted, this creates uncertainty. **Proposed change:** ….That would otherwise require in vivo bioequivalence evaluation, ~~in accordance with regional regulations.~~
53	2	**Comment:** "Early clinical development" is included in the scope of this guideline. Typically, very little formulation work is performed prior to phase 1, which is run with a drug substance in suspension, in capsule, or as a very simple tablet whereas a (more advanced) tablet formulation is introduced with the phase 2 clinical program. The allowance criteria for excipients described in Table 1 (line 183) are however so restrictive that a change in formulation from e.g. capsule to tablet is not possible within the framework of the guideline in its current version. However, a change of dosage form in the early clinical development program could be achieved with science-based in vitro and/or in vivo studies - with due consideration to biopharmaceutical classification - as long it can be demonstrated that patient safety is not compromised; and such a change could be handled internally. **Proposed change:** Either: the early clinical development (phase 1 to phase 2) of new chemical entities (NCEs) is deleted from the scope of this guideline and this is specified in the scope section - Or: a new section related to clinical development of NCEs is created to clarify this issue in the same manner as in ICH M7.
57-58	1	**Comment:** 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. *Suspensions designed to deliver drug to the systemic circulation* - Does this applicable for the parenteral which are suspensions, if so, what kind of in vitro data is expected
58-59	4	**Comment:** "Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver in this guidance."

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		It needs a clear definition for narrow therapeutic index. Drug products having a narrow therapeutic index should not be excluded. If a bio-waiver assumes that the rate and extent of absorption of BCS 1 and BCS 3 APIs can be inferred or is a function of its solubility and permeability, a narrow therapeutic drug should be also applicable for a biowaiver, when these requirements are fulfilled. **Proposed change:** ~~Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver in this guidance."~~
59	2	**Comment:** A definition of a "narrow therapeutic index" would be beneficial **Proposed change:** Add the definition of "narrow therapeutic index" in section 5. Glossary
59	3	**Comment:** The term "narrow therapeutic index" without reference might not be clear. **Proposed change:** A reference/definition of "narrow theroateutic index" should be include in the guideline.
59	5	**Comment:** Definition of narrow therapeutic index applicable to ICH region would be helpful. It may be possible to know if a comparator is a narrow therapeutic index, but it would be more difficult for a test product under development.
60-62	3	**Comment:** If all criteria outlined in section 2 and 3 of the draft guideline are fullfilled for one API in a FDC, it is not clear, why a corresponding biowaiver for this API is not applicable. **Proposed change:** To allow for BCS-based biowaivers for individual APIs in a FDC and a corresponding clarification that any other API in the FDC has to be identical in both products.
64-69	4	**Comment:** A waiver for drug products with different salts or moiety should be possible during development. The counter-ion does influence the dissolution of the product but if the different salt/moiety dissolves at a similar rate over the entire pH range the absorption of the drug will be the same. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"Different salt may be accepted in development if scientifically justified".
66–68	5	**Comment:** The draft ICH guideline does not allow BCS-based biowaiver applications in case the test and reference product contain different salts of the same active ingredient. This is in contrast to the EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr), which permits the use of different salts of the active substance provided that both drug substances belong to BCS class I (high solubility and complete absorption). Notably, EMA recently issued a product specific guideline that supports the eligibility of different salts (particularly in the form of cocrystals) of agomelatine for BCS-based biowaiver (Agomelatine tablet 25 mg product-specific bioequivalence guidance, EMA/CHMP/800802/2017). We are of the opinion that if the solubility of two different salts is similar and the salts do not significantly differ in other physical-chemical properties, the product shall be eligible for BCS-based biowaiver. Once the drug substance is in solution, the properties of the molecule will be identical and linked only to the original base or acid. **Proposed change:** The possibility to apply for a BCS-based biowaiver for different salts of the same active substance that can be classified as BCS class I shall be implemented.
67-68	6	**Comment:** In our opinion the provision that "(…) a biowaiver is not applicable when the drug substance in the test product is a different salt (…)" is too strict regarding BCS-class I substances, which are highly soluble and highly permeable. **Proposed change:** We propose adding the following sentence in line 68: "A biowaiver is only applicable when the drug substance(s) in test and reference products are identical. For example, a biowaiver is not applicable when the drug substance in the test product is a different salt, ester, isomer, or mixture of isomers from that in the reference product. Biowaiver may also be applicable if the test and reference products contain different salts provided that both belong to BCS-class I."
67–68	7	**Comment:** According to the draft ICH guideline, the BCS based biowaivers are not possible in case the test and reference product contain different salts of the same active ingredient. Current situation described in the EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr) permits the use of different salts of the active substance provided that both belong to BCS class I. We endorse the current opinion as there are active substances e.g.

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		amlodipine, where the active substance exists in different salts exhibiting similar in vitro (solubility) as well as in vivo (permeability/intestinal absorption) properties. Therefore, the current acknowledged approach should be maintained in the new ICH guideline as well. **Proposed change:** The BCS-based biowaiver for different salts classified as BCS class I compounds can be acceptable and the eligibility of different salts will be judged on case by case basis. However, additional in vitro permeability data and/or in vivo intestinal absorption data may be required to provide a supportive evidence.
71-75	5	**Comment:** Even if the BCS concept is different from the in vivo approach, its sole purpose in the context of this guideline is to replace bioequivalence studies. Therefore, it is not at all understandable why the highest dose has to meet high solubility criteria and not the highest strength which is to be considered for in vivo studies. The choice of the highest strength is aligned with the approach taken for the selection of the dose in bioequivalence studies and the same approach should be used for biowaivers. Furthermore, the current draft guideline provides little information (in lines 134 - 138, see comment below) which additional data should be submitted in case the highest strength, but not the highest dose meets the high solubility criterion. **Proposed change:** A drug substance is classified as highly soluble if the highest strength~~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.~~
72 and 78	5	**Comment:** It seems 1.2, 4.5 and 6.8 to be mandatory pHs. **Proposed change:** Replace "including buffer at" by " typically buffers at pH 1.2, 4.5, 6.8 but other pHs could be suggested (e.g. pKas etc...)".
73-75	2	**Comment:** Consider rephrasing the sentence in line 49-51, as it is unclear what it is exactly meant by **dose** of **drug substance** compared to **strength** of **reference product**? Why does "strength of reference product" impact the solubility classification?

