EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 July 2017
EMA/CHMP/CVMP/QWP/257305/2017
Committee for Medicinal Products for Human Use (CHMP)/ Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on "Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action" (EMA/CHMP/CVMP/QWP/37330/2016)

Original title: "Dissolution specification for generic oral immediate release products"

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

Stake holder no.	Name of organisation or individual
1	International Consortium For Innovation & Quality in Pharmaceutical Development
2	AESGP (Association of the European Self-Medication Industry)
3	American Association of Pharmaceutical Scientists
4	AstraZeneca R&D
5	Bayer AG
6	Commission on Human Medicines, Chemistry, Pharmacy and Standards Expert Advisory Group
7	EDQM (European Directorate for the Quality of Medicines & HealthCare)
8	EGGVP – European Group for Generic Veterinary Products
9	HELM AG
10	IFAH-Europe
11	International Pharmaceutical Federation (FIP)
12	Jyoti Tiwari
13	Medicines for Europe
14	Michal Ostrowski Ph.D.
15	Sanofi
16	SciencePharma (Poland)
17	SUN Pharma
18	Synthon BV
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1. General comments – overview

Comment no.	Stakeholder no. *(See cover page)*	General comment (if any)		Outcome (if applicable)
1	2	The reflection paper should include discussion on applicability of recommendations for variations (e.g. change in formulation or manufacturing process) requiring comparative dissolution testing. It is important to acknowledge that registered dissolution method considered meeting the discriminatory requirements can help reduce unwarranted studies on healthy volunteers, if justified. It is in line with "*the next best approach is to reproduce the rank order between batches and discrimination of batches with different quality attributes without knowing about the in vivo relevance of these differences*".		The primary focus of this document is not the post approval changes but the same principles could be applied post approval in variation procedures. In case of formulation or other changes please refer to the bioequivalence guidelines regarding in vivo bioequivalence requirements.
2	2	More guidance on suspension products would be helpful. Much of current guidance refers to solid dosage form, which does not necessarily cover challenges faced with suspension products.		Out of scope of this reflection paper; see new title.
3	5	When setting a specification with Q=85% one should consider that at stage 1 the limit is for each single value is Q+5 %: That means each single value has to be		Criterion of Ph.Eur. reflects the mean value of 12 units.

Comment no.	Stakeholder no. *(See cover page)*	General comment (if any)		Outcome (if applicable)
		above 90%. This limit interferes with the acceptance criteria for content uniformity. Therefore the limits for Q should not exceed 80%.		
4	6	At its June 2016 meeting, the Chemistry, Pharmacy and Standards Expert Advisory Group of the Commission on Human Medicines reviewed the reflection paper and has the following general comments: 1 We congratulate the Rapporteur and drafting group in preparing a clear and well-written reflection paper. 2 The advice provided in the reflection paper is appropriate. 3 The standardisation of time points to 15, 30, 45 minutes is acceptable. 4 A shortest time set point is 15minutes is practical and acceptable.		Thank you. Thank you. Thank you. Thank you.

Comment no.	Stakeholder no. *(See cover page)*	General comment (if any)		Outcome (if applicable)
		5 Consideration should be given to upgrading the reflection paper to a guideline, to strengthen its recommendations to requirements i.e. a dissolution test should be developed as stated, unless otherwise justified.		It is a reflection paper.
5	7	The section “expression of dissolution specifications” of conventional-release dosage forms in General Chapter 5.17.1 of the Ph. Eur. should not be understood as a definition of IR dosage forms stricto sensu. We have the impression that there is a misunderstanding, leading to the use of the specification given therein as a definition throughout the entire reflection paper (See response in comments on lines 45-47 (49-51), 217-221 (248-251) and Annex). In line with the definition of “immediate release” provided in ICH Q6A “…. allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug”, the Ph. Eur. glossary defines a conventional-release dosage form as *“a preparation showing a release of the active substance(s) which is not deliberately*		Comment acknowledged.

Comment no.	Stakeholder no. *(See cover page)*	General comment (if any)		Outcome (if applicable)
		modified by a special formulation design and/or manufacturing method".		
6	11	It is noted that the period for comments on this document is quite short – a mere three months. In particular, this is of concern because the comment period ends on 13 August 2016 and, August is often a "dead" month in Europe because of holidays etc. Consequentially, comments really need to be in to the EMA by the end of July, which is a little over two months' consultation. The title should be changed to: "Reflection paper on the dissolution specification for generic immediate release oral solid dose forms", because the guideline relates to this type of oral products. When setting a specification with Q=85% one should consider that at stage 1 the limit is for each single value is Q+5 %: That means each single value has to be above 90%. This limit interferes with the acceptance criteria for content uniformity. Therefore, the limits for Q should not exceed 80%.		Accepted. See response to comment 3.
7	13	Medicines for Europe appreciates the development of a 'reflection paper on the dissolution specification for		Thank you.

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		generic oral immediate release products', as there has not been guidance on this specific topic before in the EU. We hope that this reflection paper will facilitate the setting of dissolution specifications. However, the use of this reflection paper should be considered a framework in which to guide development of a dissolution method and specifications and It should not be considered mandatory to adhere to every point in this reflection paper. It is important to note that a method is developed for a particular formulation in order to detect differences in batches of that formulation. A method should be developed to give a true dissolution profile rather than an artificial one based on general pre-defined criteria (e.g. for products that display coning or sticking, it is better to increase rpm to get adequate dissolution which allows like-for-like comparison of different batches via a method proven to be discriminatory, than be forced to use an inferior method at lower rpm purely because lower rpms are considered inherently more discriminative). Therefore it is assumed the points in the guide should be considered as best practice, rather than to be enforced		A reflection paper is meant to convey the current thinking.

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		as a whole for every application.		
8	13	Recommendations provided within this paper should apply only for newly developed products submitted from the time the Reflection paper becomes effective. This document is considered to consolidate best practices. For products which are already approved in one or more European countries (i.e. DCP, MRP etc.), the approved dissolution method will have already undergone a comprehensive assessment to ensure fitness for purpose. It should therefore be acceptable in any additional DCP/MRP/repeat-use/duplicate procedures, even if not all requirements of the new reflection paper are fulfilled. It should not be in the sense of the new reflection paper that additional development work (e.g. at 50rpm) is needed for a generic product which was already approved for several years and is submitted to additional countries.		Agreed; the RP is not intended to be used retrospectively where dissolution methods and specifications have already been evaluated for suitability.
9	13	The reflection paper does not cover requirements for locally applied locally acting products. It is requested that requirements for these products are included, or the scope altered to specify these are excluded from the		Locally applied locally acting (LALA) products are out of scope of the RP; title of the RP has been changed.

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		paper.		
10	13	The current EU reflection paper applies one set of conditions to set specifications, regardless of BCS class. The FDA draft guidance on this topic for BCS Class 1 and 3 Drugs specifies that the drug product dissolution specification will depend on the BCS class. Within the guide general specification requirements are given, but these differ depending on BCS Class. The intention of the FDA guidance is to describe when a standard release test and criteria may be used in lieu of extensive method development. This standardized approach is proposed for BCS class 1 and 3 drugs, which are considered to be relatively low risk regarding the impact of dissolution on performance. In general, it is requested that EU and US requirements are harmonised on this topic as currently the proposed EU reflection paper differs from the draft FDA paper in approach.		The objective of the Reflection Paper is to harmonise the way specifications are set based on European requirements. This Reflection Paper makes recommendations regardless of the BCS class.
11	13	It is suggested in the Reflection paper that the rank		It is not the intention to ask for new *in vivo* data

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		order of *in vitro* and *in vivo* results should be compared. In case the rank order of *in vitro* and *in vivo* results do not match it is suggested that the dissolution method should be further optimized to reflect the *in vivo* trend. For many immediate release generic products, with often only one pivotal BE study performed (only one test and one reference sample tested *in vivo*), this approach is not realistic. This approach is more suited towards Originator products with multiple clinical studies, but this reflection paper is for generic products only. The major target of a discriminatory dissolution method should only be batch to batch consistency and not simulation of *in vivo* results. It is requested that this concept and its inclusion in the reflection paper is reconsidered, as it is not applicable to the vast majority of generic immediate release products for which this paper is intended. If this concept is retained, it should be made explicitly clear that this principle will only be applicable if more than one clinical study is performed due to the requirements of the bioequivalence guidance (and as		but just look at the data already generated.

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		such the data is available to make analysis of rank order possible) and that there is no expectation to generate extra *in vivo* data in order to fulfil the proposals or create the rank order. This is not only important from ethical aspects (i.e. avoidance of additional BE studies), but also to enable/ motivate companies to continue with generic developments and later market generic products at a suitable price		
12	13	As stated within the scope, this reflection paper does not discuss the dissolution tests required in support of biowaiver of strengths. In Lines 38-39 (*40-41*) it is stated that in the last few years the suitability of dissolution specifications has been discussed in MAAs, some leading to referrals. In this period there have also been significant discussions during MAAs regarding the dissolution method used to support a biowaiver of strengths (e.g. in terms of rpm/volume of method). It is requested to take this opportunity to also issue separate guidance on this topic, which has also led to MAA approval delays, and will allow harmonisation of opinion across the National Competent Authorities.		Biowaiver of strengths is a different topic. The RP concerns the setting of specifications for new products as per the title.

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13	15	In chapter 1.2. of the draft guideline, subchapter 1.2.1 to 1.2.2. (lines 104 to 172, *115-203*), the discriminatory power of dissolution release method is discussed in connection to the results of bioequivalence study/ies. Notably, it is expected that dissolution release method will be able to perfectly mimic the in-vivo results. This requirement basically assumes a direct linear relationship between in-vitro and in-vivo data to be reflected by one single time point measurement (i.e., the amount of active substance dissolved at specified time point). However, the in-vitro/in-vivo correlation (IVIVC) is a more complex and often very challenging task that requires considerably more data to be analysed. Also, there will be a limited number of examples where one particular dissolution method will mimic the in-vivo behaviour; often dissolution at several media is needed to find an appropriate correlation. According to our experience, it will be generally difficult (or even impossible in some cases) to develop a release method capable to discriminate in the manner as proposed by the draft guideline. In summary, the purpose of the release method should be to identify problems during the manufacturing		Refer to response to comment #11.

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		process and limit the dissolution profile close to the biobatch, where the bioequivalence was proven.		
14	17	Whether this is applicable to the drug products which are available in the OGD (Office of Generic Drugs) dissolution database.		The methods mentioned in the OGD database may be used as a starting point for the method development. However the selection of dissolution method should be justified by development data and not merely by reference to the OGD database.
15	16	It is recommended stating that the range of required studies on development of the dissolution test conditions and discriminatory power is dependent on the proposed specification acceptance criteria, i.e. the more restrictive acceptance criteria are proposed, the less data may be needed.		Not agreed. The amount of development data for the dissolution test should not be correlated to the specification limit itself.
16	19	The draft reflection paper enforces that the dissolution release method has to be capable of detecting the in-vivo difference. In some sections such as 1.2.1 or 1.2.2, based on the currently proposed wording, it is expected that there will be a simple linear relationship between the amount of API dissolved at a single time point and the in-vivo data represented either by pharmacokinetic		This paper is not about IVIV correlation but about selection of meaningful dissolution text conditions and specifications.

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		parameters or test-to-reference ratios (with confidence intervals). Overall, this expectation represents a simplification of in-vitro / in-vivo relationship. In the section 1.2.2, a direct relation between the in-vivo criteria such as test-to-reference ratio and in-vitro dissolution is required, leading to construct a relationship on a single point. Apart from the fact that no predictability of the model could be built, many assumptions are taken: (i) the critical quality attributes are known for the test (expected to be the case) but also for the reference (not true as that is not the sponsor's formulation), (ii) the dissolution test shows exactly the right discriminatory power and is not over discriminatory, (iii) the dissolution specifications build on this approach are relevant for stability, (iv) the bioequivalence (BE) study is not performed in fed conditions (mandatory for drugs that must be given with food) as in this case the in-vivo pharmacokinetic (PK) parameters could depend of the gastric emptying time, biliary secretions (= physiology) and not on the formulation, and finally, (v) in case of fasted BE study, the limiting factor between the two formulations is not a physiological factor such as gastric emptying (influence of stomach residence time together with a favourable pH for dissolving the API) or a late window of absorption. In		

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		those cases the rate of absorption will not be linked with the formulation that disappears long time before reaching the site of absorption. Obviously, the above listed assumptions will be violated in many cases. In most cases, the correlation between in-vitro and in-vivo data is more demanding not only by the amount of data to be generated, but also by their mathematical evaluation. A direct correlation of pharmacokinetic profiles and dissolution data may not be always suitable. Plasma concentration curve represents sum of several processes including absorption, distribution, elimination / excretion. Preferably, the in-vivo absorption profiles calculated by deconvolution are being correlated to in-vitro data. The in-vitro / in-vivo correlations usually need the analysis of entire dissolution profile (at different time points), not interpretation at one single time point. Also, the choice of in-vitro sampling times should take into the consideration that the data will be combined with in-vivo data (absorption profiles). In summary, the draft reflection paper approach of a simple relationship between the in-vitro dissolution and pharmacokinetic parameters (or test-to-reference ratios) lacks all these considerations.		

Comment no.	Stakeholder no. *(See cover page)*	General comment (if any)		Outcome (if applicable)
		It should be mentioned again that not all bioequivalence studies will be conducted in fasting state. For some products (in line with the reference product SmPC recommendation), only fed studies will be conducted. This fact will complicate evaluation of any in-vitro / in-vivo relationship, for particular reasons described above. In conclusion, the purpose of the release method should be to identify problems during the manufacturing process and maintain the dissolution limits for production batches in order to reflect the key quality attributes of the biobatch.		

