20 March 2014
EMA/CHMP/QWP/428694/2013
Committee for Human Medicinal Products (CHMP)

Overview of comments received on 'guideline on quality of oral modified release products' (EMA/CHMP/QWP/428693/2013)

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

Stakeholder no.	Name of organisation or individual
A	EFPIA
B	EGA
C	AESGP
D	Ranbaxy Laboratories Limited
E	MEB (NL)
F	EDQM
G	Synthon BV
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1. General comments

Stakeholder - page number	Comment number	General comment (if any)	Outcome (if applicable)
<A>	**1**	We welcome revision of this guidance. The general concepts are consistent with a high-level expectation for the development of oral modified release products. The new guidance is better aligned with QbD concepts, more prescriptive and expectations spelt out clearly. The draft guidance presents a comprehensive perspective on (1) methods of developing in vitro dissolution methods (2) methods of developing an IVIVC, and (3) using an IVIVC to set drug product performance specifications. More information has been discussed in this draft guidance about discriminatory power of dissolution methods (section 2.1.4), specifications for zero order release kinetics (lines 134-139 and 249-252), and adding numeric specifications for the drug release from a prolonged formulation at early time points to avoid dose dumping (line 249). However, we see some areas where further clarity could be provided and some where we have concerns with the text as it currently stands. We offer these detailed comments below for consideration.	N/A
<B>	**2**	<B> welcomes the opportunity to comment on the draft EMA guideline on the quality of modified release medicinal products.	N/A

Stakeholder - page number	Comment number	General comment (if any)	Outcome (if applicable)
		Overall, the present draft guideline provides sufficient elements for the development of prolonged and delayed release dosage forms, for the reasons to determine an IVIVC or on how to set up a specification.	
<B>	**3**	An additional section on the investigation of "Dose Dumping" should also be considered to complete this draft guideline.	Comment noted however it is that up to the applicant to demonstrate that the performance of the product is the desirable.
<B>	**4**	Furthermore, the draft guideline provides only limited information on IVIVC than other regulated regions (eg, US FDA guidance). The approach on how to develop a level A IVIVC could in this regard be further elaborated in the final EMA guideline.	Harmonisation is always desirable but this is an EU guideline. The guideline is not a stand-alone textbook. It is expected that the users obtain their knowledge elsewhere, and it is considered that for the purpose of this GL, it is sufficient to present an overview, and to distinguish between IVIVC levels A, B and C in terms of their use. See comment 8.
<B>	**5**	The draft guideline refers in several occurrences to the need to perform dissolution testing under physiological conditions. There is however no section dedicated to what could constitute a 'physiological' dissolution. We recommend, for clarity and alignment purposes that when referring to 'physiological conditions', the final guideline makes a clear statement regarding pharmacopoeial buffers (with or without, for example, enzymes) as well as to the applicable pH range (e.g. pH 1 to pH 8).	The comment is noted. It should however be noted that even the "pharmacopeial buffers" as presented in the non-mandatory chapter 5.17.1, are only recommendations. It is always up to the applicant to justify his choice of testing conditions. See comment 29.
<A>	**6**	**IVIVC:** A major concern is that the reader of the guidance could reach	Revised text is included clarifying the issue (lines 72-80).

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		the conclusion that an IVIVC is a mandatory requirement for a modified release (MR) product whereas previously it was more of a recommendation that you attempt to develop an IVIVC. It appeals scientifically but is extremely difficult to execute. It would likely mean companies having to run more clinical studies comparing bioavailability to develop IVIVC models and developing more CR formulations with differing release profiles to evaluate in these studies. The guidance generally raises the bar as to what will be required in an MR type filing. However, the establishment of an IVIVC is not always possible and should thus not appear to be a 'must' in the text of the guidance (please see our detailed comments on this matter against specific lines of the draft text.) Also, it is unclear whether Unit Input Response treatment arms are required for developing the IVIVC (annex 2). Clarification on this is recommended.	See comments 26, 27, 88 & 99 & 106
<A>	**7**	**Modelling:** The present document does not include the use of predictive mathematical models as supplemental data to strengthen an IVIVC/R or for comparing in vitro dissolution profiles.	This is now included in the PK draft guideline.
<A>	**8**	**Harmonization:** In general, a harmonization between the EMA Guideline on quality of oral modified release products and the"FDA guidance for industry: *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo*	Harmonisation is always desirable however this is an EU guideline. Essentially, a level A IVIVC can be used to support changes and extrapolation of the in vivo results of one strength to another strength in a

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		Correlations" would be deemed useful since specific guidance is given on applications of the IVIVC (as described in Section VII, Applications of an IVIVC), in the FDA guideline, including: A) Biowaivers for Changes in the Manufacturing of a Drug Product (manufacturing, composition changes, lower dosage strengths) and B) Setting dissolution specifications. Please refer to the following section for more specific comments. Also for more clarity, we recommend to ensure that the guideline is aligned with the upcoming guidance on BE studies.	series of drug products. Further guidance on such extrapolation (biowaiver for strengths) is provided in the Bioequivalence guideline. *See comment 4.*
<A>	**9**	**Dosage forms:** The guideline seems to actively discourage the use of a single unit non-disintegrating gastro resistant dosage forms due to the perception of a higher risk of dose dumping and/or erratic PK profiles. It is recommended that the guideline focuses on methods to characterize the potential for dose dumping and/or erratic PK profiles, rather than discouraging a particular type of dosage form. It is worth mentioning that there are already many restrictions on the application of single unit non-disintegrating dosage forms including tablet/capsule size, selection of polymers, inherent PK variability due to drug substance permeability/metabolism, etc.	*See comment 100*. This understanding is correct.
<A>	**10**	**Scope**: The title of the revised draft guideline is broad "Quality of oral	The guideline covers specific issues of orals modified release products. ICH Q8 is highly relevant also for this type of products. There is