Line no.	Stakeholder no.	Comment and rationale; proposed changes
74	3	**Comment:** For the sake of clarity EMA´s expectation on the nature of additional data should be specified. **Proposed change:** Revision to include a clear outline of EMA´s expecatation on additonal data.
74-75	8	**Comment:** A cross-reference to the section 3 should added here in order to inform the reader that this topic is detailed further. **Proposed change:** "additional data should be submitted to justify the BCS-based biowaiver approach **(see an example of additional data in section 3)**."
78-79	8	**Comment:** In order to avoid misunderstanding, the following sentence should be written as proposed. **Proposed change:** "At least three ~~**buffers**~~ **pH** within this range, including buffer~~**s**~~ **solutions** at pH 1.2, 4.5 and 6.8, should be evaluated."
		Comment: "*At least three buffers within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated*." Harmonize buffer compositions as these vary between pharmacopeia. For example, pH 1.2 buffer includes 0.1 N HCl medium, which theoretically could be perceived as outside the current range of pH 1.2 – 6.8. Further, Japan pharmacopeia includes McIlvaine buffers at pH 3.0 - 5.0 (for products containing neutral or basic drugs, and coated products) and pH 5.5 - 6.5 (for products containing acidic drugs). Similar concerns exist for pH 6.8 buffer as well. **Proposed change:** Additional text for harmonized compositions for buffers to avoid sponsors from having to perform multiple experiments across different media of the same pH.
78-80	4	**Comment:** "*At least three buffers within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated*." Harmonize buffer compositions as these vary between pharmacopeia. *In addition, solubility at the pKa of the drug substance should be evaluated if*

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		it is within the specified pH range." The rationale for the solubility measurement at the pKa, is not clear, especially considering that minimum solubility would not be observed at the pKa where equal concentrations of ionized and unionized drug would be found. We propose to delete the additional measurement at pka. **Proposed change:** At least three buffers within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated. Pharmacopoeial buffers should be employed. ~~In addition, solubility at the pKa of the drug substance should be evaluated if it is within the specified pH range.~~ When the drug substance is a zwitterion, solubility should also be determined at mid-point to the pkas (isoelectric point)
79	3	**Comment:** APIs might posses more than one pKa value within the physiolgical pH range. **Proposed change:** Revision to include a clarification that solubility at all pKas within the physological range should be determined.
84-86	4	**Comment:** The method need not be fully validated per ICH requirements, but should be shown to be accurate and precise. **Proposed change:** A minimum of three replicate determinations at each solubility condition/pH is necessary to demonstrate solubility using a ~~validated~~ stability-indicating method.
84-86	6	**Comment:** If it is known from other studies that the substance is stable in particular pH conditions, there is no rationale to always apply stability-indicating methods. Such methods should be applied while there are no other data addressing the issue of stability of the active substance under conditions concerned or suitability of the analytical methods. Therefore we propose to slightly reword the sentence as given below. **Proposed change:** We propose the following wording in lines 84-86: "A minimum of three replicate determinations at each solubility condition/pH is necessary to demonstrate solubility using a validated stability-indicating method (if necessary), with appropriate compendial ~~references for the~~ media employed."
87–90	5	**Comment:** The draft ICH guideline excludes a possibility to apply for a BCS-based

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		biowaiver if the drug substance exhibits >10% degradation over the extent of solubility assessment. This is too strict. There may be cases when the drug substance is unstable only in certain pH range. If, for instance, degradation is observed in acidic pH for a weakly basic drug substance (which has the lowest solubility in neutral pH) such substance would have to be excluded from a BCS-based biowaiver application despite a fact that sufficient solubility can be demonstrated in the low solubility pH region. In cases where the drug substance is unstable over the pH range 1.2-6.8 one can still, in theory, prove a sufficient solubility by employing Henderson-Hasselbalch theory and calculating the entire solubility profile based on intrinsic solubility and dissociation constant(s) (provided these parameters may be measured). Yet another possibility to determine the equilibrium solubility of a degrading drug substance may be waiting until the solution is saturated with degradation products and measure the amount of dissolved and non-degraded drug substance. **Proposed change:** BCS-based biowaiver application for a drug substance with degradation >10% will be considered if solubility data are properly justified and explained.
87-90	6	**Comment:** In our opinion the issue of active substance degradation should be discussed in the context of the properties of the active substance e.g. even if the substance is degraded in solution, still the solubility might be well above the threshold defined in the guideline. Therefore there is no rationale for fixed 10-percent threshold. **Proposed change:** We propose the following change in line 88 (added text in bold): "In cases where the drug substance is not stable with >10% degradation over the extent of the solubility assessment, <u>additional data should be submitted to justify the BCS-based biowaiver approach.</u> ~~solubility cannot be adequately determined and thus the drug substance cannot be classified~~ <u>In addition to experimental data, literature data may be provided to substantiate and support solubility and stability 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."</u>
88-90	4	**Comment:** "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….." Scientific justification and literature may be used to interpret solubility measurements, providing insight into the reproducibility of the solubility or degradation. In these cases, degradation > 10% may be highly reproducible

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		and could be explained with understanding of the degradation. **Proposed change:** Allow literature data or scientific justification to support the use of solubility data towards applying a BCS-based biowaiver.
90-93 vs 107-110	3	**Comment:** It is noted that literature data on solubility "may be provided to substantiate and support" whereas published literature on permeability "may be acceptable". As the reasoning "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" is the same in both paragraphs the different acceptance for solubility vs permeability data is not clear. **Proposed change:** Unify wording for the acceptance of literature data for solubility and permeability.
91 and 109	3	**Comment:** Related to the use of literature data for solubility and permeability the draft refers to "not containing the necessary details". **Proposed change:** To clarify EMAs expectation, the term "necessary details" should be defined, e.g. referring to lines 76-86 or Annex I.
97-106	2	**Comment:** It is unclear if the text relates only to human studies or can be derived from animal studies also. **Proposed change:** Please clarify text.
107-110	5	**Comment:** In contrast to e.g. solubility data, human in vivo data on absolute bioavailability are usually taken from literature since there is little added value to conduct an in vivo study in order to avoid another study. Therefore, we suggest to re-phrase the paragraph (see below). **Proposed change:** Human in vivo data derived from published literature (for example, product knowledge and previously published bioavailability studies) ~~may be~~ <u>are usually</u> acceptable, ~~keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding~~<u>provided that there are no issues compromising</u> the quality of the