2. Specific comments on text

**the line numbers correspond to the original paper published for consultation; the respective lines numbers in the final paper are shown in parentheses.*

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
1	41 *(45)*	13	**Comment:** The term “drug with very narrow therapeutic ranges” does not seem to be well-defined. It appears that this is something beyond the usual “narrow therapeutic index” drugs, though a clarification on this would be considered useful.	Definition elsewhere.
2	45 - 46 (49-51)	1	**Comment:** Definition of immediate release not consistent with other typically accepted definitions such as at least 80% (Q) of the active substance dissolved within 60 minutes or less. **Proposed change:** At a minimum, the definition for immediate release should be extended to 60 minutes.	Not agreed.
3	45 (49)	7	**Comment:** It is not clear what the 75 % release refers to. It is recommended to add Q in brackets. The internationally harmonised Ph. Eur. chapter 2.9.3 does allow individual tablets to release less than Q. **Proposed change:** … is identified as at least 75 % (Q) of the active substance …	Added [Q].
4	45-47 (49-51)	4	**Comment:** In the Ph Eur 5.17.1 referred to, it actually says for conventional-release dosage forms that the acceptance criteria at level S_1 are at least 80 per cent of the active substance is released within a specified time, typically 45 min or less.	Wording aligned with Ph. Eur.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Proposed change (if any): correction in accordance with Ph Eur 5.17.1	
5	45-47 (49-51)	7	**Comment:** Ph. Eur. 5.17.1 states that conventional-release dosage forms, when tested under reasonable and justified test conditions, release **in most cases** 80 per cent at stage S_1 (equals Q = 75 %) within **typically** 45 minutes or less. There are immediate release finished products approved, e.g. by the European Commission, which have a release specification at 60 minutes. This can be due to the fact that it can be more appropriate to avoid the use of surfactants for poorly aqueous-soluble active substances and to accept a longer release to have a more discriminatory method. With the current wording manufacturers might tend to use a less discriminatory method just to meet the limit of 45 minutes. **Proposed change:** As the first sentence (lines 45/46 (49/50)) is not aligned with the statement in 5.17.1, we suggest to either delete the entire paragraph (lines 45-47 (49-51)) or the second sentence linking the specification to 5.17.1. (lines 46/47 (49/51)).	Comment considered.
6	45-47 (49-51)	13	**Comment:** It is noted that there is no strict definition in the Ph. Eur. for immediate release products. The actual statement in 5.17.1 suggest that more than 45 minutes can also be accepted ("**typically** 45 min or less"), therefore a strict limit at 45 minutes is not considered justified. See also comment on lines 218-221 (249-251). **Proposed change (if any):**	See response in comment #5.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			In the context of this reflection paper immediate release is identified as at least 75% of the active substance is dissolved within **a specified time (typically** 45 minutes **or less)**. This derives from the Ph. Eur. (5.17.1) recommendation for conventional release dosage forms.	
7	44-58 (48-62)	9	**Comment:** Scope is defined on batch to batch consistency, but the following chapters are focusing on bioequivalence correlation. **Proposed change (if any):** The following chapters should focus on quality aspects.	The intention of this paper is the specification to derive from the biobatch.
8	51 (55)	13	**Comment:** In line with the general comment above, it should not be mandatory to apply this paper retrospectively for products where a dissolution method and specifications have already been developed and approved in the EU in previous applications. **Proposed change (if any):** […] Where applicable, this reflection paper should be read in conjunction with the principles of relevant guidelines listed as references. **This guide does not need to be applied retrospectively, where a dissolution method has already been developed and specifications approved via previous Marketing Authorisation Applications in the EU.**	Not retrospectively applicable.
9	53 (57)	5	"bioinequivalence" rather than "bioavailability"	Accepted.
10	53	11	"bioinequivalence" rather than "bioavailability"	Accepted.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
	(57)			
11	59 (63)	3	**Comment:** Include additional definitions **Proposed change (if any):** Please add the definition of bad batches and side batches	Explained in lines 126 (143) and 145 (76-79). Bad batch explained in lines 143-147 and side batch definition included.
12	60-62 (64-66)	13	**Comment:** Specifications as per ICH are defined as a combination of method and acceptance criteria. The reflection paper however only focusses on acceptance criteria in its definition of specifications. It is however important to also take the method into consideration as the percentage dissolved is much dependent on the used method. (media, agitation speed, and apparatus). **Proposed change (if any):** Please define specification as per ICH	Refer to chapter 1.1 and 1.2.
13	64 – 67 (68-71)	1	**Comment:** Discriminatory power is also the ability of the test procedure to discriminate for changes in the product due to sensitivities to certain storage conditions (e.g., high temperature and humidity). **Proposed change:** Update section accordingly.	No change.
14	64-66 (68-70)	16	Reference to critical process parameters and critical material attributes are unclear in the definition of the discriminatory power. **Proposed change:** *The discriminatory power is the ability of a test procedure to discriminate between batches with <u>different in vitro release characteristics</u> ~~respect to critical process parameters and /or critical material attributes~~ which may have an*	No change.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			impact on the bioavailability.	
15	66-67 (70-71)	9	**Comment:** As the scope of a generic development is to obtain an essentially similar product, identification of non-bioequivalent batches is not in focus. Scope of a suitable dissolution method/specification is to identify potential differences between batches with regard to changed processing conditions or changed material characteristics (PSD) but not a decision on bioequivalence. **Proposed change (if any):** Deletion of the last sentence in this paragraph.	No, this is the spirit of the RP.
16	66-67 (70-71)	13	**Comment:** While it is acknowledged that ideally the method should detect all non-bioequivalent batches, it is also reasonable to expect that most, if not all bioequivalent batches should pass, i.e. the number of falsely rejected batches remains low and the method should not be over-discriminatory. In our opinion the prerequisite to an ideally discriminatory dissolution method is the existence of an IVIVC, but it should be accepted that this is not normally possible for simple generic immediate release products, where there may only be 1 pivotal biostudy.	No change.
17	66-67 (70-71)	19	**Comment:** Strictly speaking, the term non-bioequivalent applies only to products for which bio-in-equivalence has been proven. In all other cases, bioequivalence has been or has not been proven, for example due to inadequate number of subject. It should be recognized that not all studies are conducted with the aim to prove bioequivalence. Typically, pilot studies to assess the bioavailability of several lead prototypes are not powered sufficiently to	This is the definition of the discriminatory power and not the requirement.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			demonstrate bioequivalence. As an example, in a pilot bioavailability study test-to-reference ratio could be =1.00 but calculated 90% confidence intervals will range from 0.70 to 1.43 due to inadequate number of subjects. Therefore, any interpretation towards passing or not-passing acceptance criteria and link to in-vitro dissolution would be misleading. **Proposed change:** Delete corresponding wording from lines 66 to 67 (70 -71).	
18	69-71 (73-75)	10	**Comment:** It is not clear what "Bioequivalence" means in this context, whether it corresponds to in vivo or in vitro equivalence study (experimental dissolution study). **Proposed change:** Our understanding is that it corresponds to **in vivo study**. Please amend the definition to clarify this notion.	Word "Bioequivalence" is deleted.
19	73 (81)	11	**Proposed change:** Dissolution test method	Accepted.
20	74-103 (82-114)	9	**Comment:** Recommendation for other pharmacopeia apparatus is missing.	Agree to include recommendation on basket-apparatus.
21	74 (82)	12	**Comment:** Volume of dissolution media should also be discussed under dissolution method development. **Proposed change (if any):** As the heading mentions development of dissolution method, discussion on volume of dissolution media should also be included here.	See lines 88 and 90-91.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
22	75 - 77 (83-85)	13	**Comment:** 'altered' is in the wrong place **Proposed change (if any):** A dissolution procedure intended to be used as a routine control test for immediate release drug products should be robust, reproducible and discriminatory in order to assure a consistent product quality *and to detect product quality attributes that, if altered, may affect the in vivo performance.*	Accepted.
23	81-82 (90-91)	1	**Comment:** Statement that " it should be ensured that sink conditions are met" is not consistent with other guidelines (see FDA Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Form, Appendix A) **Proposed change:** Reword this sentence for example: "Sink conditions should be met, but are not mandatory."	Accepted. See lines 90-91.
24	80-81 (88-91)	7	**Comment:** In addition to the composition of the dissolution medium the choice of an appropriate volume and its influence on discriminatory power should be considered during development of the method. A standard recommendation (e.g. 900 mL) might be given as for stirring speed (see lines 88-89 98-99). **Proposed change:** Selection of a suitable dissolution medium **and volume** should be based …	Comment considered; refer to comment #21. See also lines 99-100.
25	80-82 (88-91)	2	**Comment and rationale:** Reference to "sink conditions" should be avoided. Strict adherence to sink conditions can undermine discrimination for poorly soluble drugs, and there is	See response in comment #23.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			confusion as to what term means. **Proposed change:** *"Selection of a suitable dissolution medium should be based on the physico-chemical characteristics of the active substance(s) and the intended dose range of the drug product to be tested.* ~~***It should be ensured that sink conditions are met.***~~ *"*	
26	80-82 (88-91)	4	**Comment:** Dissolution medium should also be selected based on suitability for the entire drug product and not only limited to the Active Pharmaceutical Ingredient.	Acknowledged.
27	81-82 (90-91)	11	**Comment:** Sink conditions are appropriate in many cases, indeed. However, dissolution testing under sink conditions may not always be adequate to signal potential problems with in vivo BA. In some cases it can be an ideal test for setting specifications: - "enabling" drug products (they are considered IR products, and, therefore, are covered by this paper, based on the definition of IR products provided in lines) - lipophilic weak bases -amorphous active ingredients **Proposed change:** It should be ensured that sink conditions are achieved for the active substance, unless the use of non-sink conditions can be justified	See response in comment #23

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
28	80-82 (88-91)	12	**Comment:** Acceptable sink condition ranges should be specified. **Proposed change (if any):** Ph.Eur mentions acceptable sink conditions are achieved when the volume of dissolution medium is 3 to 10 times the saturation solubility of API. If any other criterion is there, this needs to be specified here so as to have clarity on agency's expectations.	Reference included.
29	80-82 (88-91)	13	**Comment:** first bullet point: according to our understanding the dissolution medium should not only be selected according to the physico-chemical characteristics of the active substance(s) but also of the formulation/ composition of the finished product/selected excipients as they also influence the release of the active substance into the dissolution medium.	Comment considered.
30	80-82 (88-91)	13	**Proposed change (if any):** It is proposed to change the sentence 'It should be ensured that sink conditions are met.' into 'Generally it should be ensured that sink conditions are met, *however, in some circumstances, it may only be possible to demonstrate discrimination by using non- sink conditions.'*	See response in comment #23.
31	82 (91)	13	**Comment:** Sink conditions should be clearly defined for the purpose of this guideline. E.P. general texts 5.17.1 for sink conditions mentions a range of 3-10 times the saturation volume, and this is not clear. For this reason, especially for poorly soluble substances, we believe that the discriminatory power should be the main target even if sink conditions criteria are not fully met. A similar provision is also mentioned in an FDA guidance document: Guidance for Industry; Dissolution Testing of Immediate Release Solid Oral Dosage Forms, page A-1 in Appendix A.	Reference included. See response in comment #28.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
32	81-82 (90-91) and 84-87 (93-96-)	13	**Comment:** In cases when surfactant is used for low soluble APIs: It is stated in the Reflection paper that the concentration of surfactant should be as low as possible and be justified by relevant solubility and dissolution data. It should be clarified whether the level of surfactant should be primarily chosen as the level of surfactant needed to meet sink conditions (at least 3x solubility) or as the lowest level needed to achieve complete dissolution (as these two are not always the same). In other words, is adding surfactant to achieve sink conditions acceptable even though complete dissolution profiles are achieved at levels of surfactant lower than sink conditions?	See lines 90-91.
33	83 – 87 (92-96)	13	**Comment :** For poorly soluble substances in several cases the use of a surfactant is also needed; the reflection paper does not give sufficient guidance on how to handle cases where there is a need to use a surfactant and if in these cases the discriminatory power or the sink conditions criteria should prevail. **Proposed change (if any):** We would also propose to state more clearly the acceptance criteria for using surfactant in dissolution medium.	See response in comment #23.
34	84 (93)	3	**Comment:** for medium selection is stated in line 81 (89) and 82 (90) that “it should be ensured that sink conditions are met” Would it be acceptable to use	See response in comment #23.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			sinking condition as a rationale for the addition of a surfactant **Proposed change (if any):** Please consider changing "The addition of surfactants should be avoided. When surfactants are used, for instance to achieve sink conditions for poorly aqueous-soluble active substances, the type…" to "The addition of surfactants should be avoided, unless necessary to achieve sink conditions. When surfactants are used, the type…".	
35	84 (93)	1	**Comment:** Statement that "the addition of surfactants should be avoided" should be modified since as stated in the next sentence the use of surfactants is appropriate in some circumstances. **Proposed change:** Recommend to change to "If sink conditions cannot be achieved using buffered aqueous medium, the addition of surfactants may be considered."	See response in comment #23 and comment #28.
36	83-85 (92-94)	2	**Comment and rationale:** Often surfactants cannot and should not be avoided. Surfactants are common because poorly soluble drugs are common. Use of surfactants is actually preferable to extremes of pH or addition of co-solvents. **Proposed change:** *"In general, an aqueous medium should be used and the pH should first be evaluated in the physiological pH range.* ***~~The addition of surfactants should be avoided.~~*** *When surfactants are used, for instance to achieve* ***~~sink conditions~~*** ***adequate release*** *for poorly aqueous-soluble active substances, the type of surfactant should be justified."*	Accepted. Replace sink conditions by adequate release.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
37	83-87 (92-96)	12	**Comment:** Use of Hydro-alcoholic dissolution media has not been discussed, whether acceptable or not? **Proposed change (if any):** In case of very low solubility drugs, whether use of hydro-alcoholic medium is allowed or not, needs to be clarified. This should be included as a ready reference in this guidance.	Hydro-alcoholic media may not be used in dissolution testing.
38	85 (94)	18	**Comment:** Could EMA explain how the nature of surfactant is expected to be justified? Will justification be sufficient based on the need to achieve sink conditions? Or is agency expecting that nature of the surfactant is discussed in terms of similarity in behaviour to natural biological surfactant in the GI tract (viz, bile salts)? **Proposed change (if any):** Not applicable	The justification is expected to be based on the need to achieve sink conditions.
39	88 (98)	5	"The development of methods using the paddle apparatus should start with a stirring speed of 50 rpm. Higher stirring speeds may be applied with an appropriate justification." Higher variability of the single test results are often observed at stirring speed 50 rpm due to coning. In most cases 75 rpm resolves this artifact. In most of the cases discrimination between batches can be improved by decreasing the variability at stirring speeds 75 rpm. Therefore, 75 rpm should be the preferred stirring speed for the paddle apparatus	Already mentioned in the existing text; lines 88-92 (98-101).