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		modified release products" but the content is primarily focused on dissolution and IVIVC. There is no reference to the ICH Q8 Pharmaceutical Development guideline, nor mention of the new quality concepts QTPP and design space, which we believe is significant omission. We believe that the scope of the guideline should be broader. Some gastro-resistance polymers are designed to dissolve at relatively high pH (pH 7.0) and used to target the lower GI tract & colon rather than the upper GI tract. Would drug products based on this polymer type (pH trigger) be considered within the scope of the guideline? It was highlighted that products targeting specific areas of the GI tract are out of scope but those using the principle of gastro-resistance are within scope.	mention of CQAs in the guideline. The products that dissolve at relatively high pH would be covered by the general remarks under delayed release dosage forms (3.1). The guideline is not intended to cover every possibility and very specific forms but rather the majority of MR products. *See comment 11 and 12.*
<C>	**11**	The title of the revised draft guideline is broad "Quality of oral modified release products" but the content is primarily focused on dissolution and *in vitro-in vivo comparison* (IVIVC). We believe that the scope of the guideline should be broader. There is no reference to the ICH Q8 Pharmaceutical Development guideline, nor mention of the new quality concepts QTPP and design space, which we believe is a significant omission.	*See comment 10 and 12.*
<C>	**12**	Scope: Some gastro-resistance polymers are designed to dissolve at relatively high pH (pH 7.0) and used to target the	*See comment 10 and 11*

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		lower GI tract & colon rather than the upper GI tract. Would drug products based on this polymer type (pH trigger) be considered within the scope of the guideline? It was highlighted that products targeting specific areas of the GI tract are out of scope but those using the principle of gastro-resistance are within scope.	
<A> & <C>	**13**	**Excipients**: We believe there would be value in providing some high level guidance on the potential impact of key modified release excipient material properties.	This is outside the scope of this guideline.
<A> & <C>	**14**	**Drug Substance Particle Size**: For modified release products where the drug substance is released in the un-dissolved state, the absorption of the drug substance may be sensitive to particle size and the magnitude of this sensitivity may be dependent on the region of the GI tract. We recommend providing guidance on the options for considering the impact of particle size that would be acceptable.	This issue relates to pharmaceutical development. It is outside the scope of this guideline, no need for specific reference.
<A>	**15**	**Format:** It is not clear how the full guidance will be presented, as the title of this draft applies to quality only and doesn't mention any "Section". Will there be one guideline (with a different title) with sections one and two, two separate guidelines with different titles (but then where do sections come into play?), or something else? Strategy, titles and text need to be cohesive.	Comment noted. Final format to be available upon publication of documents
<A> & <C>	**16**	**Literature references**: Supportive literature references for specific areas of concern would be welcomed, such as scored vs.	Comment is noted but no action is proposed.

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		non-scored drug products or single unit vs. multiple unit drug products. This would help the reader better understand the fundamental basis for the concern.	
<A>	**17**	**Terminology**: We also note that the terms 'drug substance', 'active ingredient' and 'active substance' are used in the document and that there may be value in use of one term wherever possible.	Agreed. The term "active substance" will be used.
<D>	**18**	Draft guideline does not give information for proportionality of gastro-resistant coating with respect to surface area to have the same gastro resistance as mentioned in Questions & Answers: Positions on specific questions addressed to the pharmacokinetics working party The general requirements for biowaiver of an additional strength detailed in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 rev 1) are applicable also for delayed release tablets and recommendations regarding which strength to study is given in the same section of this guideline and also in section 2 "Requirements for food-interaction studies for modified release formulations". When evaluating proportionality in composition, it is recommended to consider the proportionality of gastro-resistant coating with respect to the surface area (not to core weight) to have the same gastro-resistance (mg/cm2). **Proposed change (if any):** Recommendation for consideration of the proportionality of gastro-resistant coating with respect to the surface area (not to core weight) may be captured in the	The comment is acknowledged however it is outside the scope of the quality part of the guideline as it relates more to the pharmacokinetics working party.

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		section 3.1 development pharmaceutics	
<E>	**19**	In the concept paper on the revision of this guideline it is indicated that the following main topics needed to be discussed during the revision of the guideline: 1. The functionality of the excipients and their role in drug release mechanism should be considered. 2. The choice of the appropriate dissolution test in terms of media and hydrodynamics according to physicochemical properties of the drug substance and formulation properties (i.e. type of excipients, drug release mechanism). The use of biorelevant media for MR of Class II compounds. Food effect. 3. New technologies (e.g. PAT) can provide in vitro in vivo relationships based on performance of individual dosage form units. Quality by Design for dissolution specifications. 4. More details on the development of in vivo/in vitro correlation. Description of the usual two-stage process (e.g. deconvolution followed by comparison of the fraction absorbed to the fraction dissolved) or other approaches that can be used. Details on the development of linear correlations (usually obtained), but also on non-linear correlation that may also be acceptable. In vitro release variability to be taken into account on IVIVC method. 5. Dissolution specifications for evaluation of generics. 6. Interaction of alcohol with modified release oral dosage forms	Comment is noted but it is also noted that no modifications/amendments are proposed.