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		results.
111-112	4	**Comment:** "Permeability can be also assessed by validated and standardized in vitro methods using Caco-2 cells". Caco-2 cell lines are most preferred due to historic precedence but limiting use to Caco-2 only is scientifically restrictive as new advances mean other, improved methods with better predictions may become possible. With appropriate justification and validation, there should be no restriction on the use of alternative cell lines. The principles stated for Caco-2 cell use could be applicable to other cell lines if suitable / similar method development and validation were conducted. This would make the guidance more future-proof. **Proposed change:** line 111-116: "Permeability can be also assessed by validated and standardized in vitro methods such as Caco-2 cells or another cell line, provided the assay is fully validated with reference compounds (see Annex I)."
111-112	5	**Comment:** Caco-2 cells are the only in vitro model that is being suggested to use to assess permeability, but other cell lines can be used such as, for example, MDCK. Methods such as in vivo or in situ intestinal perfusion in a suitable animal model (e.g., rats), and in vitro permeability methods using excised intestinal tissues, or monolayers of suitable epithelial cells, should be possible to use, provided they are sufficiently validated. **Proposed change:** It is suggested to mention that other models can be used to evaluate permeability.
111-116	4	**Comment:** In addition to using Caco-2 cells for permeability assessment, the FDA guidance on biowaivers allows other options as well, such as, *in vivo/in situ* perfusion using animal models, and in vitro permeation using excised human/animal intestinal tissues. The same principals pertaining to demonstration of model suitability and validation as mentioned for Caco-2 cell line can also be applied. **Proposed change:** "Other validated methods, such as *in vivo* intestinal perfusion in human subjects, *in-situ* intestinal perfusion in a suitable animal model (e.g., rats), and *ex vivo* permeability methods using excised intestinal tissues, may also be used to determine drug permeability".

Line no.	Stakeholder no.	Comment and rationale; proposed changes
111-116	7	**Comment:** The draft ICH guideline is proposing the use of supportive permeability data derived solely from Caco–2 cells. We are of the opinion that some other approaches for evidence of the extent of absorption should be also mentioned, ranging from simple physicochemical characteristics (such as logP) and PAMPA testing to in situ/in vivo perfusion models. Especially in case of older substances, there is often a lack of published, high quality evidence on the extent of the compound´s absorption. However, multi-approach permeability considerations may clearly lead to the permeability level estimation. In cases where total body of evidence is convincing enough, the additional Caco-2 cells testing seems redundant. **Proposed change:** Additional, recognized methods for the permeability estimation should be added to the guideline. Specifically following methods should be added: - in vivo intestinal perfusion studies in humans - in vivo or in situ intestinal perfusion studies in suitable animal models - in vitro permeation studies using excised human or animal intestinal tissues Overall, the total body of evidence comprising thorough physicochemical API characterization and demonstrations of the permeability level based on various approaches may be also deemed acceptable.
122-124 vs 125	3	**Comment:** If a justification has to be provided for the prove of gastrointestinal instability, the referred conditions in line 125 should be given as e.g. rather than i.e. **Proposed change:** Revision of this paragraph to include exemplary conditons.
131-134	4	**Comment:** Capsule/tablet switches should be permissible when both are rapidly dissolving. In addition, the term "pharmaceutically equivalent" needs clarifying. **Proposed change:** "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) and the drug product is an immediate-release oral dosage form with systemic action.
131-134	5	**Comment:** For BCS class I, it is not clear why pharmaceutical equivalence is requested in respect to dosage form. To receive a biowaiver the release principle must be

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		immediate release as mentioned in line 132. The formulation as tablet or capsule will mainly affect the dissolution profile and the comparative dissolution testing will disclose those differences. Please consider the following example: Reference product is a capsule. Test product is a tablet. If a test tablet is over-encapsulated, then reference and test products are capsules and pharmaceutically equivalent and may be eligible to grant a biowaiver. If a test tablet is not over-encapsulated, then reference and test products are capsules and tablets, respectively, and pharmaceutically not equivalent and a biowaiver cannot be granted. Why is the dosage form regulated when the excipients are allowed to be qualitatively different? If the dosage form has an impact, then again, the comparative dissolution tests will demonstrate it. Therefore, for any immediate release (e.g. capsules and/or tablets) that comply with the biowaiver requirements there is no scientific reason not to accept a biowaiver. **Proposed change:** delete "that is pharmaceutically equivalent to the reference product" and replace by: "The dosage form is if no relevance as soon as they fulfil all criteria (dissolution and excipients) for granting a biowaiver."
131-138	1	**Comment:** 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 - demonstration of dose proportional pharmacokinetics (i.e. AUC and Cmax) over a dose range that includes the highest therapeutic dose What is meant by highest single therapeutic dose and how different it is from Maximum Daily Dose? Example - Capecitabine 150mg and 500mg Tablets Highest Strength – 500mg, MDD – 2000mg so the highest single therapeutic dose to be considered as 4 tablets of 500mg = 2000mg?
134-138	5	**Comment:** See comment on lines 071-075. Requirement that highest single therapeutic dose meets high solubility requirements should be removed. If ICH decides against it, the lines 134-138 ("In cases where … therapeutic dose") should be merged with lines 071-075.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Remove the lines 134-138 ("In cases where … therapeutic dose").
138	3	**Comment:** Does the demonstration of dose proportional pharmacokinetics include reference to literature data as well? **Proposed change:** Include reference to literature data.
139-141	4	**Comment:** There is no reason why biowaivers cannot be applied to orodispersible products taken with or without water, provided test and reference are dosed in the same way. **Proposed change:** Drug products that are designed to utilize buccal or sublingual absorption are not eligible for a BCS-based biowaiver application. In addition, orodispersible products are eligible for a biowaiver application only if proposed label dosing instructions (e.g. co-administered water volume) are identical to the reference product.
139-141	5	**Comment:** Please explain what kind of evidence is expected to demonstrate that there is no buccal or sublingual absorption for an orodispersible product. **Proposed change:** Add examples what kind of data are expected.
		Comment: In case both the test and reference product are orodispersible tablets, it is not clear why orodispersible products which can be taken without water but have no buccal / sublingual absorptions are not eligible for a biowaiver. If the requirement is related to make sure that a drug is in solution in general, administration with water should be described in a separate paragraph independent of buccal / sublingual absorption of orodispersible products. **Proposed change:** Remove "… and the product is labelled to be taken with water only".
141	6	**Comment:** In our opinion a part of the sentence regarding intake with water should be removed. If the buccal or sublingual absorption is excluded, it is not justified to differentiate the approach to the products taken with or without water. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"(…) As such, an orodispersible product is eligible for a biowaiver application only if there is no buccal or sublingual absorption. ~~and the product is labelled to be taken with water only.~~"
151	4	**Comment:** In silico PBPK absorption modelling is widely used in industry to assess the risk of changes in formulation performance. Suggest including this in the discussion on risk assessment as a useful tool to assess the potential impact (inclusion/exclusion) of an excipient change.
158-160 and 165-172	5	**Comment:** It is not clear in what situations the considerations in these lines, which are beyond the amount of excipients, have to be taken into considerations. Other paragraphs (e.g. lines 161-164, lines 173-184 and annex II) define clear criteria in terms of acceptable deviations in quantity of excipients. Please explain whether the additional considerations in lines 158-160 and 165 – 172 are relevant only in case the differences in the amount of excipients exceed those described in the guideline or whether both an evaluation of the amount of excipient differences and the additional considerations is expected. **Proposed change:** Please explain in which cases the requirements described in these lines have to be taken into consideration.
171	5	**Comment:** A typographical error is observed. **Proposed change:** Text should read: "for a" not "fora".
176-178	7	**Comment:** In the particular part of the text of the draft guideline, BCS class III drug substances are collectively regarded as "poorly permeable" and more strict rules in terms of excipient content are consequently applied. This approach should not be fully endorsed. Numerous compounds having extent of absorption between 50–84% although classified as low permeability (BCS class III) drugs still have good permeability properties with not such a strong propensity to absorption modification by excipients in formulation. Therefore, moderate permeable compounds should be regarded on case-by-case basis in terms of content of excipients. However, the appropriate justification of the possible difference from the reference formulation should be required.
169	3	**Comment:** Caco II cells do not cover active update, hence this feature cannot be assessed following the guidance. **Proposed change:**