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Proposed change (if any): Stirring speeds of 50-75 rpm are mostly used for the paddle apparatus. Other agitation speeds are acceptable with appropriate justification.	
40	88 (98)	7	**Comment:** Important for development of a suitable dissolution procedure is in addition the choice of the apparatus to be used **Proposed change:** **The selection of a suitable apparatus should be evaluated.** The development of methods using …	See response in comment #20.
41	88 (98)	10	**Comment:** Only the "paddle apparatus" is specified, however basket apparatus can also be used and are not indicated here. When "basket apparatus is used, the stirring speed to be used is 100 rpm as indicated in the bioequivalence GL. **Proposed change:** Please modify the sentence to read: "The development of methods using paddle apparatus should start with a stirring speed of 50 rpm **(100 rpm in the case of basket apparatus)".**	See response in comment #20.
42	88 (98)	11	"The development of methods using the paddle apparatus should start with a stirring speed of 50 rpm. Higher stirring speeds may be applied with an appropriate justification." Higher variability of the single test results are often observed at stirring speed 50 rpm due to coning. In most cases 75 rpm resolves this artefact. In most of the cases, discrimination between batches can be improved by decreasing the variability at stirring speeds 75 rpm. Therefore, 75 rpm should be the preferred	See response in comment #39.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			stirring speed for the paddle apparatus. **Proposed change (if any):** Stirring speeds of 50-75 rpm are mostly used for the paddle apparatus. Other agitation speeds are acceptable with appropriate justification.	
43	89-92 (98-104)	2	**Comment and rationale:** It is balance of discriminatory power of test to product (desirable) versus the unhelpful discrimination to artifacts of test method that really matters. Avoid stating a desired paddle speed - it encourages development of inappropriate methods. **Proposed change:** ~~*"The development of methods using the paddle apparatus should start with a stirring speed of 50 rpm. Higher stirring speeds may be applied with an appropriate justification.*~~ ***The stirring speed used for the paddle apparatus in the development of methods should be appropriately justified by balancing discrimination to product variants with variation linked to hydrodynamic effects (e.g. coning) or other factors (e.g. tablet sticking).*** ~~*A higher stirring speed may be justified by high variability of the results (e.g. > 20% RSD at time points ≤ 10 minutes, > 10% RSD in the later phase for a sample size of 12) observed at lower speed rates*~~ ***Variability of the results*** *due to hydrodynamic effects (e.g. coning) or other factors (e.g. tablet sticking)* ***may be taken into account in the justification.****"*	Wording revised. See also Comment #20 and #39.
44	88-89 (98-100)	7	**Comment:** A suitable stirring speed as starting point for the development may also be recommended for basket apparatus.	See response in comment #20.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Proposed change: ... should start with a stirring speed of 50 rpm **and using the basket apparatus of 100 rpm, respectively**.	
45	88-89 (98-100)	13	**Comment:** The recommendation to start method development with stirring speed of 50 rpm is not in line with recommendations from FDA draft guidance Dissolution testing and specification criteria for IR solid dosage forms containing BCS class 1 and 3 drugs (Aug 2015). Due to the need for increased efficiency and reduction of costs to patients for generic products, global developments are increasingly common. FDA guidance and EMA recommendations should be harmonized to avoid the need to do additional dissolution work specifically for the EU, which is not required in the US (and vice versa).	See response in comment #39.
46	88-98 (98-100)	16	Recommendations on method using the basket apparatus are recommended to be added.	See response in comment #20.
47	89-92 (99-104)	8	**Proposed change:** A higher stirring speed may be justified by high variability of the results (e.d. > 20% RDS at time points < 10 min, **> 10% at time points >= 10 min and < 15 min , > 5 %** RSD in the later phase **(>= 15 min)** for a sample size of 12) …….	See response in comment #39.
48	89-92 (99-104)	18	**Comment:** In these lines higher stirring speed than 50 rpm is justified by the need to	This will be evaluated on a case by case basis. Any

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			reduce variability caused by for example coning effect. However, a more common consequence of coning effect is not high variability but an unwanted, artificial reduction of dissolution due to drug substance which is physically trapped in an (insoluble) matrix of disintegrated tablet or capsule at the bottom of the dissolution vessel. This phenomenon must be eliminated by means of an appropriate (higher) agitation speed to develop a dissolution method for quality control purposes. A coning effect can be proven by the use of non-compendial peak vessels. Alternatively, a coning effect can be demonstrated by applying “final spinning” (i.e. applying shortly a higher rotation speed when after e.g. 60 minutes the dissolution has reached a plateau but when complete dissolution has not been reached). As an alternative justification to increase the rotation speed, would the EMA accept the following data set: 1) comparative dissolution data between a peak vessel and regular vessel, or 2) “final spinning” dissolution profiles which clearly demonstrated a coning effect? Would the EMA accept that for above justification a data set with less than 12 tablets can used because coning effect is not always related to a high variability as mentioned in the reflection paper? **Proposed change (if any):** Not applicable	scientifically plausible justification / data could be acceptable in this regard.
49	88-98 (97-109)	1	**Comment:** Add a similar discussion for the basket apparatus.	See response in comment #20.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Proposed change: Add indicated additional information.	
50	88-98 (97-109)	8	**Comment:** Lines 88-98 (97-109) provide recommendations for method development using paddle apparatus and discuss effect of stirring speed on reducing variability vs. discriminatory power. However, there is no recommendation for methods using basket apparatus, sometimes basket mesh size is critical and generally the regular mesh size (#40) could have higher variability in early time points (because of blockage of the basket pores). Because of this artefact, it would be difficult to meet the %RSD criteria in the early time points. However, using a slightly bigger mesh size could reduce the variability in early time points without changing the other method parameters. **Proposed change (if any):** A recommendation for using different basket mesh size / rotation speed for reducing the variability in early time points should be included in the method development section.	See response in comment #20. The selection of the dissolution apparatus is up to the applicant and should be sufficiently justified.
51	88–98 (97-109)	10	**Comment:** The need for increasing the stirring speed (paddle apparatus) over 50 rpm is sometimes required not only when results are variable, but also when the plateau cannot be reached (for instance due to a coning effect). **Proposed change:** Please amend the lines 89-92 (100-104) to read: "A higher stirring speed may be justified by high variability of the results… **or the difficulty to reach a 100% plateau**"	See response in comment #48.
52	88-98 (97-109)	12	**Comment:** Method development using basket method for dissolution has not been explained.	See response in comment #20.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Proposed change (if any): Minimum information on choice of stirring speed using basket method should also be included for reference as this is one of the widely used methods for immediate release products.	
53	88-98 (97-109)	13	**Comment:** The complete development using basket apparatus or any other apparatus is missing and should be included. Alternatively it is proposed to add the wording below. **Proposed change (if any):** However, in all cases the dissolution profiles at increased stirring speeds should have sufficient discriminatory power for drug product quality control. **The use of other apparatus is also possible if discriminatory power is shown. For a basket apparatus it should be acceptable to start development with 100 rpm.**	See response in comment #20.
54	88-98 (97-109)	13	**Comment:** High RSDs (as defined in the paper) are due to the inherent behaviours of formula, physicochemical properties of drug and nature of dissolution media. However, the high RSD values may be overcome by opting a modified dissolution vessel to some extent. The option of use of modified dissolution vessels are not addressed in the reflection paper. **Proposed change (if any):** It would be highly desired to mention the advice for the possible approaches to avoid high RSDs. Option may be mentioning to use modified dissolution vessels (Flat or peak vessel) with standard agitation to	See response in comment #39 and #20.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			have adequate discrimination.	
55	89-95 (100-106)	13	**Comment:** There is a contradiction between the statements within these lines. On the one hand it is stated that “a higher stirring speed may be justified by high variability”, however, it is also stated that “increasing the stirring speed […] to reduce variability” should be avoided. It should be clarified that using a higher stirring speed to reduce high variability below the stated levels is possible. This is in line with lines 99-100 (110-111) which say that the variability of the results should be reduced to a minimum. To achieve this, the adaption of rotation speed is considered as a very important tool. It is also noted that the FDA/USP often recommends 75 rpm paddle speed instead of 50 rpm (to avoid coning), therefore it could be included that in case 50 rpm paddle speed results in the above artefacts, 75 rpm may be used instead, while further increases should be fully justified. **Proposed change (if any):** The development of methods using the paddle apparatus should start with a stirring speed of 50 rpm. ~~Higher stirring speeds may be applied with an appropriate justification. A higher stirring speed may be justified by~~ **In case the results show** high variability ~~of the results~~ (e.g. > 20% RSD at time-points ≤ 10 minutes, > 10% RSD in the later phase for a sample size of 12) ~~observed at lower speed rates~~ due to hydrodynamic effects (e.g. coning) or other factors (e.g. tablet sticking), **75 rpm can be used instead.** ~~However, it is known that methods with increased stirring speeds may be less discriminatory.~~ **Even higher stirring speeds may be applied with an appropriate justification.** Increasing the stirring speed at the expense of the discriminatory power ~~simply~~	See response in comment #39. There is no contradiction. What is meant is that it is not accepted to increase the stirring speed at the expense of discriminatory power merely to reduce variability. If increased stirring speed does not affect the discriminatory power that may be acceptable.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			~~to reduce variability of the results or~~ to obtain complete dissolution in a shorter time should be avoided. An increase of the stirring speed may **also** be considered in case of over-discriminatory conditions towards *in vivo* performance. However, in all cases the dissolution profiles at increased stirring speeds should have sufficient discriminatory power for drug product quality control.	
56	93-95 (104-107)	10	**Comment:** Lines 94 (105-106) appears to be incoherent with the line 90 (101-102). Line 94 (105-106) first part of the sentence says: "…simply to reduce variability of…"and line 90 (101-102): "A higher speed may be justified by high variability of the results…" It should be kept in mind that RSD at time-points should comply with specific requirements (less than 20% or 10%) if a statistical f2 test is applied. **Proposed change:** Please clarify.	See response in comment #39.
57	95 (106)	13	**Comment:** It should be clearly defined what complete dissolution means in terms of % dissolved and time point for an immediate release product.	No unequivocal definition for "complete dissolution" available.
58	93-95 (104-107) and 97-98 (108-109)	18	**Comment:** In these lines it is stated that *"increasing agitation speed at the expense of discriminatory power is not an acceptable practice"*. Also it is said that *"the dissolution profiles at increased stirring speeds should have sufficient discriminatory power for drug product quality control* ". Both statements are clear and logical, however, it needs also to be considered that stirring speed needs to be increased to eliminate artificial reduction of dissolution due to hydrodynamic phenomena such as coning. Then discriminatory power of final method can only be considered until coning is avoided by increasing speed.	See response in comment #39.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			As an example, if a paddle rotation speed of 50 rpm or 60 rpm leads to coning effect (and a basket method is not a suitable alternative) and 75 rpm is the minimally required speed, is the agency expecting that the applicant discusses the discriminatory power at lower speeds of 50/60 rpm even still coning occurs? Or does the EMA agree that any artefact in dissolution must be eliminated before any discussion of discriminatory power takes place? **Proposed change (if any):** Not applicable	
59	97-98 (108-109)	9	**Comment:** Does not comply with the decision tree of ICH Q6A, which allows dissolution methods without discriminatory power.	Refer to section 1.2 for details.
60	95-96 (107-108)	2	**Comment and rationale:** It is impossible to know the relationship between the in-vitro and in-vivo without some IVIR data. In case of method with a lot of variation due to test artifacts, increasing the paddle speed could improve in-vivo predictability. **Proposed change:** *"Increasing the stirring speed at the expense of the discriminatory power* ***to products variants*** *simply to reduce variability of the results or to obtain complete dissolution in a shorter time should be avoided.* ~~***An increase of the stirring speed may be considered in case of over-discriminatory conditions towards in-vivo performance.***~~"	See response in comment #39.
61	95-96 (107-108)	10	**Comment:** Lines 95-96 (107-108) are unclear: "over discriminatory conditions towards in vivo performance". Does it mean or imply that if two batches	This understanding is correct.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			(generic and pioneer) are found in-vivo bioequivalent, the dissolution results should show the same conclusion? Do the dissolution conditions need to be adjusted in order to give a consistent conclusion by comparison to the in vivo study's outcome? Should the dissolution study intended to be used in routine, be developed and optimized a posteriori once the in vivo bioequivalence is performed? **Proposed change:** Please clarify.	
62	101-102 (112-113)	13	**Comment:** In order to increase efficiency of global developments, it should be considered to add a statement that methods published on the FDA database or in a monograph (e.g. USP/BP) are considered as a suitable starting point for development of a discriminatory dissolution method. **Proposed change (if any):** [To be included after line 101 (112)] **<u>The use of a method published on the FDA database or in a monograph (e.g. USP/BP) is also considered as an acceptable starting point for development of the dissolution method.</u>**	It will not be a good idea to refer to FDA databases or USP monographs in an EU reflection paper. However, these US compendia or guidelines represent the state of pharmaceutical science.
63	105–107 (117-119)	11	**Comment:** In relation to the amount of active substance released, is in vitro or in vivo intended here?	In vitro is meant.
64	107-108 (119-121)	3	**Comment: "The test conditions should be chosen to allow discrimination between batches with different in vitro release**	Text revised.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			characteristics". Not clear what the author(s) are trying to say here. Clearly should different release characteristics be identified already **(different in vitro release characteristics)** the dissolution method is already discriminatory otherwise this knowledge would not be available. **Proposed change (if any):** Clarify statement.	
65	107-108 (119-121)	13	**Comment: "The test conditions should be chosen to allow discrimination between batches with different in vitro release characteristics".** It is not clear what the author(s) are trying to say here. If the batches have different in vitro release characteristics in the chosen in vitro conditions, this immediately implies that the dissolution method is discriminatory otherwise this knowledge would not be available. **Proposed change (if any):** Please clarify the statement.	See response in comment #64.
66	109 (110)	16	The phrase "reproduce the rank order between batches" is not fully clear. More explanations are recommended to be provided.	In our opinion the rank order is defined; see lines 197-201.
67	108-109 (121)	1	**Comment:** "in vivo situation" is vague **Proposed change:** Please define "in vivo situation" in terms of pk performance (possibly link to section 1.2.2)	Text revised, see line 121.
68	110	10	**Comment:** This sentence "without knowing about the in vivo relevance of these differences "is unclear. **Proposed change:** Please clarify.	Revised text 122-127.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
69	109-111	1	**Comment:**" the next best approach is to reproduce the rank order between batches and discrimination of batches with different quality attributes without knowing about the *in vivo* relevance of these differences. **Proposed Change:** Clarify "quality attributes" because quality attributes can be very broad.	In this context "quality attributes" are the ones which are critical for dissolution behaviour of the active ingredient. See also lines 133-142.
70	108-111	2	**Comment and rationale:** What is meant is that it is most preferred if the dissolution method is shown to reject non-equivalent batches, but if that data is not available, then discrimination to batch variant properties may suffice. **Proposed change:** "In an optimal case the in vitro results can ~~**mimic the in vivo situation**~~ **differentiate between bioequivalent and bioinequivalent batches, enabling a specification to be set that rejects the latter;** the next best approach **is** ~~**to reproduce the rank order between batches and**~~ the discrimination of batches with different quality attributes without knowing about the in vivo relevance of these differences. ~~**Both approaches may be used for routine batch control.**~~**"**	Revised text 122-127.
71	109-111	3	**Comment: "the next best approach is to reproduce the rank order between batches and discrimination of batches with different quality attributes without knowing about the in vivo relevance of these differences."** This is a circular argument. If the quality criteria with respect to *in vitro* performance is the dissolution, what is the "quality" that is being evaluated?	See lines 133-142.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			This is a requirement that can lead to an over-discriminating dissolution method that will result in rejection of quality batches. **Proposed change (if any):** Clarify "quality attributes" because quality attributes can be very broad.	
72	109-111 166-172 (197-203)	13	**Comment:** It is suggested in the Reflection paper that the rank order of *in vitro* and *in vivo* results should be compared. For many immediate release generic products, with often only one pivotal BE study performed (only one test and one reference sample tested *in vivo*), this approach does not seem realistic. This approach is more suited towards Originator products with multiple clinical studies but this reflection paper is for generic products only. It is requested that section 1.2.2 is reconsidered. If the decision is to retain the concept of rank order, the reflection paper should be amended to reflect that this scenario may not be common for simple straightforward generic immediate release products, with potentially only 1 pivotal study and there is no requirement to do additional clinical studies to create a rank order. Some example wording is proposed below. **Proposed change (if any):** In an optimal case the *in vitro* results can mimic the *in vivo* situation; the next best approach is ~~to reproduce the rank order between batches and~~ discrimination of batches with different quality attributes without knowing about the *in vivo* relevance of these differences. Both approaches may be used for	The reflection paper recommends to the comparison of "in vitro" rank order and the "in vivo" rank order results between the originator and the generic drug product.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			routine batch control.	
73	113-115 (130-132)	9	**Comment:** unclear what “meaningful changes” and “input parameters” means. **Proposed change (if any):** Add explanation or delete both sentences.	This is further elaborated in lines 129-142.
74	113 (130)	11	…using batches with different quality attributes Proposed change: … using batches manufactured under different manufacturing conditions	See response in comment #73.
75	114 (131)	9	**Comment:** Sentence should be given as example only and not as a mandatory requirement. **Proposed change (if any):** exchange “should” by “can”	See response in comment #73.
76	115 (132)	11	**Comment:** …input parameters and/or using slightly modified process parameters. “Slightly” is not well defined. **Proposed change:** …input parameters and/or modified process parameters.	See response in comment #73.
77	114-115 (131-132)	16	**<u>Proposed change:</u>** *Such changes may relate to the quantitative formulation, input parameters and/or using ~~slightly~~ modified process parameters.*	See response in comment #73.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
78	112-125 (129-142)	3	Same comment as above. A critical process parameter or material attribute are defined as: ones impacting on the quality (in this case performance) of the product. For example particle size; a predictive dissolution method can be used to establish particle size specification. This is the correct QBD path, not the other way around. Formulation and composition in a commercial manufacturing environment will not be subject to changes therefore it is not the role of the dissolution to differentiate but the firm's quality systems will ensure the correct composition. **Proposed change (if any):** Clarify "quality attributes".	See response in comment #69.
79	112-125 (129-142)	13	**Comment:** Advice on how to show meaningful changes for BCS Class 2/4 (particle size) and 1/3 substances (formulation or process) are useful but should not be considered mandatory for every case. There are alternative ways to show discriminatory nature of methods and these should be accepted in place of the above, if scientifically sound. It is noted that e.g. the particle size for BCS 2/4 might be a good option to demonstrate discriminatory power, however it should be noted that it strongly depends on the availability of drug substance and the supplier agreement. As such, it is proposed to specifically include other options for the drug product like change in manufacturing process etc. also and not limit the options to drug substance specific criteria.	The wording is not limited to particle sizes for BCS 2 and 4. See lines 129 to 142.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Proposed change (if any): The suitability of the test conditions for routine batch testing should be demonstrated using batches with different quality attributes. To achieve this, batches with meaningful changes compared to the applied finished product should be manufactured. Such changes may relate to the quantitative formulation, input parameters and/or using slightly modified process parameters. Current knowledge of both the characteristics derived from the Biopharmaceutics Classification System (BCS) and the finished product must be taken into account when choosing the quality attributes to change. For instance, for a finished product where the *in vivo* absorption (rate and/or extent) is expected to be limited by solubility / intrinsic dissolution of the active substance, i.e. BCS 2 and 4, suitable quality attributes may be particle size of the active substance or other attributes **(composition, manufacturing process etc.)** that would have an impact on the *in vivo* dissolution. For a finished product where the *in vivo* absorption is expected to be limited by gastric emptying or intestinal permeability, i.e. containing BCS 1 or 3 class active substance with rapid or very rapid dissolution (refer to BE Guideline), suitable quality attributes may be factors in the formulation and/or manufacturing process that will have an impact on the disintegration of the finished product and significantly affect the rate of *in vitro* dissolution. **These should be taken as examples, and alternative approaches can be accepted, where justified.**	
80	115-125 (132-142)	19	**Comment:** For BCS class 2 and 4 drugs the current wording seems to limits their problems to intrinsic solubility only. Class 2 and 4 drugs could also be weak acids that will not experience any issues until they leave the stomach. In those cases, also formulation is an important factor.	See response in comment #79.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
81	126-128 (143-145)	1	**Comment:** Further clarification is needed for the following statement “changes to the composition of the drug product to create a ‘bad batch’ should be covered by the proposed qualitative batch formula”. Define “bad batch”. Does it mean a batch with unacceptable bioavailability or a batch that shows different release rate?	A “bad batch” is a batch showing different release rate.
82	126 (143)	11	**Comment:** What is meant by a “bad batch”? It is probably best to avoid such a term unless it is defined	See response in comment #81.
83	126-130 (143-147)	12	**Comment:** Change in manufacturing process as a tool for detecting discriminatory power of dissolution method should be discussed. **Proposed change (if any):** Usually for demonstration of discriminatory power of dissolution method, we use 2 tools i.e. change in composition and change in manufacturing process. Hence latter one also needs to be included in this section for better clarity.	See response in comment #73.
84	128-130 (145-147)	2	**Comment and rationale:** Even by varying the proportion of excipients, extremes can be created that are just as unrealistic as leaving out an excipient altogether. It would be better to say that “bad batches” should be created preferably by altering manufacturing process, rather than varying excipient quantities. However, in some situations, it may be necessary/desirable to alter excipient quantities, or even omit	See response in comment #73.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			excipients if non-equivalent batch is to be created. **Proposed change:** *"Changes to the composition* ***of the drug product secondary manufacturing process conditions are preferred to create a "bad batch" should be covered by the proposed qualitative batch formula and only the proportions of the employed excipients might be changed. The complete omission of one or more specific excipients from the formulation (e.g. binder, disintegrant) is not supported. The dissolution test conditions should be able to detect these changes by setting a suitable specification, rather than excipient level changes to the proposed quantitative batch formula. If excipient levels are altered, then these changes should still be within typical ranges for the formulation type. "***	
85	126-130 (143-147)	1	**Comment:** It is unclear what is meant by "changes to the composition of the drug product to create a 'bad batch'. Also, it is unclear why the text states (line 128 (145)) that "the complete omission of one or more excipients for the formulation" is not allowed as a means of demonstrating method discriminatory power if lesser changes are not discriminated. **Proposed change (if any):** Reconsider this text to allow a wider set of means of evaluation of method discriminatory power. This should include not only quantitative changes to the composition, including, if appropriate, complete omission of an excipient (e.g. the disintegrant), but also, modifications to the processing parameters, as described in line 145 (173) to produce so called "side-batches", and stressed formulations.	See response in comment #73.
86	126-130	3	**Comment:** It is unclear what is meant by "changes to the composition of the	See response in comment