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		which may lead to "dose dumping". 7. Narrow and non-narrow therapeutic range drugs. Most of these issues have been adequately addressed and additionally the guideline has been modernised with inclusion of concepts like control strategy and real-time release. Specific guidance is also added on the discriminatory power of the dissolution methods, the use of enzymes (if relevant for the release of the active substance) and acceptance criteria for dissolution profiles of drug products with zero-order release. For some issues, like setting specifications and control strategy, reference is also made to other, some recently introduced, guidelines, which is appropriate. The issues narrow and non-narrow therapeutic range drugs and non-linear correlation have not been included in this revision, yet are included in the also revised PK /clinical guideline on modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). Guidance on the topic new technologies that can provide in-vitro in vivo relationships based on performance of individual dosage form units has not been included. A clarification on this by the drafting group would be welcomed. Except for the combined discussion of the expected amount of dissolution data as part of the development studies and the development of a drug product quality control dissolution method, the guideline is clear and well organised. In section 2.1.3 – ***Development of dissolution methods*** **, the amount of dissolution tests to be performed on the product to**	

Stakeholder - page number	Comment number	General comment (if any)	Outcome (if applicable)
		examine its robustness and performance is described, but also the development of the dissolution method for quality control (release testing), which is rather confusing. It is advised to discuss these two issues in separate paragraphs. For some guidance, like on demonstration of the robustness of the formulation in a variability of physiological conditions, preferably details of examples of acceptable methods would be helpful. In the section on variations of gastric resistant formulations it should specifically be stated that the in-vitro comparison performed at pH 4.5 and pH 6.8 after initial storage for 2 hours in the acidic medium, should also be done after initial storage for 2 hours at pH 3-5 if the SPC requires the co-administration with food or does not exclude the co-administration with food. The revision of the guideline, performed with the participation of a Dutch quality assessor, has resulted in a guideline that adequately includes the intended additional guidance and requires only some minor adjustments. The revision is greatly appreciated as it is expected to result in an improvement of the quality and consistency of assessment of the quality of modified release products.	

2. Specific comments on text

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 49 (scope)	**20**	**I. Comment**: "This guideline only covers delayed release oral dosage forms with the principle of **gastro-resistance** and prolonged release oral dosage forms." **Proposed change (if any):** Provide a definition of **gastro-resistance** in the glossary in Annex 1. **II. Comment:** The sequence should be adjusted according to sequence of occurrence in the document. **Proposed change (if any):** Replace by "This guidance covers prolonged release oral dosage forms and delayed release oral dosage forms with the principle of gastro-resistance."	Definition of **gastro-resistance** can be found in Ph.Eur. Order replaced. "This guideline only covers prolonged release oral dosage forms and delayed release oral dosage forms with the principle of gastro-resistance."
<A> 53 and 436	**21**	**Comment**: "Current" is generally used to infer time. **Proposed change:** Replace by ..**are out of scope**. (If desired, "**of this guideline**".)	"Current" replaced by "out of scope of this guideline" "pulsatile and accelerated release dosage forms are **out of scope of this guideline**."

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<C> 57	**22**	There is a reference to "Paragraph 2" in both lines. We assume that this is referring to "Section 2".	*"Paragraph 2" replaced by "Section 2"* "Many principles discussed under *Section* 2 with respect to…"
<A> 62 <F> 62-68	**23**	**I. Comment**: The text states that the quality of a prolonged release dosage form is continuously improved during development. It is noted that the same comment is not made in section 3 related to delayed release products. **Proposed change (if any):** We propose that for consistency across the document this statement be removed. (After all clinical investigational products are not of 'low' quality. --- **II. Comment**: Not sure of the relevance of this to prolonged release products as opposed to all products. Choice of composition is usually made early, and then adjusted as the manufacturing process develops. **Proposed change (if any):** ~~The quality of a prolonged release dosage form is continuously improved during the development of a new drug product. The choice of the composition is normally made early in the development based on small-scale batches and takes into account physicochemical properties of the drug substance, stability and drug absorption characteristics throughout the gastrointestinal tract. As soon as the constituents are chosen, gradual scaling up of~~	The same text is added in section 3 but is also highlighted that many of the principles discussed for prolonged release dosage forms are also relevant to delayed release dosage forms. *See above comment 23 (I) & 23 (III) below.*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 63		~~the manufacturing process will start. During this period it is reasonable to expect that adjustments will be necessary to reach full-scale production. These adjustments might be changes in composition, manufacturing processes, equipment or manufacturing site.~~ ~~In some cases these adjustments may have an effect on the properties of the drug product. It is therefore recommended that an *in vitro* dissolution test is developed which is able to detect changes which may have an effect on the efficacy or safety of the product.~~ For prolonged release products, changes made as development progresses may have greater impact on the Critical Quality Attributes relating to release of the drug substance. The basic composition will be established based upon the physicochemical properties of the drug substance and the required release rate. This composition may be adjusted during development of the manufacturing process, and the effects of these adjustments on the release characteristics should be assessed by means of a suitable *in vitro* dissolution test. --- **III. Comment:** "the choice of the composition is normally made early in the development …." Somehow, the message should be conveyed that not all development aspects (strength, composition, mfg process,	*Words "normally" and "early" deleted:* "the choice of the composition is ~~normally~~ made