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		Inclusion of other alternative models.
170-171	2	**Comment:** It is unclear why a class I compound would have slow absorption. Is it due to slow dissolution even though the molecule has high solubility? **Proposed change:** Please add examples of BCS class I compounds with slow absorption.
170-172	4	**Comment:** How is slow absorption for BCS Class I defined? BCS correlates the extent of absorption with fraction absorbed but not the absorption rate. **Proposed change:** Definition of a criteria or deletion of the statement
173-175	4	**Comment:** The restriction of absorption-affecting excipient changes to a hard and single value of 10% is questioned as it does not appear to be scientifically justified or necessary. It is also unclear as to whether it is in line with current regional position(s) on the application of BCS-based biowaivers to Class1 containing products. It also appears inconsistent with the mechanistic, risk-based approach mentioned earlier in Section 3.1 (line 156-160), and does not account for the inherently lower risk BCS1 drugs have to PK change with excipients that may affect absorption. Recommend removing this one-size-fits-all 10% limit on absorption-affecting excipient change. **Proposed change:** Remove: "except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, i.e., within ± 10.0% of the amount of excipient in the reference product".
173-175	8	**Comment:** Remove the text regarding BCS1 drugs "*except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, i.e., within ± 10.0% of the amount of excipient in the reference product"*. This is inconsistent with the mechanistic, risk-based approach mentioned earlier in Section 3.1, and does not account for the inherently lower risk BCS1 drugs have to PK change with excipients that may affect absorption. **Proposed change:** Remove: "*except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, i.e., within ± 10.0% of the*

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		amount of excipient in the reference product".
174	3	**Comment:** The term "excipients that may affect absorption" leaves room for interpreatation. In various other secions the guideline reminds to carfully evaluate the suitability of even peer reviewd literature data. In this respect it is greatly unclear how to judge/demonstrate that an excipient "may affect absorption". **Proposed change:** Inclusion of a list with all excipients, which "may affect absorption" should be included in this guideline for clarity.
		Comment: Qualitative similarity of exciepients is not defined. Does this refer to compliance to the same monograph only or does this include also similarity in FCRs resp. grades of the excipient? **Proposed change:** Inclusion a definition of "qualitatively the same".
174-176	4	**Comment:** It is not clear how to determine the right quantities that reference listed drug product use for specific excipients when this information is not available/published? All pre-formulation analysis on the reference product brings some uncertainty to the results. **Proposed change:** Include a statement or literature reference for clarification, or provide a list in the appendix of excipients that may affect absorption.
175	3	**Comment:** The term "+/- 10 % of the amount of excipient in the reference product." is not clear – as it could be understood as relative of absolute. **Proposed change:** Addition of a corresponding clarifiacation in line with Table 1.
		Comment: Typically, the quantitative composition of the approved reference product is not known to a generic applicant. How to prove the quantitative composition for a generic biowaiver? **Proposed change:** A clarification should be included on EMAs expectations for generic BCS-based biowaiver applications related to the prove of quantitative composition of the

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		reference product, e.g. reference to patent literature, de-engineering etc.
176-181	4	**Comment:** The proposed criteria for excipient change for BCS 3 drug products are very restrictive. Propose that a risk-based approach is adopted where the potential of an excipient change to impact absorption is mechanistically assessed on a case-by-case basis. Alternatively, wider limits for non-critical excipients should be adopted. If a "critical" excipient is utilized at the levels where it is expected to impact drug absorption via solubility, gastrointestinal motility, transit time, and intestinal permeability "qualitatively the same and quantitatively similar" aspect should be considered. In effect change the excipient criteria for BCS3 to allow sponsors to provide product-specific justification that the proposed excipient change will not impact on drug absorption, for non-critical excipients. **Proposed change:** For BCS Class 3 drugs, qualitative and quantitative differences in excipients that do not affect absorption, are permitted. For BCS Class 3 drugs, all excipients that may affect absorption should be qualitatively the same and quantitatively similar, unless additional mechanistic justification is provided (e.g. to support that the mechanism by which the excipient can impact absorption is not relevant for the API, or that the level of change is below the level where an effect of the excipient on absorption has been demonstrated). Qualitatively similar also includes changes in the technical grade of an excipient. The sponsor should submit the mechanistic risk assessment to justify that the proposed excipient change will not affect product performance in the patient, as part of the biowaiver application.
178-180	8	**Comment:** "*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).*" For BCS 3 drugs, applicants should provide evidence that the level of change in excipients that may affect absorption is significantly below any previously observed threshold of impact. For instance, the levels of mannitol/sorbitol that induce a change in GI transit/ drug PK can be elucidated from literature. Only if no such evidence is available should a "quantitatively similar, i.e., within ± 10.0% of the amount of excipient in the reference product" be applied for BCS 3 drugs. If a "critical" excipient is utilized at the levels where it is expected to impact drug absorption via solubility, gastrointestinal motility, transit time, and intestinal permeability "qualitatively the same and quantitatively similar" aspect should be considered. **Proposed change:** "For BCS Class 3 drugs, qualitative and quantitative differences in excipients