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
	(143-147)		drug product to create a 'bad batch'. Also, it is unclear why the text states (line 128 (145)) that "the complete omission of one or more excipients for the formulation" is not allowed as a means of demonstrating method discriminatory power if lesser changes are not discriminated. Define "bad batch". Does it mean a batch with unacceptable bioavailability or a batch that shows different release rate? **Proposed change (if any):** Include in this text alternative approaches for the evaluation of method discriminatory power and provide guidance on the appropriate tools to select which composition and/or process variations would be most appropriate to evaluate "bad batches". This text should include not only quantitative changes to the composition, including, if appropriate, complete omission of an excipient (e.g. the disintegrant), but also, modifications to the processing parameters, as described in line 145 (173) to produce so called "side-batches".	#73.
87	126-130 (143-147)	18	**Comment:** This section gives a possibility to challenge the discriminatory power of the QC dissolution method by creating and dissolution testing of a "bad batch". This requires an intentional adjustment in the final formulation. However, can the EMA agree in demonstrating the discriminatory power of the final dissolution method with batches made during formulation development that are not far deviating from the final formulation in regards to qualitative and quantitative composition? **Proposed change (if any):** Not applicable	See response in comment #73.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
88	128-130 (145-147)	4	**Comment:** Omission of one or more excipients in order to create a bad batch should be allowed with proper justification, e.g. creating safe spaces for BCS class I/III.	See response in comment #73.
89	129-130 (146-147)	18	Dissolution methods should be able to detect/differentiate changes in ´bad batches´ (i.e. discriminatory power). What does EMA consider to be two different dissolution profiles? Are plotted profiles with a difference larger than random method variability sufficient to prove that profiles are different? Or is agency expecting any statistically analysis or (e.g. f2 factor) calculation to support the differences in dissolution profiles? **Proposed change (if any):** Not applicable	Reference is made to the guideline on the investigation of bioequivalence (Appendix I) or for veterinary products section 8 of the respective guideline.
90	131-134 (155-160)	1	**Comment:** Indicate that use of disintegration as an alternative to dissolution may be considered in such situations. **Proposed change:** Add indicated additional information.	See lines 158-160. For omission of dissolution test in favour of a disintegration test see guideline ICH Q6A.
91	131-134 (155-160)	2	**Comment and rationale:** It would be useful to clarify what is meant by "*very high solubility*" specifying for instance a threshold such as "*above x mg/mL*". Conversely, low dose, low solubility drugs may well show differences despite BCS 1/3 status. **Proposed change:** *"However, for drug products containing a BCS class 1 or class 3 active substances with very high solubility* ***(above x mg/ml)*** *over the physiological*	The term "very high solubility" is connected to BCS approach stated on page 26 of Guideline on the investigation of bioequivalence. A substance is highly soluble depending on solubility of its highest single dose administered. As such the dose is individual for every

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			pH range, it may not always be possible to detect any differences in dissolution behaviour after meaningful changes in relevant formulation and/or manufacturing parameters have been made."	substance; it is not possible to state any exact value in the document. "
92	131-134 (155-160)	9	**Comment:** Conclusion is missing. **Proposed change (if any):** Reference to disintegration testing as more discriminatory test method should be made (ICH Q6A).	See lines 158-160. Reference is made to ICH Q6A for those cases that dissolution testing can be replaced by disintegration testing.
93	131-134 (155-160)	13	**Comment:** It is good for the reflection paper to acknowledge that it is not always possible to detect differences in release for high solubility Class 1/3 substances after meaningful changes, which is in line with ICH guidance too. However, it is noted though it does not specifically mention what to do in these cases. This is an opportunity to specify how these cases should be handled in the future, to avoid doubt. It is requested to add a statement that in these cases when meaningful changes do not show a difference, the discriminatory nature of the method should be assumed without further justification. However, the definition of "very high solubility over the physiological pH range" is not clear. This paragraph should be applicable to all BCS Class I/1 active substances, and not just a subset with solubility considered to be "very high". **Proposed changes (if any):** However, for drug products containing a BCS class 1 or class 3 active	