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		equipment, site) are being fixed during early development, but may change along the development process. **Proposed change (if any):** Replace by "The choice of the composition **is made during the development** …"	~~early~~ in the development …."
<A> 70	**24**	**Comment**: "… which may have an effect on …" The wording is not strong enough. **Proposed change (if any): Delete "may"** to read as " … which have an effect on …"	"may" is wider and reflects better the actual message. "may" should remain.
<C> 71 <A> 69-71	**25**	**I. Comment**: During pharmaceutical development, efficacy has not been established so it is not possible to develop a dissolution method that could detect effects on efficacy. **Proposed change**: Replace "efficacy" with "PK/PD". **----------** **II. Comment**: The text, very reasonably, recommends that an in vivo-relevant in vitro dissolution test is developed. This is a reasonable recommendation but can take time to develop (if indeed such a test can be established). Thus it should also be clarified that certain 'adjustments' can be managed by PK evaluation in	The target of dissolution method development should be a method that could detect effects on efficacy to facilitate the establishment of the link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate. Comment noted but original text is considered sufficient and therefore no amendment is made.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		patients. **Proposed change (if any):** Modify text to read "It is therefore recommended that an in vitro dissolution tests is sought which is able to detect changes which may have an effect on the efficacy or safety of the product. This will be a useful tool in development and in the management of post-approval changes and will minimise (or 'remove') the need for pharmacokinetic studies to evaluate major changes. "	
<C> 72-73	**26**	**I. Comment**: It is not clear why pharmaceutical development should establish this link and not other functions like clinical PK or Pharmacometrics. **Proposed change:** ~~Pharmaceutical development should establish the~~ <u>The</u> link from pharmacokinetic parameters through *in vivo* drug release to *in vitro* dissolution rate <u>should be established</u>. ------- **II. Comment**: The draft guideline seems to systematically request the establishment of a link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate. This approach implies that an IVIVC would be required as	*Comment taken into account and a slight rewording has been made together with the addition of the following sentence further down: "It is encouraged to establish an in vivo-in vitro correlation (IVIVC)."* *See comment 6, 88, 99 & 106.* *See comment 6 and 26 (I, III, IV, V) and 27.*
<B> 72-73			

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 72, 303-304, 346-347, and 373-374.		a general requirement. Experience shows this is not always relevant and it should therefore not be required in all cases. (See similar comments on lines 303-304, 346-347 and 373-374. Proposed change (if any): Please amend as follows: "Pharmaceutical development should establish**, where relevant and necessary**, the link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate. -------- **III. Comment**: The development of an IVIVC is an important goal for pharmaceutical development, while the science and technology may not always permit meaningful IVIVC. Therefore, we would suggest adding more flexibility to the statement. **Proposed change** (if any): Replace by "Pharmaceutical development should establish [...], **if possible**." -----	*See comment 6, 88, 99 & 106.*
<A> 72-73, 303-304		**IV. Comment**: This sentence seems to make the establishment of a dissolution method capable of in vivo correlation a MUST – this is considered to be an escalation	*See comment 6, 88, 99 & 106.*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		of expectations. In the past such a test has been (as per the earlier text at line 70) a recommendation, and it is considered that it should remain at this level (i.e. a want not a must) and indicate that establishment of this relationship is not always possible. **Proposed change (if any**): Replace by "Pharmaceutical development should establish ~~the link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate~~ **a relationship** between the in vivo and in vitro drug release rates or should demonstrate efforts to achieve this if a relationship cannot be established." --- **V. Comment:** Proposed, simplified statement would eliminate some confusion. **Proposed change (if any):** Replace by: "Pharmaceutical development should establish the link between **in vivo drug release and in vitro dissolution rate and extent**."	*See comment 6, 88, 99 & 106.*
<G> 72-73 303-304 and	**27**	**Comment**: Clarification is needed on what is expected from (generic) applicants. The proposed text seems to suggest that an IVIVC should always be established. Does	*Comment taken into account and a slight rewording has been made together with the addition of the following sentence further down:*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
346-347		it mean that an IVIVC should always be developed for e.g. generic product? For example when a generic product is developed having a similar qualitative and quantitative composition as the reference product and is bioequivalent, an IVIVC could be considered to be superfluous. **Proposed change (if any):** Pharmaceutical development **<u>could</u>** establish the link from pharmacokinetic parameters through *in vivo* drug release to *in vitro* dissolution rate. The need for developing an IVIVC should be considered on a case by case basis.	*"It is encouraged to establish an in vivo-in vitro correlation (IVIVC)."* *See comment 6, 88, 99 & 106.*
<A> 74	**28**	**Comment**: Extensive testing under different dissolution conditions in early development is not realistic, particularly if Proof of Concept for efficacy in the target patient population has not yet been demonstrated. Less strict timing of the recommended testing is advocated. **Proposed change (if any):** Replace by "The formulation chosen **in development** should be tested..."	the word "early" in the sentence is deleted: *"The formulation chosen in **~~early~~** development **should** be tested under different dissolution conditions"*
<B> 74-75	**29**	**Comment**: This section is quite general, and it is not clearly understood what the expectations are. (See also general comment on 'physiological dissolution media').	Comment noted- the following text in the guideline is considered sufficiently clear: "The formulation chosen in development should be evaluated under different dissolution conditions

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Proposed change (if any): Please replace this section by the following: "**The development section of the dossier should preferably provide a summary overview of early development dissolution tests undertaken on the chosen formulation, particularly addressing its predicted sensitivity / robustness in the physiological environment after administration**".	to determine its sensitivity/robustness to the expected physiological environment after administration."
<A> 79	**30**	**I. Comment:** Clarification is required about the 'qualifying control method with in vivo relevance'. Does this statement refer to a biowaiver of a bioequivalence study? If so, it is recommended to specify this. **Proposed change (if any):** Replace by "qualifying control method with in vivo relevance **and allowing biowaiver of bioequivalence studies."** --- **II. Comment**: Line 79 "qualifying control method" is unclear. **Proposed change** (if any): Line 79: replace "qualifying control method" with "bio-relevant dissolution method"	Please refer to 2.1.7 of the guideline for further clarification. Please refer to 2.1.7 for further clarification.
<C> 79			