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		that may not affect absorption, are permitted. For BCS Class 3 drugs, all of the excipients that may affect absorption should be qualitatively the same and quantitatively similar, i.e., within ± 10.0% of the amount of excipient in the reference product (except for film coating or capsule shell excipients) unless additional mechanistic justification is provided to support the change for the level of excipients in formulations relative to the level where an effect of excipient on absorption has been demonstrated."
178-181	1	**Comment:** 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). This is defined in Table 1. Examples of acceptable differences in excipients are shown in Annex II. What about the excipients which are not commonly used now a days, like Potato Starch, Al Stearate but are part of reference products, in this situation Q1Q2 formulation with reference may not be feasible
178–181	5	**Comment:** The draft ICH guideline requires for BCS Class III drugs that all the excipients should be qualitatively the same and quantitatively similar (except for film-coating or capsule shell components). Typically, in case of generic submissions, the quantitative composition of the reference drug product is not known and methods of reverse engineering have to be applied. However, in some cases, these methods do not allow to distinguish whether a particular excipient is part of coating or core of the product unless clearly described in the summary of product characteristics. Moreover, these methods have also other limitations, e.g., in certain cases large analytical error over 10% may be present. From this point of view, some of the criteria of acceptable differences as defined in Table 1 seem too restrictive (refer to Comment on lines 180 – 184).
180–184	5	**Comment:** The maximum allowable percent difference of ±0.5% in the amount of magnesium (or calcium) stearate, is considered too restrictive. Taking the Example 2 composition in Annex II, increasing the amount of magnesium stearate in test product just by 1.5 mg (in total 3.5 mg of magnesium stearate, i.e. 1.62% of core weight), the absolute percent difference between test and reference will be outside the limit of ±0.5%. Based on human bioavailability study (Vaithianathan et al., J Pharm Sci. 2016, 105(2): 996-1005), the amount of 40 mg of magnesium stearate was not able to modulate the bioavailability of BCS class III model drug cimetidine. In this study, bioequivalence in terms of rate and extent of absorption was proven within the standard bioequivalence acceptance criteria for capsule formulation containing 7.1% of magnesium stearate versus oral solution of cimetidine. Magnesium stearate is typically added in formulation at concentration of 0.25% to 5% (Rowe, Sheskey & Quinn, Handbook of pharmaceutical

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		excipients, sixth edition; Pharmaceutical Press, 2009), therefore, the maximum percent difference should allow for a higher difference. Similarly, the maximum percent difference of ±0.2% for other glidants seems restrictive, also in the view of capabilities of analytical methods used in reverse engineering. **Proposed change:** Relax the requirements for magnesium (or calcium) stearate and other glidants to allow maximum percent difference of at least ±1%.
183 Table 1	3	**Comment:** Any rationalisation/references on the different acceptable ranges for different excipients in the same excipient class would be of interest. Especially taking into account the vague nomenclature applied in this table.
		Comment: As the table in Example 2 refers to "absolute" percent difference relative to core weights, the corresponding column in Table 1 should be named in the same way. **Proposed change:** Harmonisation between Table 1 and the corresponding table in Example 2.
		Comment: : Please reformate Table 1 for better visualisation. Excient classes as header etc.
		Comment: It is noted that the excipients in Table 1 are listed without using the title of the corresponding Ph.Eur. monograph, e.g. starch (native starches or pre-gelatinised stach), resulting in unclearity with regards to applicable limits. The same applies to several excipients, which could be grouped in more than one of the reffered excipient classes of Table 1, e.g. microcrystalline cellulose (filler or desintegrant). **Proposed change:** Inclusion of a comprehensive list for all standard excipient with applicable ranges for each individual excipient instead of the very general Table 1.
183	5	**Proposed change:** Divide second row (excipients which may affect absorption) into 2 columns since the criterion ±10% of the excipient amount is applicable only on this category of the excipients.
183	6	**Comment:** In our opinion the approach presented in the guideline e.g. setting narrow limits for all excipients compromises the probability for waiver of BCS-class III

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		generic products. Firstly, most of the excipients in the product are not routinely tested for assay and it is practically unfeasible to determine the exact amount of these substances in finished dosage forms. This is especially true in view of high heterogeneity of huge part of excipients of natural origin widely used for manufacture of oral dosage forms (including all excipients specifically listed in the table 1, i.e. starch, Ca or Mg stearate and talc). For example, according to Ph.Eur. talc contains hydrated magnesium silicate, however may also contain "variable amounts of associated minerals among which chlorites (..), magnesite (..), calcite (..) and dolomite (..) are predominant". A similar situation is in case of magnesium stearate which is a mixture of magnesium salts of different fatty acids consisting mainly of stearic and palmitic with minor proportions of other fatty acids. In our opinion, the difference limits proposed in the draft are extremely low. It should be also taken into account, that the quantitative composition of excipients is not given for the reference product (except several substances, which amount should be given in SmPC/PL). Therefore, taking into consideration the abovementioned methodological limitations, it is not feasible to meet the requirements for BCS-class III biowaiver. Secondly, if there are no excipients in the formulation that may influence the bioavailability and the dissolution profiles are similar, there is no rationale to suspect that small differences in the amount of other typically used excipients may hamper bioequivalence. Generally, in our opinion the requirements regarding the composition of BCS-class III drugs are extremely restrictive. It may lead to the need of performing unnecessary in vivo bioequivalence studies due to even small differences in composition of excipients between generic and reference drug. In our opinion current European requirements regarding these issue are sufficient to ensure similarity of BCS-class III generic vs reference formulation. **Proposed change:** We propose adding the following comment to Table 1: "<u>The difference limits given in Table 1 should be met provided that that the quantitative composition of the reference product has been published or it is technically feasible to determine the amount of excipients in the reference products. Otherwise, the BCS-class biowaiver is still feasible, however, additional data should be submitted to justify the BCS-based biowaiver approach.</u>"
183-184	4	**Comment:** For quantitatively similar the allowable differences should be defined with no decimal places (aligned with FDA guidance) **Proposed change:**

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		Excipients which may affect absorption: ±10% • Filler: ±10% • Disintegrant, Starch:± 6% • Disintegrant, Other: ± 2% • Binder: ± 1% • Lubricant, Calcium or Magnesium Stearate: ± 0.5% • Lubricant, Other: ± 2% • Glidant, Talc: ± 2%) • Glidant, Other:± 0.2% • Film Coat: ± 2% The total additive effect of all excipient changes should not be more than 10 percent.
187-188	5	**Comment:** The sentence "This is applicable to FDCs which are pharmaceutically equivalent." is redundant since pharmaceutical equivalence is a general requirement according to line 134. **Proposed change:** Remove the sentence "This is applicable to FDCs which are pharmaceutically equivalent."
190-192	4	**Comment:** It is considered that a more appropriate comparison for the post-change material would be to a representative range (not a single lot) of the pre-change product. This makes the comparison more meaningful, by e.g. including any variation in historical results, and avoids any 'preference selection' of a single batch which may skew the comparison. **Proposed change:** "When applying the BCS based biowaiver approach, comparative in vitro dissolution tests should be conducted using a representative sample of the proposed commercial manufacturing process for the test product relative to a representative sample of the reference product."
191-192	3	**Comment:** This reflection paper specifically calls for the comparision of each one batch. However, section IV.1.1 of Annex III of the EMA BE guidleline PMP/EWP/QWP/1401/98 Rev. 1/ Corr ** calls for: *In line with these requirements it is advisable to investigate more than one single batch of the test and reference products.*