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			substance~~s with very high solubility over the physiological pH range~~, it may not always be possible to detect any differences in dissolution behaviour after meaningful changes in relevant formulation and/or manufacturing parameters have been made. **In these cases, the method can be considered to be adequate without further justification.**	See also comments #91 and #92.
94	131 -134 (155-160)	13	**Comment:** Because of smaller dose (10 mg or less) or because of sink conditions (required for discriminatory media) it may not always be possible to demonstrate differences in dissolution behaviour after a meaningful changes for class II and IV drugs. **Proposed change (if any):** Please advise how to define discriminatory media for class II and class IV drugs with small dose and high solubility in sink conditions.	See response in comment #91. Reference is made to the bioequivalence guidelines (human and veterinary) e.g. Appendix III (section III) of the human guideline. The BCS classification is defined considering the dose as well.
95	131-134 (155-160)	14	**Comment:** The BCS class 2 or 4 active substances also have high solubility in certain conditions and discriminatory power may not be possible to achieve. The proposal of the additional text after line 134 (160) is presented below. **Proposed change (if any):** *The same applies to active substances, which are weak acids or weak bases belonging to BCS class 2 or 4. In sink conditions, where their solubility may be very high (depending on difference between their pKa and pH of dissolution medium) the discriminatory power of the dissolution method may not be possible to achieve.*	See response in comment #94. See also comment #28.
96	131-134 (155-160)	18	**Comment:** In is stated in these lines that BCS class 1 or class 3 drug substances due to	See response in comment #92.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			their high solubility usually present dissolution profiles where no discriminatory power can be found. How is agency expecting the applicant to justify lack of discriminatory power in such situations? Will literature data supporting BCS classification be enough? Should experimental drug substance solubility data be submitted? Can dissolution test conditions be adapted without regard to discriminatory power as per ICH Q6A decision tree #7? Secondly, in case of BCS Class 1 and 3 drug substances for which the applicant has justified that no discriminator power exists for dissolution, can then dissolution be removed from the specification if in addition a relationship between disintegration and Critical Process Parameters and/or other Critical Quality Attributes have been established? **Proposed change (if any):** Not applicable	See response in comments #91 and #93.
97	131-134 (155-160)	19	**Comment:** The paper acknowledges that for BCS class 1 and 3 drugs, despite meaningful changes in the formulation (or manufacturing parameters), no differences in dissolution may be observed. This implies that in those situations the proposed dissolution method will be accepted. However, it is not clear how similar situations will be dealt if present for BCS class 2 and 4 drugs.	See response in comment s #91 and #93.
98	134 (160)	1	**Comment:** It is unclear as to what action, if any, should be taken by the sponsor in the case where they are unable to detect any differences in dissolution behaviour after meaningful changes in relevant formulation and/or manufacturing parameters have been made. It should be clear that further development in an attempt to obtain a discriminatory method is not required; this would be consistent with the recent FDA US Draft Guidance for Industry	See response in comment #90.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs. **Proposed change:** Add "In these cases, no further development on a more discriminatory method is necessary."	
99	134 (160)	3	**Comment:** It is unclear as to what action, if any, should be taken by the sponsor in the case where they are unable to detect any differences in dissolution behaviour after meaningful changes in relevant formulation and/or manufacturing parameters have been made. It should be clear that further development in an attempt to obtain a discriminatory method is not required; this would be consistent with the recent FDA US Draft Guidance for Industry Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs. **Proposed change (if any):** Include "In these cases, no further development on a more discriminatory method is necessary." Add reference to FDA Draft guidance on BCS 1/3 or the corresponding European Guidance …	See response in comment #90.
100	134 (160)	11	**Comment:** A new heading should be inserted (Batch Data)	No.
101	135-140 (139-145)	13	**Comment:** We believe that this should be valid only for test batches that have same qualitative composition, because dissolution method and the dissolution specification are developed for the specific product with the specific	Text revised.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			composition.	
102	135-140 (161-167) Section 1.2.1.	19	**Comment:** Should several batches of the test drug product be tested in-vivo, the draft reflection paper proposes that the dissolution method should be able to distinguish between batches with acceptable and non-acceptable pharmacokinetic parameters. Is should be recognized that there will be issues in interpretation what is considered acceptable versus non-acceptable (parameters) and in relation to which formulation (e.g. in case of innovator products). E.g., if the term acceptable means that 90% confidence intervals are within pre-defined (bioequivalence) acceptance criteria, the interpretation will be linked with sample size/power of the concerned studies. During development, pilot bioequivalence studies are frequently conducted for exploratory purposes. These trials are typically not powered to prove bioequivalence, but to provide sufficient sensitivity to detect product prototypes eligible for further development. Application of acceptability defined as proof of bioequivalence would be flawed for these studies since even a truly bioequivalent product doesn't have sufficient chance (at least 80%) of passing the acceptance criteria. In case of innovator products, the question arises which formulation(s) shall constitute the base for decision on acceptable or non-acceptable behaviour (e.g., early stage phase II formulation, phase III clinical service formulation or final market image). Potentially, specific changes in quality parameters of the formulation or dosage form compared to the IMP used in earlier clinical trials could have been made and these may be relevant for in-vivo performance. It is acknowledged that a more specific definition of what is acceptable / non-acceptable is rather difficult, but the current draft guideline text represents a very general definition that may even be prone for a subjective judgement.	Text revised.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
103	135 (161) (Section 1.2.1)	10	**Comment:** This section makes the hypothesis that several in vivo studies could be performed during the pharmaceutical development of the generic product. This situation where testing of different batches in vivo seems to be quite unusual. **Proposed change:** Please clarify.	It is acknowledged that this situation is not usual but it does occur (e.g. pilot bioequivalence studies, failed bioequivalence studies etc.). The RP caters for all three scenarios described in 1.2.1, 1.2.2 and 1.2.3
104	Section 1.2.1	10	**Comment:** The aim of this section as well as the descriptive is unclear. As written previously, there is no in-vivo comparison between side-batches and reference product. Moreover, the discriminatory power of the dissolution test is mentioned in this section but from our point of view there is an issue on the timing. Indeed, with regards to the development of the drug product, it seems usual to develop a method to compare reference product and the generic prototype. At this stage, the method is not finalised yet. After that step, when a formula prototype seems adequate, the in vivo testing is performed and a biobatch is found acceptable. The work on the method for the routine testing is completed and only then, the discriminatory power could be done based on the retained formula of the biobatch and by manufacturing other prototypes with definition and/or modifications of critical process parameters and / or critical material attributes. **Proposed change:** Please clarify what is the aim of this section.	See response in comment #103.
105	137-140 (163-167)	2	**Comment and rationale:** If data is available from several batches of the drug product tested during development in vivo leading to batches with acceptable and non-acceptable	Text added: "*Priority should be given to in-vivo discrimination over other*

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			pharmacokinetic parameters, then priority should be given to discrimination as means by which appropriate method is selected, and method preferences relating to sink conditions, specific paddle speed recommendations or use of surfactants, etc. should be secondary. **Proposed change:** *"In cases where several batches of the drug product have been tested during development in vivo leading to batches with acceptable pharmacokinetic parameters and those with non-acceptable pharmacokinetic parameters, dissolution test conditions should be chosen which allow discrimination between acceptable and non-acceptable batches by setting a suitable specification.* ***Priority should be given to in-vivo discrimination over other factors influencing method selection.****"*	*factors influencing method selection."*
106	140 (166)	11	**Proposed change:** Delete "setting a suitable specification" and insert "in the product specification"	It is clarified that the term "dissolution test conditions" is understood as all the particulars of the method (e.g. medium composition and volume, apparatus, rotation speed, sampling method). The term "suitable specification" should be understood as the amount released (Q) at a specific time-point; the time-point being part of the specification. It is the

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
				combination of a discriminatory method and a suitable time point and Q that allow discrimination between acceptable and non-acceptable batches and thus consistent performance of commercial batches.
107	141 (168)	5	**Change title of section 1.2.2.:** Proposed change: In vivo studies between generic- and reference product	See response in comment #103.
108	141 (168)	11	**Change title of section 1.2.2.:** Proposed change: In vivo studies between generic- and reference product	See response in comment #103.
109	143 (171)	9	**Comment:** "different *in vitro* profiles" is unclear Does that mean f2 values < 50?	Different in vitro profile does not necessarily means f2<50 but differences larger than variability.
110	143-146 (171-175)	9	**Comment:** The concept of "side-batches" needs more explanation. In line 143 (171) different in vitro performance is mentioned. Is one BE study sufficient to justify the dissolution specification based on "side-batches" and other batches? **Proposed change (if any):** Clarification on different *in vitro* performance and number of BE batches needed to support "side-batch" dissolution specifications.	Text is clear. See also definition of side-batch, lines 76-79.
111	143-151	10	**Comment:** The rationale to set the dissolution specification only focuses on the	Publication of these data is not

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
	(171-179)		potential variability of the generic product and does not consider the comparison of the dissolution performances to the reference product that might also differ from the biobatch. In order to facilitate the comparison of dissolution performances between generics and reference products, access to the dissolution method of the reference product would be a good initiative. Is it intended to publish a public dissolution database like other regulatory authorities do? **Proposed change:** Please clarify.	possible due to their confidentiality.
112	143-151 (171-179)	13	**Comment:** The concept of side batches is acknowledged but is considered only relevant e.g. for originator companies. It is not applicable or ethically supported for generic developments where usually only one BE study takes place. As such, it is proposed to delete the part from the reflection paper	It is clarified that the text under 1.2.2 should not be understood as a requirement to conduct additional BE studies with “side-batches” but rather to advise in case these results are available how they may be used in setting dissolution specifications.
113	145 (173)	1	**Comment:** We agree that a side batch shown to be bioequivalent with a slow profile may be used to establish the extreme of acceptable dissolution performance. We believe such a batch can be prepared either using compositional variation or process variation and, moreover, that the process variation need not be within the proposed manufacturing process conditions but could be outside this normal operating (and validated) range. Furthermore, we do not see that ‘fast profile’ batches are also needed for BCS 1 and 3 materials in IR products or for batches with rapid permeability. **Proposed change (if any):** Please clarify this section to focus on the study of	Proposal not acceptable. This section does not describe IVIVC. Definition of side-batch has been included in the reflection paper.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			slow releasing IR product lots and allow both process variability and formula variability to be considered in this approach, as well as allow for a wider process variability range to be utilised beyond the normal operating range or validated range as sometimes is necessary. Also, consider substituting the term 'side batches' which already has a common meaning in IVIVC development.	
114	145 (173)	3	**Comments:** Side batch that shown to be BE with a slow profile may be used to establish the extreme of acceptable dissolution performance. Such a batch can be prepared either using process variation OR product variation and that a process variation need not be within the proposed manufacturing process conditions but indeed could be outside this normal operating (and validated) range. Furthermore we do not see that 'fast profile' batches are also needed for BCS 1 and 3 materials in IR products or for batches with rapid permeability. **Proposed change (if any):** Please clarify this section to focus on the study of slow releasing IR product lots and allow both process variability and formula variability to be considered in this approach AND allow for a wider process variability range to be utilized beyond the normal operating range or validated range as sometimes is necessary. Also, consider substituting the term 'side batches' which already has a common meaning in IVIVC development.	See response in comment #113.
115	150-151 (178-179)	10	**Comment:** It is understandable to set a Q specification to discard batches showing slower dissolution profiles as proposed in this sentence"…a suitable specification may be set based on the in vitro dissolution profile of the side batch with the slowest dissolution" but what would be the conclusion if a batch shows a very rapid dissolution at release (quicker than the generic tested in	For the drug products in the scope of this reflection paper, there is no upper limit for release. So a rapid release will not raise clinically relevant

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			vivo)? It is unclear whether it can be concluded or extrapolated that it would be bioequivalent to the originator product. **Proposed change:** Please clarify.	concerns.
116	155-160 (184-190)	3	**Comment:** The discussion of Cmax being a measure of 'dissolution speed in vivo' seems to be an over-simplification of a more complex biological process, as it does not account for permeability, especially in the case of rapidly dissolving drugs, in which differences in dissolution rate may have no bio-relevance. **Proposed change:** Consider replacing 'dissolution speed in vivo' with 'rate of drug absorption'.	Changed to: "The latter is ~~a measure~~ an indication of dissolution speed *in vivo."*
117	156-158 (184-188)	10	**Comment:** Please also refer to comment on lines 69-71 (73-75). Does the bioequivalence word refer to in vivo bioequivalence or in vitro dissolution study? Does it mean that the in vivo bioequivalence study design should be linked to dissolution kinetics obtained on both batches used? **Proposed change:** Please clarify.	An in vivo bioequivalence study is meant.
118	159 (189)	10	**Comment:** This is not clear why the discriminatory power is mentioned with a link to the in vivo tests. **Proposed change:** Please clarify.	The discriminatory power is the ability of a test procedure to discriminate between batches with respect to critical process parameters and /or critical material attributes which may have an impact on

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
				the bioavailability. Ideally all non-bioequivalent batches should be detected by the *in vitro* dissolution test results.
119	162 (192)	9	**Comment:** According to the BE guideline the results have to be within a range of 80.00 to 125.00%.	Acceptable. Number of decimals.
120	163-165 (193-196) 168-170 (199-201)	11	**Comment:** The sentence from lines 163 – 165 (193-196) needs further clarification. "Small differences without clinical relevance will be accepted as long as the 90% confidence interval fulfils these criteria." What does this mean?	In BE studies small differences (in AUC and C_{max}) are be accepted as long the 90% confidence interval fulfils these criteria (between 80% and 125%).
121	159-172 (189-203)	1	**Comment:** This text was complicated and not fully understood by this reader. While it may be generally true that Cmax and dissolution rate should exhibit the same rank order, this may not be the case for products wherein the rate of oral absorption is controlled by permeability, especially when the generic and innovator's products comprise different sets of excipients, one or more of which impact permeability. The requirement to further optimize the method to obtain the same rank order may not be appropriate in some cases. **Proposed change:** Please reconsider these points.	Text slightly modified, now reads: "… if possible".

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
122	166-172 (197-203)	9	**Comment:** Does not comply with the scope. batch-to batch consistency vs *in vivo*/*in vitro* correlation.	It is clarified that the purpose of the text in lines 166-172 (197-203) is to question the discriminatory power of the method in case of an opposite rank order because a discriminatory method is expected to reflect the in vivo behaviour of different batches of the product to a certain extend.
123	167 (198)	9	**Comment:** "significantly larger C_{max}" unclear **Proposed change (if any):** "significantly larger C_{max}" needs to be defined.	"Significantly larger" depends on the difference plus the variability.
124	166-172 (197-203)	13	**Comment:** It is suggested in case the rank order of *in vitro* and *in vivo* results do not match that the dissolution method should be further optimized to reflect the *in vivo* trend. This is in contrast to the Bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *) Section 4.2.1 which says: "In the event that the results of comparative in vitro dissolution of the biobatches do not reflect bioequivalence as demonstrated in vivo the latter prevails. However, possible reasons for the discrepancy should be addressed and justified."	There is no contradiction. The guideline on bioequivalence-studies adds: "however, possible reasons for the discrepancy should be addressed and justified." In the reflection paper it is stated that the selection of the conditions for dissolution testing may not be the reason for their deviant behaviour.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			It is re-iterated (as per the general comment above) that a dissolution method is developed for a particular formulation in order to detect differences in batches of that formulation. In the context of a generic application, that means the method should be capable of detecting batch to batch differences of the generic product. If reverse rank order is seen between test and reference product (i.e. a test product with significantly larger C_{max} shows slower *in vitro* dissolution behaviour, or vice versa) this should not be considered relevant, as the dissolution method should be developed based on the *in vitro* characteristics of the generic test product (found to be bioequivalent) and not the reference product. It is requested this sentence is deleted to avoid any conflict with other guidance. **Proposed change (if any):** In such a case the rank order of the *in vivo* and *in vitro* results should be compared. If a test product with significantly larger Cmax shows faster *in vitro* dissolution than the reference product, this may be used as an indicator for suitability of the chosen test conditions. The larger the difference of the *in vivo* point estimates is, the greater the chance that this difference may also be reflected *in vitro*. ~~In case of an opposite rank order, i.e. a test product with significantly larger Cmax shows slower *in vitro* dissolution behaviour or vice versa, the test conditions should be further optimised in order to reflect the *in vivo* trend.~~	It is clarified that the quoted text of the Bioequivalence guideline refers to the different pH media (pH 1.2, 4.5, 6.8 plus QC method) dissolution profiles comparisons. The in vivo results indeed prevail with regard to establishing bioequivalence. In other words the discrepancy between in vitro and in vivo data would not normally question the bioequivalence shown in vivo. In case of an opposite rank order discussed in lines 166-172 (197-203) the discriminatory power of the method is questioned; not the bioequivalence. Therefore there is no conflict between the guidance documents The above mentioned wording applies to the opposite scenario as well. Refer to