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<C> 81-85	**31**	**I. Comment**: More precise guidance on the term "compare the **laboratory/pilot scale batches** with …" should be given; furthermore, it should be stated that such studies can be replaced by *in vitro* testing in case a Level A IVIVC is established. **Proposed change (if any):** After ~~completed~~ scale-up is complete it is reasonable to compare the laboratory/pilot scale ~~batches~~ biobatch(es) with ~~the~~ a representative full production scale ~~batches~~ batch(es) in a bioavailability study if the scale-up factor exceeds 10 (compared to the laboratory/pilot scale biobatch) in order to verify that the dissolution test conditions chosen are appropriate for the release of clinical materials, scale-up and manufacture (see also 2.1.3. and 2.1.4 and 2.1.5). Such a study might be replaced by *in vitro* testing in case a Level A IVIVC is established. ----------	Please refer to 2.1.7 and other guidelines.
<A> 81-85		**II. Comment***:* The text states that it is reasonable to compare the lab / pilot scale batches with full production scale lots in a BA	Please refer to 2.1.7 and other guidelines.

Stakeholder - page number	General comment (if any)	**Outcome** (if applicable)
	study. However, the current adopted note for guidance on quality of modified released products (CPMP/QWP/60496) language indicated this was not needed with an established IVIVC. The new draft does not have that exception. It would be useful to add a clause for biowaiver justified by predicted equivalence based on a validated IVIVC. It should also be made clearer that this is only needed for products made at lower scale and used in pivotal clinical studies **Proposed change (if any):** A revised statement is proposed for line 81-85: "After completed scale-up **and without an established IVIVC,** it is reasonable to compare laboratory/pilot scale batches with full production scale batches **used in pivotal clinical studies** in a bioavailability study if the scale-up factor exceeds 10 (compared to the laboratory/pilot scale biobatch) in order to verify that the dissolution test conditions chosen are appropriate for the release of clinical materials, scale-up and manufacture. **This is only needed for products made at lower scale.**	

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<B> 88-90	**32**	**Comment**: Only $t_{1/2}$ is characteristic of the active substance, AUC, C_{max} and T_{max} are parameters which are formulation dependent. Proposed change (if any): Change the sentence as follows: "~~**Pharmacokinetic (e.g. AUC, C_{max}, T_{max}, $t_{1/2}$) and p**~~**P**hysico-chemical characteristics of the active substance (e.g. solubility at different pH, partition coefficient, particle size, polymorphism) **and pharmacokinetic parameters (e.g. AUC, C_{max}, T_{max}, $t_{1/2}$)** relevant to the development of the product should be given."	Change accepted.
<A> 90-91	**33**	**Comment**: Reference to the guidelines is unclear and the wording "detailed information" is rather non-specific. **Proposed change (if any):** Please describe in more detail the guidelines on pharmaceutical development reference is made to.	Comment disregarded because proposal is not practical.
<B> 94	**34**	**Comment**: The description of the release kinetics can only be considered relevant where a specific order of release (e.g. zero order) is targeted. **Proposed change** (if any):	Proposal accepted.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Change the point as follows: "• the release mechanism ~~**and kinetics**~~ (diffusion, erosion, osmosis, etc. or a combination of these**), and also the release kinetics where applicable;"**	
<H> 97-99	**35**	**I. Comment**: We agree that the prolonged release product should maintain its release characteristic regardless of relevant variability in physiological conditions. With regards to the 'pathological gastrointestinal fluid composition', we would like to have clarification on what should be understood by 'it should be demonstrated…' and the expectations in that context (in vivo studies ?) **Proposed change** (if any): / -------- **II. Comment**: This paragraph is too general and may be interpreted inappropriately such that unnecessary in vivo studies are requested for submission. The impact on drug release characteristics by many of the physiological factors mentioned can be tested by appropriate in vitro model. It is noteworthy that the variability due to food effect is usually addressed via the need for fasting and fed studies or a food effect study. A more specific wording could prevent inappropriate interpretation and expectations.	It is the applicant's burden to justify his approach (e.g. *in vitro* model) that the formulation maintains the release characteristics in the intended patient population and expected conditions of use. See above.
<B> 97-100			

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<C> 97-100		**Proposed change** (if any): Please amend this section as follows: "It should be demonstrated that the **drug release characteristics of the** prolonged release product ~~**maintains its drug release characteristics**~~ **are well understood and characterised for a range of** ~~**regardless of relevant variability in**~~ **relevant** physiological conditions. Physiological conditions of main importance include food effect and, where relevant, ~~**Examples of such variability include gastric and intestinal transit time, food effect, pathological gastrointestinal fluid composition and**~~ concurrent alcoholic intake~~**, if and where relevant**~~ **Beyond the food effect, in vitro tests may be considered sufficient to establish the drug release profile of the prolonged release product in various physiological conditions, if justified**. --- **III. Comment**: The current statement in essence requests the development of a formulation with pH-independent release characteristics, which are furthermore not affected by alcohol. From a development perspective this is highly challenging and might limit development options, tentatively resulting in a limited number of helpful and convenient products available for the patient. However, it	See above.