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		Proposed change: Harmonisation of these conflicting regulatory guidances and clear definition of the required number of batches.
194	5	**Comment:** It is not clear in which cases a BCS-based biowaiver supported by dissolution profiles generated during the development phase on smaller batches than 1/10 of production scale or 100,000 units would be acceptable. **Proposed change:** Please explain.
197-203	7	**Comment:** In the draft ICH guideline, the conditions for dissolution testing particularly the rotation speed (i.e. paddles 50 rpm, basket 100 rpm), are strictly set. In the current EMA bioequivalence guideline where only "usual" experimental conditions are defined there is a possibility for justification when the conditions used are different. For example, in some cases of oral suspensions containing BCS class I substances, rapid dissolution cannot be obtained under conditions prescribed by the draft (i.e. paddles 50 rpm) for the test as well as for the reference due to the high viscosity of the formulation. The case-by-case approach should be justifiable when assessing the suitability of dissolution conditions for BCS-based biowaivers. **Proposed change:** The following conditions should be employed (unless otherwise justified) in the comparative dissolution studies to characterize the….
200	2	**Comment:** All commercially available dissolution apparatuses can contain a volume of 1000 ml. In order not to restrict the volume and hereby in some cases limit the fulfilment of sink conditions, the maximum volume capacity is suggested to be permitted. This is also in accordance with *Ph. Eur. 5.17.1 Recommendations on dissolution testing*. **Proposed change:** Volume of dissolution medium: <u>1000 ml</u> or less.
200	3	**Comment:** 900 mL appears to be the largest accepatable volume, whereas compendial dissolution test could be based on 1000 mL as well. **Proposed change:** Allow for dissolution media up to 1000 mL.
202	3	**Comment:**

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		A temperature range of +/- 1 degree does not reflect the harmonised pharmacopeial parameters for dissolution, which tolerates 37 +/- 0,5 °C. **Proposed change:** Harmonise temperature ranges with pharmacopeial standards.
203	4	**Comment:** The agitation rate with paddles should be allowed to be above 50 rpm (i.e. at 75 rpm) if necessary to overcome product-related hydrodynamic effects (e.g. coning) and when baskets at 100rpm does not overcome such phenomena. This is frequently observed when an insoluble, dense filler (e.g. granular grades of microcrystalline cellulose or dicalcium phosphate) is used in the product. Switching to basket may not be feasible as insoluble fillers also cause basket mesh blockage. Suggested change – allow agitation rates above 50rpm in certain circumstances. **Proposed change:** Agitation paddle apparatus: 50-75 rpm
207	3	**Comment:** It is noted that no buffer system is defined for pH 4,5 media, e.g. acetate or phosphate. **Proposed change:** The nature of buffer system used for pH 4,5 media should be defined to allow for acceptance of data within all ICH regions.
207-209	5	**Comment:** The requirement to use purified water as additional dissolution medium is unjustified. Purified water lacks buffering capacity and thus, in some instances, the pH of the medium may change and so influence the drug dissolution. Also, because purified water is not representative of the gastrointestinal environment (including ionic strength), it is not considered a physiologically relevant medium. The quality of water is known to vary among different laboratories and more importantly, it is not objectively defined for the use as dissolution medium. Overall, purified water has inferior properties as compared to compendial dissolution media. Thus, its use shall not be enforced unless it can be clearly proven that its performance as dissolution medium has major advantage over standard compendial buffers. We are not aware of any situations in which dissolution profiles generated in purified water provided any added value. **Proposed change:** The use of purified water should not be requested. "Three buffers: pH 1.2, pH 4.5, and pH 6.8. Pharmacopoeial buffers should be employed. Additional

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		investigation may be required at the pH of minimum solubility (if different from the buffers above). ~~Purified water may be used as an additional dissolution medium in some regions."~~
208	3	**Comment:** It is noted that dissolution at the pKa values of the API(s) is not explicitly listed here.
209	4	**Comment:** The current text suggests the use of water as a dissolution medium may be expected in some regions. **This is a significant concern.** Water as a medium is known to be an inconsistent medium, to be non-robust, to be subject to variability and absorption of CO2 from the air, all of which compromise dissolution consistency evaluation. The medium is also unbuffered and thus unlike the body organs involved in product dissolution and over-discriminatory to in vivo performance (e.g. donepezil tablets showed in vitro dissolution differences in water BUT products were bio-equivalent in vivo). Furthermore, the inclusion of such regional specific expectations is counter to the harmonisation intent of ICH guideline development and should be avoided whenever possible. **Proposed change:** Please remove the expectation for testing in water.
		Proposed change: Delete: ~~Purified water may be used as an additional dissolution medium in some regions.~~
209	8	**Comment:** "*Purified water may be used as an additional dissolution medium in some regions*." Remove the sentence regarding the use of purified water. Water is a poor mimic of the gastrointestinal tract, and its lack of buffer capacity often leads to artefactual in-vitro variation. **Proposed change:** Remove, "Purified water may be used as an additional dissolution medium in some regions."
211	2	**Comment:** No flexibility is allowed in agitation speed. It should be possible to use other speeds than stated, if justified. This is also in accordance with *USP <1092> The dissolution procedure: Development and validation* and *Ph. Eur. 5.17.1 Recommendations on dissolution testing*.