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
				comment #121 as well.
125	166-172 (197-203)	18	**Comment:** Does section 1.2.2 refer only to pivotal (bioequivalence) studies with the final formulation or as well to pilot studies (i.e. investigational studies for bioavailability of a potential prototype) performed with development batches? If a pilot as well as a pivotal study has been performed, should the final dissolution method reflect the in vivo behavior (if possible) for pilot studies as well, even when the bioavailability of that developed prototype is not in line with a comparative (originator) product? **Proposed change (if any):** Not applicable	Section focusses on pivotal studies. However, supportive data of pilot batches can also be used to justify the specification.
126	152–172 (181-203) Section 1.2.2.	19	**Comment:** The draft guideline assumes a simple linear relationship between the in-vitro data and in-vivo data, here proposed as direct link between dissolution profile and pharmacokinetic metrics, e.g. Cmax, or the corresponding test-to-reference ratio along with confidence interval(s). As explained in the general comments, this assumption represents an overall simplification of in-vitro / in-vivo relationship and will work only in limited cases. It is not understood what is meant by significantly larger Cmax in connection to batches that passed the acceptance criteria. The difference between test and reference may be statistically significant, however, such a difference cannot be considered clinically relevant since it is within the limits allowed by regulatory authorities. If the difference between test and reference is not clinically relevant, there is no reason to optimize the dissolution release method to match strictly the in-vivo results (or rank order of dissolution profiles between test and	Change not accepted, that is an important part of the whole paper. Please refer to updated introduction and section 1.2. See response to general comment #11 & #16.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			reference product). The interpretation of a significant difference between the test and reference product will also be different in case of highly variable drugs (where larger differences in Cmax are permitted in accordance with reference intra-individual variance) or for narrow therapeutic drugs (where the difference is generally limited to ±10%). In addition, test and reference products may have completely different compositions and be manufactured by various technological processes. Such products may be still bioequivalent but differ in in-vitro behaviour. Also, different release mechanism is conceivable between test and reference product (for example due to patent issue). Therefore, the dissolution specification method should be linked with performance of test product biobatch, not the reference product. In conclusion, the need for optimization of dissolution method to reflect the rank order of in-vitro or in-vivo data should not be enforced. **Proposed change:** Delete lines 152 – 172. (157-177)	
127	173 (204)	5	**Change title:** Proposed change: Biowaiver	Partially accepted and the term “BCS based biowaiver” in the heading in brackets is added.
128	173 (204)	11	**Change title:** Proposed change: Biowaiver	See response to comment #127.
129	173-182 (204-213)	13	**Comment:** In this section only the BCS based biowaiver approach is mentioned as a	LALA products out of scope. Title amended.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			condition in which a bioequivalence study may be waived. However e.g. for Locally applied locally acting products of the GI tract, Bioequivalence studies may also be waived as plasma concentrations for e.g. products with no oral or GI absorption are not measurable. For those products it would be also good to know, which batch may be considered as Biobatch, or LOLAs should be excluded as a scope for this Reflection paper.	
130	175-179 (206-210) (Section 1.2.3)	19	**Comment**: The paper proposes the current wording: "In such instances there is no batch used in a bioavailability/bioequivalence study or in clinical testing (biobatch) and by analogy, the batch that has been shown to be equivalent with a reference product based on satisfactory in vitro discriminatory dissolution data in at least three different pH media is considered to be the test batch." However, in the EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**), Appendix III, specific dissolution conditions are required as follows: "Agitation: paddle apparatus - usually 50 rpm, basket apparatus - usually 100 rpm, Buffer: pH 1.0 – 1.2 (usually 0.1 N HCl or SGF without enzymes), pH 4.5, and pH 6.8 (or SIF without enzymes)." The latitude to modify those conditions and the requirements to show discriminatory power does not really exit in the text. Moreover, the requirement to demonstrate discriminatory power for three different pH media on top of QC method will effectively prevent the BCS based biowaiver submissions due to too restrictive conditions. Also, should some differences between individual strengths be present, the requirements would need to be fulfilled separately for each of the strength. The BCS based biowaiver is an approach built on standard similar dissolution setting for all formulations. Importantly, discriminatory power for formulations containing BCS class 1 and 3 drugs with very high solubility may not always be achievable. This point is highlighted in the current refection	It is clarified that discriminatory power in this RP only refers to the (proposed) QC dissolution method. Proposal accepted.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			paper in lines 131-134 (155-158) “However, for drug products containing a BCS class 1 or class 3 active substances with very high solubility over the physiological pH range, it may not always be possible to detect any differences in dissolution behaviour after meaningful changes in relevant formulation and/or manufacturing parameters have been made.” **Proposed change:** Delete the term discriminatory in line 178. (209)	
131	178-179 (209-210)	3	**Comment:** For BCS 1 and 3 IR formulations that are subject to biowaiver there should be no additional requirement for “discriminatory” attribute. The biowaiver is granted on the basis of comparison between two products (reference and test) that are potentially similar. Meeting the biowaiver criteria on its own is sufficient to ensure adequate performance in vivo; essentially being the basis for waiving the biostudy to start with, no additional “discriminatory” requirement is needed. **Proposed Change:** The requirement for discriminatory method should not strictly be applied to BCS 1 and 3 IR formulations.	See response in comment #92 and #130. Reference to amended text lines 155-160.
132	178 (209)	9	**Comment:** Test conditions acc. to the guideline have to be used. No need to demonstrate discriminatory power. **Proposed change (if any):** Delete “discriminatory”.	See response in comment #130.
133	183-206 (214-237)	19	**Comment:** The general rules defined in this paper are coherent with general practice, however, the within batch variability was not taken into account. For example, some products like sugar coated formulations (not considered as	See response in comment #156.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			modified release dosage forms) could exhibit a large variability for reference and test. In this case, variability of reference could be taken into the consideration. If the test exhibits a large but similar variability compared to reference, some adjustment of the rules could be done. E.g., suppose that at 15 minutes reference and test formulations lead to dissolution between 75% and 100% with a mean of 85%. In this case the limit is set to Q=75% which implies that for S1 release, no unit shows dissolution below 80% (Q+5%) at 15 minutes. Consequently, neither the test nor the reference would qualify for S1 release due to variability. **Proposed change:** Variability of reference could be discussed to set the acceptance criteria (Q-value).	
134	184 (215)	3	**Comment:** Specifications as per ICH are defined by method and acceptance criteria. This is important point for dissolution since % dissolved is much dependent on the method used (e.g., media, agitation speed, and apparatus). **Proposed change (if any):** Align the definition of specification with the corresponding ICH definition.	Acknowledged. In order to make clear the distinction between the discussion about the method and the discussion about the limit the word "limit" next sentence (line 216) has been added: "The dissolution specification **limit** is defined by a *Q* value**…"**
135	187-189 (218-220)	1	**Comment:** This statement is ambiguous. Is the intent that the specification be set so that testing will routinely require S2 testing to achieve compliance? Or is the intent that it is acceptable that the specification set may require S2 to	See response in comment #156.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			achieve compliance? **Proposed change:** Clarify statement to describe latter intent.	
136	187-189 (218-220)	2	**Comment and rationale:** **Proposed change:** The specification should be set in such a way so that during routine manufacture and testing it would be expected that compliance with ~~S~~$_2$ S_1 is attained.	See response in comment #156**.**
137	187-189 (218-220)	4	Our recommendation is not to set specifications so it would be expected that S2 requirements are fulfilled. The specifications should instead be set according to Annex 1 or be based on scientific risk with proper justification.	See response in comment #156.
138	186-189 (217-220)	8	**Comment:** Development of a specification that is fulfilled only at S2 level a priori is not desirable. Having to test on S2 level should remain an exception and not be implemented as routine testing in the first place. **Proposed change:** Batch results showing compliance with stage S1, S2, and S3 (Ph. Eur. 2.9.3) are acceptable. The specification should be set in such a way so that during routine manufacture and testing it would be expected that compliance with **S1** is	See response in comment #156.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			attained.	
139	187-189 (218-220)	9	**Question:** Does routine manufacture and testing also include stability analysis? **Proposed change (if any):** Clarification on shelf-life specification to be added.	Reference to lines 224-226.
140	187-189 (218-220)	9	**Comment:** If the focus of the dissolution specification is compliance to S2 level testing. Than clarification on faster dissolution performance and possible non-bioequivalence is missing.	Compliance means: average dissolution larger than Q. See response in comments #115 and #156.
141	187-189 (218-220)	10	**Comment:** When a specification for dissolution is set, it is expected to have compliance with S1 limit and not S2. Indeed, the second level (S2) is not an objective, but a security level. Please clarify why at line 189 (220), compliance with S2 is expected? Should be S1 right? **Proposed change:** Please clarify and modify the sentence accordingly.	See response in comment #156.
142	184-189 (215-220)	13	**Comment:** The sentence that S2 level testing is expected to be acceptable during routine manufacturing should be changed. It is not in line with Ph.Eur. which states that the limit testing of S2 is only done if S1 testing is not within the specification. If the limit is only set according to the mean BE batch values-10% and the BE	See response in comment #156.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			batch itself shows variability within the acceptable range as specified in line 91, there is a possibility that not even the BE batch would pass S1 limit with Q+5%. It is not considered appropriate to apply S2 level testing to a BE batch which has successfully demonstrated bioequivalence. From a statistical point of view, S1 criteria consider the dissolution results of individual units. For S2, both mean and individual results are taken under consideration. The discriminatory power of S1 is much greater than that of S2. Hofer and Gray demonstrated the probability of passing S1 based on statistical analysis. For example, if 95% individual units (of the whole batch) dissolve ≥ Q+5%, then the probability of passing S1 stage only is 74%. Assuming SD is moderate, then the mean of the batch nearly guarantee greater than Q, an individual unit dissolves less than Q-15% is also very unlikely. Therefore, the batch is guarantee pass S2 stage. Therefore, setting a slightly lower Q value to ensure each individual units (of the bio-batch) passing S1 stage is more suitable than setting a higher Q value with a frequent need (and pass) of S2. **Proposed change (if any):** Batch results showing compliance with stage S1, S2 and S3 (Ph. Eur. 2.9.3.) are acceptable. The specification should be set in such a way so that during routine manufacture and testing it should be expected that compliance with S1 is attained.	
143	186-189 (217-220)	16	If, as stated, batch results showing compliance with stage S_1, S_2 and S_3 are acceptable, it unclear why the specification should be set in such a way so that during routine manufacture and testing compliance with S_2 is attained. If this relates to the preferred option, it should be clearly stated.	See response in comment #140. See response in comment #156.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
144	186-189 (217-220)	19	**Comment:** The text proposes that compliance at all release levels (S1, S2, S3) is acceptable. However, at the same time it is expected that "compliance with S2 is attained". The later requirement is considered restrictive and gives the impression that only release at stage S2 will be considered adequate. **Proposed change:** Delete the last sentence on lines 187 – 189.	See response in comment #140. See response in comment #156.
145	192 (223)	10	**Comment:** At line 192 (223) there is only a reference to the human BE guideline while it is covering both Human and Veterinary sectors. **Proposed change:** Please modify this sentence to add the reference to the veterinary BE guideline, Appendix I or remove the word "human".	Reference to Section 8 Vet GL is added.
146	190-192 (221-223)	17	**Comment:** Before setting the *Q* value, the time range allowing discrimination should be considered from the (190 (221) dissolution profile of the biobatch. Sampling time points should be sufficient to obtain a meaningful (191 (222) dissolution profile (c.f. human BE guideline, Appendix I). **Proposed change:** In general, dissolution specifications are finalized based on systematic dissolution development as per guidance and is further applicable for routine analysis. But as per above statement, it looks like that final specification is to be set from the result of bio batch. Please clarify.	Indeed the RP suggests that the final specification limit should be derived from the results of the biobatch (when available or from the test batch used to support BCS biowaiver).
147	193-196 (224-227)	1	The guidance is clear that in-vivo performance of the pivotal bio-batches is critical to setting specs and should be built into the development program at an early stage. One concern would be if the BE batch is with BE criteria in-vivo but shows a slower dissolution than commercial lots. What will drive the	The biobatch should be used to set dissolution specification. See response in comment #115.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			specification? BE batch or the preponderance of commercial batches and registration supportive batches?	
148	195 (226)	1	**Comment:** Use of the bio-batch in this manner would seem to lead to dissolution specifications that are very tightly bound to batch data and probably to over-discriminatory methods and specification requirements. We would anticipate that other approaches can be taken to justify the bio-relevance of the dissolution acceptance criterion than this tight linkage to batch data (e.g. using slow releasing batches with known PK performance, as per section 1.2.2.). Therefore we are not convinced that this linkage to the dissolution of the bio-batch need be absolute and should not be the only approach that can be used for innovator products with e.g. broader development and product knowledge. **Proposed change:** Please reconsider if this linkage to bio-batch dissolution need be so absolute for any product and in particular for innovator products with wider development knowledge and product understanding.	Restriction of the scope to generic products only (remark: this is written in the scope).
149	196 (227)	1	**Comment:** The text states “similar dissolution of two batches may be assumed in case of differences of less than 10% in their mean results”. Whilst this may be true, a specification of ±10% vs. the bio batch may be unnecessarily tight, especially if so called ‘side-batches” exhibiting dissolution rates outside this limit have been shown to be bioequivalent. **Proposed change:** Please clarify the intent of this sentence.	If side batches are found bioequivalent the specification limit may be drawn from the slower batch shown to be bioequivalent. See scenario under 1.2.1.
150	196-198 (227-229)	2	**Comment and rationale:** The definition of similar dissolution considers the mean result of the biobatch	The difference should not be more than 10%.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			but not single values as basis for setting the specification (mean value minus 10% as Q value) is considered too tight, also taking into account the accepted variability of dissolution testing. **Proposed change:** Similar dissolution of two batches may be assumed in case of differences of less than 10% in their mean results. Therefore, the *Q* value is recommended to be set on the basis of the biobatch dissolution result (mean value) minus ~~10%~~ **15%**.	
151	196 (227)	3	**Comment:** The text states "similar dissolution of two batches may be assumed in case of differences of less than 10% in their mean results". Whilst this may be true, a specification of ±10% vs. the biobatch may be unnecessarily tight, especially if so called 'side-batches" exhibiting dissolution rates outside this limit have been shown to be bioequivalent. **Proposed change (if any**): Please clarify the intent of this sentence.	See response in comment #149.
152	197 (228)	9	**Proposed change (if any):** Clarify if 10% is relative or absolute.	It is absolute, i.e. 10% of label claim.
153	196-197 (227-228)	12	**Comment:** "Similar dissolution of two batches may be assumed in case of differences of less than 10% in their mean results". This statement needs to be elaborated.	This is a consequence of the F2. The F2 is >50 only when the absolute average difference of means between T