Stakeholder - page number	General comment (if any)	**Outcome** (if applicable)
	might be sufficient to request a justification as to why efficacy and safety of the product are not affected by relevant variability in physiological conditions. This might leave room for some changes in drug release characteristics, which do not affect the safety and efficacy of the product (e.g. products where efficacy is related to AUC and safety to a c(max) value which should not be reached). **Proposed change** (if any): It should ideally be demonstrated that the prolonged release product maintains its drug release characteristics regardless of relevant variability in physiological conditions. Examples of such variability include gastric and intestinal transit time, food effect, pathological gastrointestinal fluid composition and concurrent alcoholic intake, if and where relevant. In case the release characteristics of the product might be influenced by physiological variability, relevance of these changes on safety and efficacy of the product should be discussed. **IV. Comment**: More guidance would be appreciated on how to assess the variability of the gastric and intestinal transit time, food effect, concurrent alcohol intake etc. and if the assessment	See above.

Stakeholder - page number	General comment (if any)	**Outcome** (if applicable)
	depends on the SPC recommendations. **V. Comment**: We would appreciate if the wording "pathological gastrointestinal fluid composition" could be clarified or if examples could be provided. Is the expectation that the pathological gastrointestinal fluid composition will result in a different pH? Or ionic strength? Or enzyme/protein concentration outside the normal range? Or liquid volume? Or more free mucus or unbound bacteria, so the viscosity of the fluid is increased? **VI. Comment**: The current guideline text is as follows: "It should be demonstrated that the prolonged release product maintains its drug release characteristics regardless of relevant variability in physiological conditions. Examples of such variability include gastric and intestinal transit time, food effect, pathological gatrointestinal fluid composition and concurrent alcoholic intake, if and where relevant." **Proposed change** (if any): ➢ Please specify relevant range of ethanol in the dissolution medium. Please specify the relevant dissolution medium. (cf. QWP -	See above. See above.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 97-100		Quality of Medicines, questions and answers Part 2 - Specific types of product - Need for in-vitro dissolution studies with alcohol for modified-release oral products including opioid drug products – (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/quality_qa_part2.jsp&mid=WC0b01ac05801bf0c3) ---------- **VII. Comment**: Expectations from in vitro methods (e.g., change in pH, ionic strength, agitation rate, etc,) that could be related to physiological variations should be clarified. **Proposed change (if any):** Replace by "It should be demonstrated ~~that the prolonged release product maintains its~~ **through appropriate in vitro experiments (e.g dissolution) that the product can retain its prolonged qualitative drug release characteristics regardless of relevant variability in physiological conditions**. Examples of such variability include gastric and intestinal transit time, food effect, pathological gastrointestinal fluid composition and concurrent alcoholic intake, if and where relevant." **VIII. Comment**: While we agree with the intent here, we	See above. See above.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		see a lot of difficulty interpreting what is acceptable to demonstrate that drug release characteristics are maintained in relevant conditions (e.g. alcohol, pH, transit times etc.). We would suggest adding more flexibility to the wording. **Proposed change (if any):"**It should be demonstrated that the prolonged release product maintains **acceptable** drug release characteristics..." **IX. Comment:** We would suggest that only GI conditions typical for the target indication(s) need to be considered (rather than human GI variability for any disease state). **Proposed change (if any):** It would hence be helpful to have more specifics around the EMA expectations, acknowledging that this is a guideline to be applied on a case-by-case basis. **X. Comment**: The text states that the product must maintain its drug release characteristics regardless of e.g. food effect and concurrent alcohol intake. Is this an absolute requirement? That is, could, in some instances, a minor food effect or release change with alcohol be handled by labelling against use in such circumstances? It	See above. See above.