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		Proposed change: Rephrase to: "paddle apparatus - 50 rpm initially, increase if justified"
211	3	**Comment:** The term "should be filtered during collection" is not very precise. **Proposed change:** Amendment to include filtration through a suitable pore size and necassity for filter validation studies.
211	4	**Comment:** The statement that a sample should be filtered is only relevant in some testing apparatus. When using fibre optic technology and measuring the content of dissolved drug substance in-situ in the vessel, samples need not be filtered **Proposed change:** Delete ~~samples should be filtered during collection~~
212	6	**Comment:** In our opinion, the use of enzymes should be allowable, if justified, when gelatin is used, regardless of cross-linking. **Proposed change:** We propose deleting the following part of the sentence "~~where cross-linking has been demonstrated~~".
214	4	**Comment:** The paddle apparatus should be the preferred apparatus. At 50 rpm high variability of the individual test specimens is often obtained due to the flow characteristics in paddle apparatus at this low agitation speed. To avoid these artefacts paddle speed can be increased up to 75 rpm. In those cases it is beneficial to use the paddle apparatus at 75 rpm than to change to the basket apparatus at 100 rpm, because the basket can have a different mechanical influence on the formulation. The use of a peak vessel can also be an option to avoid these artefacts. **Proposed change:** When high variability or coning is observed in the paddle apparatus at 50 rpm, the use of the basket apparatus at 100 rpm is recommended. Alternatively it is possible to increase the paddle speed to 75 rpm with justification. Peak vessels in the paddle apparatus can be used as alternative option in these cases.
214-215	8	**Comment:** "*When high variability or coning is observed in the paddle apparatus at 50*

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		rpm, the use of the basket apparatus at 100 rpm is recommended." Paddle speeds of up to 75rpm should be allowed in cases where coning (an in-vitro artefact) prevents complete dissolution. This is frequently observed when an insoluble, dense filler (e.g. granular grades of microcrystalline cellulose or dicalcium phosphate) is used in the product. Switching to basket may not be feasible as insoluble fillers also cause basket mesh blockage. **Proposed change:** "When high variability or coning is observed in the paddle apparatus at 50 rpm, the use of the basket apparatus at 100 rpm or paddles at 75 rpm is recommended."
214-216	1	**Comment:** When high variability or coning is observed in the paddle apparatus at 50 rpm, the use of the basket 214 apparatus at 100 rpm is recommended. Additionally, use of sinkers in the paddle apparatus to 215 overcome issues such as coning may be considered with justification. Can we use the PEAK vessels for improving hydrodynamics to avoid the risk associated with Coning effect
214-216	2	**Comment:** The first choice in case of coning would normally be to introduce gradually increase of paddle speed and visually observe the physical behavior of the tablet/disintegrated material in the vessels. Together with these observations, the dissolution profiles and the Standard Deviation levels must be evaluated. The selected rpm level should be justified by the dissolution data (focusing on mean dissolution profiles and SD-levels) and supported by visual observations/pictures, describing a testing system providing proper wetting of the tested dosage units. In case of coning when using paddle 50 rpm, the introduction of basket 100 rpm is normally not the primary choice for overcoming this undesirable phenomenon. When testing in baskets, it is not possible to register whether the desired effect of eliminating coning has been obtained. Sinkers are normally not used for eliminating coning either – on the contrary the presence of sinkers normally decrease the physical movement of the disintegrated tablet material, when operating at low agitation levels, hereby actually making the coning even worse.
215-216	4	**Comment:** Sinkers are used to prevent dosage forms floating or for normalising the position of non-disintegrating dosage forms. Replace coning with floating, sticking or coning as sinkers are typically used to reduce the impact of sticking and floating. **Proposed change:** "Additionally, use of sinkers in the paddle apparatus to overcome issues such

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		as floating, sticking, coning may be considered with justification."
221	4	**Comment:** For situations where one product has rapid dissolution and the other has very rapid dissolution it is currently mandated to perform f2 testing. This is considered unnecessary as a highly soluble compound should still demonstrate similarity in vivo with either release profile. As long as the drug product meets a greater than or 85% at 30 minutes gastric emptying will be the rate limiting step for absorption, and normal inter-and intra-individual variability in gastric emptying will be greater than the dissolution rate differences so all products dissolving in the period to 30mins will be equivalent. **Proposed change:** Remove need for f2 testing (a single dissolution acceptance criteria of greater than or equal to 85% in 30 minutes will assure product quality for a Class 1 product). **IF SIMILARITY COMPARISON IS TO BE KEPT AS AN EXPECTATION (EFPIA CONSIDER SUCH COMPARISON SHOULD NOT BE NECESSARY FOR CLASS 1 API CONTAINING PRODUCTS)** the guidance should allow the use of parametric tests (e.g. bootstrapping or 2 one sided T test =- TOST; the multivariate model from FDA guidance Dissolution Testing for IR Solid Oral Dosage Forms) in cases where it is not possible to use the f2 test (for example, in case of high variability in dissolution). From a statistician's perspective it is hard to understand why a study should automatically result in a negative study result independent of the profile similarity of both products only because the variability is above a certain threshold. In case of high variability what is needed is stats approach to handle the risks of a false similarity decision caused by data variability is a suitable statistical method (and maybe a suitable sample size). In the literature there exist statistical methods which, in contrast to f2, satisfactorily control the type I error (i.e. a false decision in favour of similarity) and additionally exhibit a sufficiently high statistical power. If it is not intended to recommend a specific statistical method one could use a statement as e.g. given in the EMA guideline: statistical methods used to "demonstrate dissolution similarity are considered acceptable, if statistically valid and satisfactorily justified." (This would allow approaches other than f2 comparison). **Proposed change:** Add after 240: „In case the Coefficient of variation is too high, a suitable statistical method accounting for inherent higher dissolution data variability may be used, if justified"
222	8	**Comment:** f2 test is also required in the case where both products have rapid dissolution.

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		Therefore, the sentence should be modified as proposed. Moreover, a **decisional tree** would make this easier to understand. **Proposed change:** "In cases where **either** one product has rapid dissolution and the other has very rapid dissolution**, or both products have rapid dissolution**, statistical similarity of the profiles should be demonstrated as below."
233	5	**Proposed change:** For f2 evaluation, we would propose "not more than one mean value of ≥ 85% dissolved for BOTH products", instead for EACH product. To support this, we have created hypothetical data. Please note the following example: **Time [min]** / **Test** / **Reference** 0 / 0 / 0 5 / 83 / 80 10 / 86 / 83 15 / 86 / 84 20 / 87 / 85 30 / 88 / 86 45 / 89 / 87 60 / 90 / 88 f2 / 78.87 f2 calculation presented above is done according to approach described in the US FDA guideline, since it is not possible to calculate f2 according to the approach established in the ICH guideline. **Proposed change:** Not more than one mean value of ≥85% dissolved for both of the products.
238-239	2	**Comment:** In case of too high dissolution data variability, an f2-based procedure for profile similarity testing is not applicable. However, in such cases dissolution similarity could be evaluated by using other statistically based evaluation methodologies (e.g. point-to-point comparison by t-test using increased number of replicates, hereby increasing the statistical test strength and