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Proposed change (if any): Need clarity in cases where calculated F2 values between 2 batches are below 50 but difference between the mean results are less than 10% or vice versa, whether dissolution of 2 such batches would be considered similar or not.	and R is <10% considered for the calculation of F2.
154	196-198 (227-229)	13	**Comment:** It is agreed that similarity of results is expected when they differ less than 10%. However, due to the nature of the method some variability is expected. As stated in line 91 a maximum RSD of 10% considered acceptable. The variability should be reflected in the setting of specification limit i.e. by applying the minimum value of the BE batch dissolution testing. If this is not given e.g. a limit of Q=80% (based on BE batch data of 90%±5%) would only allow a deviation of 5% from the BE batch. This is considered overdiscriminatory and cannot be in the sense of the guideline. **Proposed change (if any):** Similar dissolution of two batches may be assumed in case of differences of less than 10% in their mean results. ~~Therefore,~~ **To reflect the variability of the method** the *Q* value is recommended to be set on the basis of the biobatch dissolution result (~~mean~~ **minimum** value) minus 10%. **The acceptable tolerances for variability are included in section 1.1.**	See response in comment #150.
155	197-198 (228-229)	9	**Comment:** With a Q level of 75% a < 10% difference could also result in differences to the high side. How to judge about similar behaviour in this case? Immediate release dissolution specifications do not contain an upper limit.	See response in comment #115.
156	197–198	19	**Comment:** Similar dissolution of two batches may be assumed in case of	The purpose of the

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
	(228-229)		differences of less than 10% in their mean profiles. Therefore, the draft reflection paper recommends setting the Q-value on the basis of the biobatch dissolution result (mean value) minus 10%. For a release at stage S1, in line with Ph.Eur. (Section 2.9.3), dissolved amount for each unit should be not less than Q-value plus 5%. Effectively, this means that for a release at stage S1 the maximum allowable difference from biobatch will be 5% or lower, depending on variability in the dissolution. Moreover, based on the rules proposed by the reflection paper, even batches with low variability in dissolution will experience difficulties to pass the S1 release. This is demonstrated by following example. Suppose a biobatch where the mean dissolved amount at 15 minutes corresponds to 88% with standard deviation of 3.5% (%CV 4%). In this case, the paper proposes to set the specification (Q) to 75%, 80% or 85% whichever is closer to Q=biobatch result – 10%. Accordingly, the Q-value would be set to 80% as being closest to 78% (=88 – 10%). In line with Ph.Eur. (Section 2.9.3), for a release at stage S1, 6 units must dissolve not less than Q-value +5%. Practically, for any production batch with dissolution identical (mean and %CV) to the biobatch, under normality assumption, at least one out of six units (~20% chance) would be expected to display the dissolved value below 85%. Consequently, such a batch does not pass S1 stage release and additional 6 units would need to be measured for a S2 stage release. It is to be noted that in this particular example, we assumed no variation in assayed content. In reality, even an acceptable variation in API content makes the S1 release less probable. In summary, for routine manufacturing, the compliance with release at stage S1 will be difficult to achieve.	specification limit is to ensure consistent in vivo behaviour of commercial batches to the biobatch and it is not intended to allow necessarily a “pass” result at the abbreviated (6 vs 12 units) S1 level. Refer to lines 217-220): “Batch results showing compliance with stage S1, S2 and S3 (Ph. Eur. 2.9.3.) are acceptable. The specification should be set in such a way so that during routine manufacture and testing it would be expected that compliance with S2 is attained.”

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
157	199-200 (230-231) & Annex 1 Decision tree	2	**Comment and rationale:** A Q value of >80% may not be workable for many products. Similarly, caution is needed regarding a Q value of 85% as this may not be feasible. **Proposed change:** "*The acceptance criteria the Q value is usually set in the range between* ~~***75-85%***~~ ***70-80%*** *(5% intervals) to demonstrate discriminatory power and satisfactory dissolution.*"	No. The rational of the RP is in lines 227-229: "Similar dissolution of two batches may be assumed in case of differences of less than 10% in their mean results. Therefore, the *Q* value is recommended to be set on the basis of the biobatch dissolution result (mean value) minus 10%." It is acknowledged that the Bioequivalence guideline criterion for similarity between different batches considers dissolution profiles which meet >85% dissolved API within 15 minutes as similar without further calculation. However if bioequivalence has been shown with a biobatch that released 95% in 15 minutes it cannot be safely assumed that future batches showing 80% in 15 minutes (as per the proposal) would be bioequivalent.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
				With regards to the argument about additional dissolution tests on S2 level refer to lines 217-220: "Batch results showing compliance with stage S_1, S_2 and S_3 (Ph. Eur. 2.9.3.) are acceptable. The specification should be set in such a way so that during routine manufacture and testing it would be expected that compliance with S_2 is attained."
158	199-200 (230-231)	2	**Comment and rationale:** Since a dissolution above 85% after 15min is defined as very rapid and in accordance with CPMP/EWP/QWP/1401/98 Ref.1/Corr** no further proof of similarity is required, a Q value above 80% is not considered useful.	See response in comment #157.
159	200- 201 (231-232)	3	**Comment:** The sentence as written needs to be simplified, "It is not considered relevant to have limit of more than 85%." **Proposed change (if any):** Consider rewriting sentence as, "A limit greater than 85% is not relevant."	Accepted.
160	201-202 (232-233)	16	**Proposed change:** Time points other than ~~Usually the time points~~ 15, 30 or 45 minutes ~~would be~~	Proposed wording seems more flexible to other time points.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			~~sufficient, but other time points~~ may be used if justified.	One of the goals of this paper is to ensure harmonisation. Therefore rejected.
161	202-203 (233)	3	**Comment:** The sentence as written needs to be simplified, "It is not considered relevant to choose a time point before 15 minutes." **Proposed change (if any):** Consider rewriting sentence as, "A time point prior to 15 minutes is not relevant."	See response in comment #160.
162	199 (230) 204-206 (235-237) 208 (238) 199 (230) 208-216 (238-247)	5	**Comment:** When setting a specification with Q=85% one should consider that at stage 1 the limit is for each single value is Q+5 %: That means each single value has to be above 90%. This limit interferes with the acceptance criteria for content uniformity. Therefore the limits for Q should not exceed 80%. **Proposed changes:** The acceptance criteria the *Q* value is usually set in the range between 75-80% to demonstrate discriminatory power and satisfactory dissolution. It is not considered relevant to have a limit of more than 80%. Q limit should not be more than 80%; change in the paragraph	See response in comment #157.
163	199 (230) 204-206 (235-237) 208 (238)	11	**Comment:** When setting a specification with Q=85% one should consider that at stage 1 the limit is for each single value is Q+5 %: That means each single value has to be above 90%. This limit interferes with the acceptance criteria for content uniformity.	See response in comment #157.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
	199 (230) 208-216 (238-247)		Therefore, the limits for Q should not exceed 80%. **Proposed changes:** The acceptance criteria the Q value is usually set in the range between 75-80% to demonstrate discriminatory power and satisfactory dissolution. It is not considered relevant to have a limit of more than 80% Q limit should not be more than 80%; change	
164	207–227 (234-258)	10	**Comment:** The rationale of the Q specification proposed: Biobatch result -10% is unclear. **Proposed change:** Please clarify the rationale.	+/- 10% is considered to be similar.
165	208-216 (235-247)	2	**Proposed change:** • If the dissolution of the biobatch is larger than or equal to 95% in 15 minutes, the specification may be set to *Q*=~~85%~~**80%** after 15 minutes[1]; • If the dissolution of the biobatch is less than 95% but larger than or equal to 85% in 15 minutes, the specification (*Q*) may be set to~~ 75%, 80% or 85%~~ **70%, 75% or 80%** whichever is closer to *Q*=biobatch result ~~-10%~~ **-15%** at 15 minutes[1]; • If dissolution of the biobatch is larger than or equal to 85% after 30 minutes, the specification (*Q*) may be set to ~~75%, 80% or 85%~~ **70%, 75% or 80%** whichever is closer to *Q*=biobatch result ~~-10 %~~ **-15%** at 30 minutes; • If dissolution is larger than or equal to 85% after 45 minutes, the specification may be set to ~~75%, 80% or 85%~~ **70%, 75% or 80%** after 45 minutes.	See response in comment #157.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
166	208-209 (238-239)	8	**Comment:** Lines 208-209 (238-239) state: "If the dissolution of the biobatch is larger than or equal to 95% in 15 minutes, the specification may be set to Q=85% after 15 minutes." Complete release is generally defined as > 85 % dissolved API within prescribed time. Also according to the BEQ guide criterion for similarity between different batches considers dissolution profiles which meet >85% dissolved API within 15 minutes as similar without further calculation. Especially when the discriminatory power of the QC dissolution method is proven for dissolution limit 80% (Q) in 15 minutes, there is no need for further tightening of dissolution limits on 85% (Q) in 15 minutes as this would, taking into account normal manufacturing and analytical variability only cause potential additional dissolution tests on S2 level and at the same time additional costs with no contribution to the quality of the product. **Proposed change:** Delete lines 208-209 (238-239). Revise lines 210-212 (240-242): "If the dissolution of the biobatch is larger than or equal to 85% in 15 minutes, the specification may be set to Q=75 % or Q=80 % whichever is closer to Q=biobatch-10 % at 15 minutes." Revise also lines 213-214 (243-245) and 215-216 (246-247) to delete Q=85 % limit. Revise Annex 1 accordingly.	See response in comment #157.
167	208-209 (238-239)	13	**Comment:** Lines 208-209 (238-239) state: "*If the dissolution of the biobatch is larger than*	See response in comment #157.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			or equal to 95% in 15 minutes, the specification may be set to Q=85% after 15 minutes." Complete release is generally defined as > 85 % dissolved API within prescribed time. Also according to the BEQ guide criterion for similarity between different batches considers dissolution profiles which meet >85% dissolved API within 15 minutes as similar without further calculation. Especially when the discriminatory power of the QC dissolution method is proven for dissolution limit 80% (Q) in 15 minutes, there is no need for further tightening of dissolution limits on 85% (Q) in 15 minutes as this would, taking into account normal manufacturing and analytical variability only cause potential additional dissolution tests on S2 level and at the same time additional costs with no contribution to the quality of the product. A dissolution of NLT 85% (mean) after 15 min. is usually acceptable as comparable without f2 calculation, as in-vivo absorption in this case is limited by gastric emptying. Thus a Q-value of 80% after 15 min. (every single value in stage S_1 is NLT 85%) is fully sufficient also for products with very rapid dissolution characteristics. A Q-value of 85% after 15 min. would not represent any additional benefit. Reference is also made to line 222 (253) to 227 (258) of the draft paper, where, in case of BCS biowaiver approach, the specification should be set to Q=80% after 15 min. resp. 30 min. **Proposed change (if any):** The term should be changed to 'the specification should be set to Q=80% after 15 minutes'	