Stakeholder - page number	General comment (if any)	**Outcome** (if applicable)
	would be unfortunate to not provide a potentially useful medicine for the sake of a minor food effect or for alcohol variation that could be managed in other ways. We also note that a food effect is known to be evaluated under certain conditions (meal description) but the alcohol evaluation is not yet described to ensure a consistent approach is taken. **Proposed change (if any):** Modify the text to read "It should be demonstrated that the prolonged release product maintains its drug release characteristics **under relevant physiological conditions (e.g. gastric and intestinal transit, pathological gastrointestinal fluid composition). Furthermore, the effect of food and concurrent alcohol intake (modelled by …) should be evaluated and understood. Any risks coming from food or alcohol effects should be managed in product use.**" **XI. Comment:** It is questioned whether the word 'demonstrated' is the most appropriate word in this context. **Proposed change (if any):** Replace by "It should be **evaluated whether** the prolonged release product	See above.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<E> 97-100		maintains its drug release characteristics […]" ------- **XII. Comment:** 'It should be demonstrated that the prolonged release product maintains its drug release characteristics regardless of relevant variability in physiological conditions. Examples of such variability include gastric and intestinal transit time, food effect, pathological gastrointestinal fluid composition and concurrent alcoholic intake, if and where relevant'. **Proposed change**: How should this be demonstrated? Preferably examples of acceptable methods / media should be included. ------ **XIII. Comment**: pH as potential relevant parameter is missing here. **Proposed change** (if any): Add pH as potential relevant parameter.	See above. See above.
<C> 101	**36**	**I. Comment**: The score line consideration is specific to modified release products that require the dosage form to remain intact to retain its drug release mechanism/control but is not valid	It is the applicant's burden to justify his approach that the formulation maintains the release characteristics in the intended patient population and expected conditions of use.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		for all single unit products. Should examples of the products viewed as high risk be specifically mentioned? **Proposed change (if any):** Consider including examples of high risk products such as matrix tablets which show significant sensitivity to the surface area to volume ratio of the dosage form or tablets which have a modified release tablet coating (i.e. osmotic tablets).	
		II. Comment: Some guidance on opening of capsules and sprinkling on food should be included if potentially needed by an expected patient group. Consider potential for food/acidity to affect MR components and well as maintenance of the integrity of MR components during ingestion. It would be useful to put forward some context around what alcohol levels should be considered to demonstrate lack of dose dumping during co-administration with alcohol. The sponsor should be able to demonstrate that the level of drug release would not constitute a safety issue **Propose change**:	*See above.*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Consider including guidance on sprinkling of prolonged release capsules and guidance around alcohol studies needed to demonstrate lack of dose dumping.	
<F> 101-105	**37**	**Comment**: The score line would only apply to tablets. It would not apply, for example, to capsules containing pellets. **Proposed change** (if any): In general, prolonged release oral ~~dosage forms~~ **tablets** should not have a score line because subdivision or other manipulation of modified release ~~products~~ **tablets** may adversely affect the modified release properties of the dosage form, possibly leading to dose dumping. Any recommendation on subdivision of a modified release dosage form should be supported by scientific justification that the subdivision does not affect the modified release characteristics, including *in vitro* and/or *in vivo* data as appropriate	Accepted.
<D> 103-105	**38**	**Comment:** Any recommendation on subdivision of a modified release dosage form should be supported by scientific justification that the subdivision does not affect the modified release characteristics, including *in vitro* and/or *in vivo* data as appropriate. Acceptance criteria for dissolution of half and full tablet should be based on similarity factor (F2). Half tablet may	Rejected.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		have different specification then whole tablet. **Proposed change (if any):** Any recommendation on subdivision of a modified release dosage form should be supported by scientific justification/similarity factor that the subdivision does not affect the modified release characteristics, including *in vitro* and/or *in vivo* data as appropriate.	
<C> 107-109	**39**	**Comment**: Please give an example what is meant by "physicochemical in vitro and in vivo characteristics..."	Reference is made to paragraph 2.1.2
<A> 110-112	**40**	**I. Comment**: The text may be over-interpreted i.e. that the dissolution method must be related to in vivo performance. We think that the expectation is to show some discrimination in the dissolution test for such factors, not necessarily to have a dissolution that is capable of being correlated to in vivo performance. **Proposed change (if any):** Modify the text to read "The dissolution tests **should** be capable of discriminating **as a quality control tool** between batches with respect to **manufacturing variables** which may have an impact on the desired bioavailability."	Proposal for comment (I) is accepted: *"The dissolution tests **should** be capable of discriminating **as a quality control tool** between batches with respect to **manufacturing variables** which may have an impact on the desired bioavailability."* See comment 51.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<F> 111-112		**II. Comment:** The text should be aligned with QbD wording **Proposed change (if any):** Replace "critical manufacturing variables" by "**critical process parameters (CPP)**" **III. Comment:** The wording is not strong enough. **Proposed change (if any):** Delete "may" and read as: "Critical manufacturing variables which **have** an impact on the desired bioavailability." -------- **IV. Comment**: The discrimination should monitor the critical quality attributes that relate to *in vivo* performance, not manufacturing variables that may impact bioavailability Proposed change (if any): discriminating between batches with respect to critical ~~manufacturing variables~~ **quality attributes** ~~which may have an impact on the desired bioavailability~~ **that differentiate between acceptable and non acceptable *in vivo* behaviour.**	See above (I). Not accepted. See above (I).

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 116	**41**	**I. Comment**: The use of the word 'tested' in the text here might be interpreted as suggesting that an MR product should routinely be tested under these various conditions. **Proposed change (if any):** To avoid this misconception, consider changing the word "tested" by "**evaluated".** ----------	Accepted.
<D> 116-117		**II. Comment:** pH range recommended may be from pH 1 to more than pH 8.0. Higher pH is recommended based on stability of drug substances at high pH and physicochemical property of drug substances. **Proposed change (if any):** Normal pH ranges 1-8; In case where it is considered necessary pH 1-12. --------	Not accepted.
<C> 117		**III. Comment**: The proposed pH value of 1-7.5 is unusual and not in line with other guidance. **Proposed change** (if any): pH value of 1-6.8 **-----**	Not accepted. *"…normally pH range 1-7.5; in cases where it is considered necessary up to pH 8".*
<G> 117		**IV. Comment**: Is it expected that dissolution at the highest pH, which was 6.8 in the previous guideline, should be replaced by pH 7.5, or is the pH 7.5 additional to pH 6.8?	*"…normally pH range 1-7.5; in cases where it is considered necessary up to pH 8".* *See above*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 116 – 119		**Proposed change (if any):** Clarification is requested. **--------** **V. Comment**: The use of multiple dissolution apparatus is not necessary to characterize a drug product. **Proposed change (if any):** We recommend deleting the word **apparatus.** **--------**	This is not the intention. It is clarified in the next sentence that *"Testing conditions, including sampling time points and frequency providing the most suitable discrimination should be chosen."*
<A> 117		**VI. Comment**: The current adopted note for guidance on quality of modified released products (CPMP/QWP/604/96) states that the normal pH range is 1-6.8, which generally constitutes sufficient ground for the development of dissolution methods. **Proposed change (if any):** "[...] (normal pH range **1-6.8** ~~1-7.5~~; in cases where it is considered necessary pH 1-8 [...]"	*"…normally pH range 1-7.5; in cases where it is considered necessary up to pH 8".* *See above.*
<A> 120-121	**42**	**Comment**: The current wording of the paragraph is confusing and could be misinterpreted. **Proposed change (if any):** Replace by ~~"If media with a low buffering capacity are used, the pH should be~~	Proposal is accepted: *"Suitable buffer capacity should be used to ensure that media pH is well controlled during the dissolution test."*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		~~controlled during the dissolution test to be sure that there is no influence of dissolved active ingredient and/or excipients on the dissolution conditions during the test period.~~ Suitable buffer capacity should be used to ensure that media pH is well controlled during the dissolution test.”	
<A> 122–123	**43**	**I. Comment**: Clarification is needed regarding the expectations to ensure quality of the surfactant. **Proposed change (if any):** Replace by: “The choice of the surfactant should be discussed and its consistent batch to batch quality **(e.g. the use of similar analytical grade)** should be ensured.” ------- **II. Comment**: Comparable surfactant quality can be controlled but not batch-to-batch quality. **Proposed change**: “If a surfactant is used in the dissolution medium, the amount needed should be justified. The choice of the surfactant should be discussed and its **comparable** ~~**consistent batch to batch**~~ quality should be ensured. ----- **III. Comment**:	Not accepted- consistent batch to batch quality is important. Applicant should demonstrate batch to batch quality. Not accepted- consistent batch to batch quality is important. Applicant should demonstrate batch to batch quality.
<B> 122-123 <B>			