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		making a valid comparison test possible). **Proposed change:** It is proposed to change l. 239-240 and add the following: ……f2 calculation is considered not accurate and reliable ~~and a conclusion on similarity in dissolution cannot be made~~. *In such cases dissolution similarity could be evaluated by using other statistically based evaluation methodologies, e.g. point-to-point comparison by t-test using increased number of replicates.*
238–240	5	**Comment:** When the variability of the individual dosage units at each sampling time is higher than acceptable for f2 calculations, several alternative methods, e.g. the confidence interval of the f2 similarity factor or the Mahalanobis distance or multivariate statistical distance based on model independent (or model dependent) approaches may be used and are described in the scientific literature (e.g., Cardot et al., AAPS J 2017; 19(4): 1091-1101; Paixão et al., Eur J Pharm Biopharm. 2017; 112: 67-74; Costa & Sousa Lobo, Eur J Pharm Sci. 2001; 13(2): 123-33). The EMA recently (July 2018) issued document 'Question and answer on the adequacy of the Mahalanobis distance to assess the comparability of drug dissolution profiles (EMA/810713/2017)', where the bootstrapping methodology to derive confidence intervals for f2 is considered to be the preferred method over Mahalanobis distance. Finally, in a survey among the regulators joining the Bioequivalence Working Group (BEWG) of the International Generic Drug Regulators Programme (IGDRP), the use of alternative approaches in case of high variability has been accepted by all participants except by one (van Oudtshoorn et al., J Pharm Pharm Sci 2018, 21(1): 27-37). Therefore, even if cases of high variability in dissolution will not be that frequent in the field of BCS-based biowaivers, the use of alternative methods shall be considered. If the coefficient of variation is too high for proper f2 calculation according to the criteria laid out in the guideline, alternative methods which are considered acceptable in other places as well according to the current regulatory thinking should also be used here. **Proposed change:** The use of resampling techniques to derive confidence intervals for f2 and/or other alternative methods shall be enabled even if cases of high variability in dissolution will not be very frequent.
240	3	**Comment:** In contrast to the EMA BE guideline Annex II this guideline solely refer to the f2 value concept for demonstration of dissolution profile similarity, whereas other statistical concepts, e.g. Mahalanobis distance or Bootstrapping are widely used and accepted by authorities. **Proposed change:**

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		Inclusion of other statistical tools.
241		**Comment:** If a BCS 3 containing product cannot meet the criterion of both the test and reference displaying very rapid in vitro dissolution in all pHs then the next step expected is to evaluate them in a BE study. This is considered to be conservative as the low solubility may be very pH dependent and slow dissolution at high pH may not be relevant in vivo. It would be more appropriate to evaluate the similarity of test and reference statistically under the conditions suitable levels of release are achieved to judge the equivalence of the two products, rather than require a bioequivalence study. It can be difficult to conduct BE studies for some medicines – e.g. oncology products with intrinsic toxicity and finding ways to obviate the need for BE studies by in vitro, modelling and prediction. **Proposed change:** Recommend changing to "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. If this criterion is not met, statistical similarity of the profiles should be demonstrated.
250	3	**Comment:** The current text leaves room for interpretation, because "dissolution profiles" could refer to both products (in one mdium) or all media. **Proposed change:** Clarification that each strength needs to be compared in all media.
250-251	1	**Comment:** 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. *Test and reference product dissolution profiles are compared at each strength* - The situation where the new strength/s are proposed for the drug substance possessing the linear pharmacokinetics
250-251	4	**Comment:** The text states that all strengths need to be separately evaluated when multiple strengths exist. This is considered to be overly conservative. For example, if the products are common in blend and the PK of the product performance is linear over the dose strengths, additional dissolution

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		comparison should not be necessary. We recommend allowing the application of BCS based biowaiver to other strengths using either the dissolution comparison of the highest strength (if strengths are compositionally similar and PK is linear across the range) and / or using bracketed based approaches (test highest and lowest strengths). **Proposed change:** 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. When the drug products are common in blend and the PK of the product performance is linear over the dose strengths, the application of BCS based biowaiver to other strengths can be justified by using either the dissolution comparison of the highest strength and / or using bracketed based approaches (test highest and lowest strengths).
250-251	5	**Comment:** Please consider allowing the use of a bracketing approach for BCS-based biowaivers by testing only the highest and lowest strength in dissolution as long as these two strengths cover as well the extremes in composition. **Proposed change:** If use of a bracketing approach is considered acceptable, the wording should be modified accordingly.
250-251	7	**Comment:** It is suggested by the draft ICH guideline that BCS-based biowaiver approach should be applied for each strength when more than one strength exists. However, we are of the opinion that there are situations, such as, unavailability or limited availability of each reference product strength, where alternative comparisons should be also accepted. In fact, recent regulatory approvals accepted alternative comparisons e.g. testing at the same dose using a score line, if present and approved as an option to divide the tablet into two equal doses used as a half dose. **Proposed change:** We suggest to extend the lines 250 – 251 with the acceptable alternative as follows: In case of limited availability of particular strength of reference product on the market, it is acceptable to use an alternative comparison, using half of the approved strength, if the reference product has a score line which is approved to divide the tablet into equal doses used as a half dose in line with the posology of the product.
253-257	5	**Comment:** The requirements detailed here seem to go beyond the scope of a BCS-based biowaiver.

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		Proposed change: Eliminate the paragraph: "The applicant should … applicant derived studies".
263–264	5	**Comment:** The draft ICH guideline asks to report: '… all excipients, their qualitative and, if possible, quantitative differences between the test and reference products'. Due to the requirements on similar amounts of all excipients between test and reference product in case of BCS class III drugs, the use of the phrase 'if possible' on line 263 does not seem to be appropriate. Comparison of quantitative composition and demonstration of similar amounts for each excipient is considered decisive for accepting or rejecting the application containing a BCS class III drug. **Proposed change:** To replace the phrase 'if possible' on line 263 by more suitable wording, e.g. 'if applicable' or 'if required'.
Annex I	3	**Comment:** For the sake of clarity the incubation temperature for Caco II experiments should be included in this Annex. **Proposed change:** Inclusion of incubation temperature.
Annex I 284 ff	4	**Comment:** The comments on the permeability annex have the same themes as those for permeability chapter 2.2. in the document (i.e. the use of cell lines other than Cacco-2, and the use of other in vitro methods to determine permeability).
Annex I 307	5	**Comment:** Examples of compounds with proven zero permeability are provided later in Table 2 and can be referred to in this sentence, similar to what was mentioned in line 300. **Proposed change:** Add in reference to Table 2 in line 307.
Annex I 324-327	2	**Comment:** pH is not specified. **Proposed change:** Specify the pH that is acceptable in the apical and basolateral chamber for Papp determinations and efflux calculations.
Annex I 354	8	**Comment:**: In the Table 2 "Examples of model drugs for permeability assay method

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		validation," 3 permeability levels are defined (high, moderate and low), while there are only 2 levels for BCS. **Is it possible to link the 3 levels of table 2 and the 2 permeability BCS levels? If so, this should be specified in the guideline.**