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Revise Annex 1 accordingly.	
168	208-221 (238-251)	18	Criteria to set Q limits in Annex 1 of the reflection paper are based on the amount released at relevant time points (15, 30, 45 minutes) using a discriminatory method and the dissolution profile of the pivotal (bioequivalence) batch. However, Q limit may then be set at one time point (for example, 45 minutes) where no discrimination in dissolution is found data used to support this method property. For example, when several batches of the same formulation are prepared with different setting (i.e. “bad batches”) differences in dissolution may be observed between 10 and 30 minutes of the dissolution curves, whereas the dissolution of the pivotal batch justifies a Q value at 45 minutes. In such case would an agency then request the applicant to change the Q limit to another (earlier) time point where discrimination in dissolution is observed? **Proposed change (if any):** Not applicable	Yes, see lines 234-251 in the reflection paper.
169	210-212 (240-242)	13	**Comment:** The term ‘the specification (Q) may be set to 75%, 80%, 85% whichever is closer to Q=biobatch -10%’ would lead worst case to a difference of only 8% between biobatch dissolution result (mean value) and Q value: e.g. in case of a dissolution of the biobatch of 88% (mean value) the specification would have to be set to Q (80%). In consequence in stage S_1 testing every single unit would have to show dissolution of NLT 85%. This represents an artificially narrow specification so that stage 2 testing would frequently occur.	It is acknowledged that S2 testing might occur for some products. Proposal not accepted. See also comment #157.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Furthermore a Q value of 85% after 15 min.is not justified in our opinion (See response in comment line 208-209 (238-239)), so that Q=85% should be omitted. **Proposed change (if any):** The term should be changed to' the specification (Q) may be set to 75%, 80% whichever is equal or next lower to Q=biobatch -10% at 15 minutes' Revise Annex 1 accordingly.	
170	208-216 (238-247)	8	**Comment:** Lines 208-216 provide the recommendations for setting specifications based on dissolution of the biobatch. In many cases where more than one strength of a product is being developed (usually 4 to 5), the dissolution of smallest strength could be usually quite high as compared to the highest strength using the same dissolution conditions. And in case of veterinary products, the biobatch usually one of the smaller strengths. In this case setting specification based on biobatch (i.e. smaller strength) will not accommodate the slow release rate of the bigger strengths. Therefore, a provision should be included for setting the specifications based on dissolution of highest strength in case of considerable difference in dissolution between biobatch (i.e. smaller strength) and highest strengths. **Proposed change:** A provision should be added for setting specification based on dissolution of highest strength if there is considerable dissolution difference between biobatch and the highest strength of the product.	If the difference in dissolution between strengths is significant no strength biowaiver will be accepted.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
171	228–232 (259-263) Conclusion	19	**Comment:** Bioequivalence studies are often integral part of development of innovator products and thus similar rules should be applied for these products unless additional data support the choice of specification. **Proposed change:** Modify line 232 – 233 (262-263) as follows. Similar principles ~~may~~ should be considered for deriving the specification for innovator products. Also, modify lines 7 and 49 to exclude the term generic.	It is agreed that the same rationale i.e. that the specifications should be derived from batches used in the clinical trial including bioequivalence studies. In case of innovator product though there are usually much more data from clinical batches where conclusions can be drawn about the appropriate specification limit. For this reason the proposed wording reads "may be considered".
172	213-215 (243-245)	1	**Comment:** The text states "…is larger than or equal to 85% after X minutes". We think for clarity this should read "…is larger than or equal to 85% only after X minutes." **Proposed change (if any):** Please make this change for clarity.	Accepted.
173	213-215 (243-245)	3	**Comment:** The text states "…is larger than or equal to 85% after X minutes". We think for clarity this should read "…is larger than or equal to 85% ONLY after X minutes." **Proposed change (if any):** Please make this change for clarity.	See response in comment #172.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
174	213-214 (243-245)	10	**Comment:** In the case where dissolution rate of the reference product is above 85% between 15 min and 45 min, it is probable that its specification is Q75% 45 min (immediate release form). It is also well-know that in this case, the dissolution profile could be variable (one batch reach 85% in 30 min, another one 85% in 35 min etc.). It is possible that even is the generic maker tested several batches, it could find for example batches above 85% in 30 min. According to the decision tree: the generic product has a norm Q-10% = 75% 30 min. Where the reference has Q 85% 45 min. **Proposed change:** if the dissolution of the biobatch is less than 85% in 15 min, and larger than 85% in 45 min, the specification (Q) may be set Q 75% 45 min as required by Ph.Eur for immediate release form.	75% after 45 minutes are not a requirement of Ph. Eur., See response in general comment #5. Generally, the specification of the generic (as with any other product) is set based on the information and data presented in the generic own dossier. The specifications of the reference product are not considered when setting the specifications for a generic product. The rationale of setting the dissolution specification is to ensure consistent in vivo behaviour of commercial batches to the biobatch and is set out in lines 227-229
175	213-214 (243-245)	13	**Comment:** See response in comment line 210-212 (240-242) **Proposed change (if any):** The term should be changed to' the specification (Q) may be set to 75%, 80% or 85% whichever is equal or next lower to Q=biobatch -10% at 30 minutes'	No. The rationale of setting the dissolution specification is to ensure consistent in vivo behaviour of commercial batches to the biobatch and is set out in lines 227-229.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Revise Annex 1 accordingly.	
176	215-216 (246-247)	13	**Comment:** See response in comment line 210-212 (240-242) **Proposed change (if any):** The term should be changed to' the specification (Q) may be set to 75%, 80% or 85% whichever is equal or next lower to Q=biobatch -10% at 45 minutes' Revise Annex 1 accordingly.	No, see response in comment #175
177	217 (248)	1	**Comment:** Since line 215 (246) states "if dissolution is larger than or equal to 85%...", line 217 (248) should be changed to "in case dissolution of the biobatch is less than 85%..." to definitely distinguish the two related instructions. **Proposed change:** Update as indicated.	Reworded to: "If dissolution is larger than or equal to 85% at 45 minutes".
178	221 (250-251)	1	**Comment:** The text states "Therefore the dissolution specification should be based on more than one time point" but gives no further guidance. It may be relevant to provide further specific guidance on how to approach specification setting in these circumstances. However we also consider, given this paper is written primarily for generic IR products, that an innovator product that is IR should lead to a generic product with non-IR performance specification. **Proposed change:** Please consider what advice should appear in this Reflection Paper on this matter.	Out of scope. These cases should be justified on a case by case basis.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
179	221 (250-251)	3	**Comment:** The text states "Therefore the dissolution specification should be based on more than one time point" but gives no further guidance. It may be relevant to provide further specific guidance on how to approach specification setting in these circumstances. However we also consider, given this paper is written primarily for generic IR products, that an innovator product that is IR should not lead to a generic product with non-IR performance specification. **Proposed change (if any):** Please consider what advice should appear in this Reflection Paper on this matter.	See response in comment #178.
180	217-221 (248-251)	7	**Comment:** See response in comment on lines 45-47 (49-51) – the Ph. Eur. Recommends in chapter 5.1.17 a timeframe for conventional-release dosage forms of **typically** 45 minutes or less. There are immediate release dosage forms on the market which have a dissolution specification at a time point later than 45 min and this is not excluded by the European Pharmacopoeia (see also definitions in ICH Q6A and Ph.Eur. in the general comment). We therefore don't share the interpretation that such a dosage form might not be considered as immediate (or conventional) release. The sentence in its current form might mislead readers. However, we fully support the consequence that for products with less than 75 % (Q) after 45 min a second time point should be included in the specification. **Proposed change to:** "Otherwise, if the dissolution specification (Q) is less than 75% after 45 minutes, the dissolution specification should be based on more than one time point."	Yes, proposal partially accepted. Text reads: "…immediate release is identified as at least 75% (Q) at 45 minutes" See also lines 249-251.
181	219-221 (250-251)	8	**Comment:** Lines 219-221 (250-251) state: "If the dissolution specification (Q) is less than	Out of scope of this paper.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			75% after 45 minutes, the drug product is not inside the recommendation of the Ph. Eur. Of an immediate release dosage form (see Annex 1: Decision tree for the principles for setting specifications). Therefore, the dissolution specification should be based on more than one time point." Further guidance should be given on how dissolution limit should be defined in cases of products which achieve >85% API dissolved after 60, 90 or 120 minutes, respectively. These products are not ordinary IR products, however, they are also not sustained release products. - Should there be two point specification where, one time point is after 45 minutes (in accordance with Ph. Eur for IR products) and one at the time point where >85% of API is dissolved? - How should the limit be stated, Not less than XX % at both time points or should there also be an interval as in case of SR products (20% interval). This approach could be overdiscriminatory for IR products as their main purpose is to release complete amount of API within prescribed time and there is no danger of dose dumping. **Proposed change:** Further guidance should be given.	See response in comments #178 and #180.
182	218-221 (249-251)	13	**Comment:** As noted for lines 45-47 (49-51), there is no strict definition in the Ph. Eur. for immediate release products, therefore a cut-off at 45 minutes is not considered justified, more flexibility is proposed, also considering e.g. the properties of the drug substance.	See response in comment #180. See also changed decision tree (line 328).

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Proposed change (if any): Otherwise, if the dissolution specification (Q) is less than 75% after 45 minutes, the drug product is not inside the recommendation of the Ph. Eur. ~~of~~ **and may not be considered as** an immediate release dosage form, **unless otherwise justified** (see Annex 1: Decision tree for the principles for setting specifications). ~~Therefore~~ **In this case**, the dissolution specification should be based on more than one time point.	
183	219-221 (249-251)	13	**Comment:** Lines 219-221 (249-251) state: *"If the dissolution specification (Q) is less than 75% after 45 minutes, the drug product is not inside the recommendation of the Ph. Eur. of an immediate release dosage form (see Annex 1: Decision tree for the principles for setting specifications). Therefore, the dissolution specification should be based on more than one time point."* Further guidance should be given on how dissolution limit should be defined in cases of products which achieve >85% API dissolved after 60, 90 or 120 minutes, respectively. These products are not ordinary IR products, however, they are also not sustained release products. Should there be two point specification where, one time point is after 45 minutes (in accordance with Ph. Eur for IR products) and one at the time point where >85% of API is dissolved? How should the limit be stated, Not less than XX % at both time points or should there also be an interval as in case of SR products (20% interval). This approach could be over-discriminatory for IR products as their main purpose is to release complete amount of API within prescribed time and there	See response in comment #180.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			is no danger of dose dumping. **Proposed change (if any):** Please provide further guidance.	
184	218-221, (249-251) Annex 1	15	**Comment:** According to the decision tree depicted as Annex 1, minimum limit of Q = 75% in 45 minutes has to be applied as a strict rule in order to define whether the drug product is an immediate-release formulation or not. In contrast, the Ph.Eur. does not allow such an interpretation since chapter 5.17.1. specifies the Q-value of 75% in 45 minutes as a 'typical value, applicable in most cases', but not all. This implies that in justified cases, formulations with less stringent limits, such as e.g., Q = 70% in 60 minutes, can still be considered as immediate release formulations and a single-point acceptance criterion is sufficient to demonstrate a complete release of active substance. **Proposed change (if any):** Harmonize the definition of the immediate-release formulation with the chapter 5.17.1. of Ph.Eur. Formulations with less stringent limits, such as e.g., Q = 70% in 60 minutes, can still be considered as immediate release formulations if properly justified.	Yes, see response in comment #180. See changed decision tree (line 328).
185	223 (253-254)	3	**Comment:** The use of Roman numerals (I, III) versus Arabic numerals (1, 3) for BCS class should be consistent in guidance. Line 119 (136) and Line 122 (139) use Arabic numerals to describe BSC class.	Accepted. Changed into Roman numbers.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			Line 223 (253) uses Roman numerals to describe BSC class. **Proposed change (if any):** Suggest using Arabic numerals for BSC class designation.	
186	224 (255)	1	**Comment:** clarify "This Q value should be 80% using discriminatory test conditions..."For BCS I or III, discriminating dissolution test conditions may not be able to be established.	RP reworded to: "This Q value should be 80% using discriminatory test conditions (i.e. the QC method applied for),..."
187	224-227 (255-258)	2	**Comment and rationale:** In case of BCS class I and III substances not always discriminatory test conditions can be achieved.	See response in comment #186.
188	224 (255)	3	**Comment:** clarify "This Q value should be 80% using discriminatory test conditions..."For BCS I or III, discriminating dissolution test conditions may not be able to be established.	See response in comment #186.
189	224 (255)	9	**Comment:** Why should the Q value be set to 80% but not 85%. **Proposed change (if any):** This section should also allow for replacing dissolution specification by tight disintegration specification (<< 15 min).	This Q value 80% refers to discriminatory test conditions i.e. the QC method(s) and should not be confused with the BCS biowaiver requirement of 85% in the different pH media.
190	229	13	**Comment:**	Agreed.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
	(260)		Typo: Reflection **Proposed change (if any):** This ref**l**ection paper should facilitate […]	
191	231 (262)	1	**Comment:** The text states (in its final sentence but not earlier or in the tile of the paper) that "similar principles may be considered for deriving the specification for innovator products. In accordance with the comment above (line 195 (226)) we are not convinced that this linkage to bio-batch performance is the only way to consider establishing a dissolution acceptance criterion for an innovator product. **Proposed change:** Omit this final sentence	The principle may be applied but it is not binding for innovative products.
192	231 (262)	3	**Comment:** The text states "similar principles may be considered for deriving the specification for innovator products". Is the expectation that this reflection paper applies to innovator product? If yes, update the title. If no, omit the last sentence. **Proposed change (if any):** Omit the last sentence or widens the title of the paper to include innovator products.	The principle may be applied but it is not binding for innovative products.
193	229-232 (260-263)	9	**Comment:** Last sentence makes no sense as the scope is on generic products. **Proposed change (if any):** Delete last sentence.	The principle may be applied but it is not binding for innovative products.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
194	234 (265)	11	**Comment:** References Add reference to the FIP guidelines: FIP Guidelines for Dissolution Testing of Solid Oral Products, Pharm. Ind. 57, 5, 362-369 (1995) These are currently under revision	Not accepted.
195	235-239 (266-270)	7	**Comment:** The 9th edition of the European Pharmacopoeia has been published in July 2016 and reference to the Ph. Eur. should be updated accordingly. **Proposed change:** European Pharmacopoeia (Ph. Eur.), **9th edition**, 5.17.1. Recommendations on Dissolution Testing European Pharmacopoeia (Ph. Eur.), **9th edition**, ~~8th edition,~~ 2.9.3. Dissolution Test for Solid Dosage Forms.	Accepted.
196	239 (270)	16	Reference to the 8th edition of the European Pharmacopoeia is recommended to be deleted.	Accepted.
197	247-248 (280-281) Annex 1 Decision tree	2	**Comment:** Decision tree assumes dissolution method is appropriate to start with - there is therefore a potential for this decision tree to be misleading.	Out of scope.
198	248	3	**Comment:** Suggest starting flow diagram with case of >95% in 15 min	Included in the first step of

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
	(281)			the decision tree
199	Annex 1	5	Change specifications above Q=80%	See response in #157
200	Annex 1, first column, last box	7	**Comment:** The sentence that the "Applied product is not an immediate release formulation according to the European Pharmacopoeia recommendations." is seen as misleading as explained in the comments above. **Proposed change:** Delete the box and point the arrow directly to the conclusion that "Specification for dissolution should use more than one time point."	Changed.
201	247 (280) - onwards (decision tree)	8	**Comment:** If dissolution > 85%/15 min specification should read Q = 75%, 80% or 85 % whichever is closer to (biobatch -10 %). As result of pharmaceutical development drug product should comply with S1. In routine batches may be compliance with S2 but this should be an exception. **At time of specification, there are no data for routine production.** A change of stirring speed may only be justified if RSD is greater 10% at 15 min. But if RSD is between 5% and 10 % problems with specification S2 at specified Q value may occur. **Proposed change:** Two solutions are proposed: Solution 1: Change of stirring speed is justified at time points >= 15 min > 5% RSD. Solution 2: If Dissolution level of development batches is at level S2 set testing	Response to Solution 1: Not accepted. Response to Solution 2: No, See response in comment #133.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
			time to 30 min as specified in decision tree stage 2.	
202	247-248 (280-281)	10	**Comment:** The decision tree assumes that any IR product needs a dissolution test, whilst in fact there are exceptions where such a test is not appropriate. There are several Vet Med solid oral products which contain two or three antiparasitic compounds all of which are BCS Class 4 i.e. have very low solubility and low permeability. The substances act locally within the animal stomach and there is little, if any systemic exposure. In fact, the combination of low solubility (to maintain a saturated solution in the stomach) and low permeability (to reduce loss from the stomach by absorption) is ideal for such products. These products are 'immediate release' by not immediate dissolution. For such products disintegration rather than dissolution is a more appropriate quality control test. To achieve sink conditions for such products means the use of such unusual media that any link to in-vivo behaviour is no existent. In fact bioequivalence studies for such products are also of limited value due to the lack of any PK profile. **Proposed change:** Please modify the decision tree to include a pre-screen to decide if a dissolution test is required at all.	The quoted cases where dissolution testing is not necessary are indeed exceptions and as such are not covered by this RP. Such exceptions should be justified on a case by case basis (e.g. disintegration test instead of dissolution).
203	Annex 1	11	Change specifications above Q=80%.	No, see response in comment #157. The rational for the proposed specs (75, 80, 85%) is explained in the RP and in principle should be as close as possible to that of the biobatch.

Comment no.	Line no. in original paper*	Stakeholder no.	Comment and rationale; proposed changes*	Outcome*
204	247-248 (280-281) (Annex I)	13	**Comment:** More flexibility should be allowed in order to set the specification. For example, for some products the dissolution profiles may be very different between originator and generic formulation but not have a significant effect *in vivo*. This should be considered in the reflection paper, especially for cases where the originator formulation is significantly slower than the generic formulation. More flexibility should be allowed considering the following cases: - literature data are available demonstrating that the dissolution is not critical for bioequivalence - BCS class 1 and 3 drug substances - BE batches which are very similar *in vivo* to the originator	No contradiction to the approaches described in the reflection paper. The objective of the RP is harmonisation in the way dissolution specifications are set.
205	247-248 (280-281) (Annex I)	13	**Comment:** It is requested that the reflection paper takes a similar approach to the FDA draft guidance on BCS Class 1 and 3 Drugs on this topic which specifies differing requirements depending on BCS Class.	No. The objective of the RP is harmonisation in the way specs are set based on the EU guidelines
206	247-248 (280-281) (Annex I)	13	**Comment:** Please include a list of abbreviations or at least explain those abbreviations where it is unclear where they stand for, e.g. “A” on page 9/9. (10/10)	Amount dissolved.