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
126		Comparable enzyme quality can be controlled but not batch-to-batch quality. See also similar comment on surfactant, lines 120-123 [128-129]. **Proposed change:** "If enzymes are added to the dissolution media, a rationale should be given for the type and concentration of enzymes added. Further, **comparability** ~~**consistency**~~ of the ~~**batch-to-batch**~~ quality of the enzymes should be ensured […]"	Not accepted- consistent batch to batch quality is important. Applicant should demonstrate batch to batch quality.
<A> 124-127	**44**	**Comment:** It is welcomed that the use of enzymes is encouraged under certain conditions. It might be helpful to provide an example of the enzymatic conditions that are considered useful to mimic the delivery in colonic conditions so that such conditions can be used without further rationalisation. (A rationale is requested in line 126) **Proposed change (if any):** Consider adding some further advice on enzymatic conditions that are recognised as useful in such circumstances.	This GL is not product specific. The rational should be given by the applicant.
<B> 124-125	**45**	**Comment**: Enzymes can also be justified in the case of capsule formulations. This is in line with the revised bioequivalence guideline for	Only "gelatin capsules" is added.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		immediate release products. **Proposed change**: "The inclusion of enzymes in the media is acceptable, and even encouraged, when justified (e.g., colonic delivery**, capsules**)."	
<A> 128-129	**46**	**I. Comment**: It is unclear whether this comment on SGF / SIF media as described in the Ph.Eur. has any bearing on the use of such Ph.Eur. media in development and if this guidance suggesting a need to amend the Ph.Eur. **Proposed change (if any):** Please clarify.	The fact is highlighted for awareness.
<A> 134 -136 and 254-255	**47**	**II. Comment:** The development of a specification for the dissolution rate is feasible for most zero order release cases, while the science and technology may not always permit meaningful measurement for the dissolution rate. So, we would like to suggest adding more flexibility to the statement. **Proposed change for line 134-136**: Replace by "For formulations having a zero order release kinetics (with or without lag time) a specification of the dissolution rate over time (percent of label claim per hour) for a given interval may be ~~suitable instead of the cumulative amount dissolved at a given time point~~ established (see also	Accepted to delete "*…~~suitable instead of the cumulative amount dissolved at a given time point…~~"* Not accepted. If zero order is claimed then it has to be specified. Revised text reads: *" For formulations having a zero order release kinetics (with or without lag time) a specification of the dissolution rate over time*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<D> 134-139		section 2.2)." **Proposed change for line 249-251**: Replace by "For drug products showing a zero order release a specification of the dissolution rate/time for a given time interval may be more appropriate than the cumulative amount dissolved at a distinct time point. In cases where a zero order release kinetic is combined with a variable lag time, such a specification is ~~mandatory~~ recommended." ---------- **III. Comment:** For zero order release kinetic Dissolution rate over time (% of label claim per hour) can be evaluated only as a part of development. **Proposed change (if any):** For formulation having a zero order release kinetics (with or without lag time) a specification of the dissolution rate over time (% of label claim per hour) for a given interval may be suitable instead of the cumulative amount dissolved at a given time point shall be described as a part of development. It is not required for setting specification	*(per cent of label claim per hour) for a given interval should preferably be established…"* See above.
<A> 140-142	**48**	**Comment:** It should be specified that mentioned variations are those with expected impact on the in vivo bioavailability. **Proposed change (if any):** Replace by "... the importance of any variation in the active substance […] or	Accepted.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		manufacturing process **with regard to its impact on the in vivo bioavailability**."	
<C> 143-146	**49**	**Comment**: It is high effort to validate all potential "biorelevant" dissolution methods. **Proposed change (if any):** The assay method of the active ingredient in dissolution samples <u>generated using the intended quality control or the selected in vivo predictive dissolution method (ideally they are identical)</u> should be validated according to the relevant ICH guidelines….	It is clear in the document already, comment not relevant.
<A> 151-153	**50**	**Comment:** The requirement of "for any changes" is likely to be too strict. **Propose change (if any):** Replace by "… and, ~~if relevant,~~ for any **relevant** changes in …."	Accepted.
<A> 154-171	**51**	**I. Comment:** The section 2.1.4 on Discriminatory power of the dissolution test looks like a step above and beyond the current expectations for external IVIVC validation. **Proposed change (if any):** It would be helpful to get more clarification on the intention and what is driving it.	2.1.4 is not about external IVIVC validation. See comments 40, 75 & 113.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 155-159		---------- **II. Comment:** The way that this sentence is worded implies that the manufacturer must test batches in clinical trials which have "non acceptable *in vivo*" performance. The subsequent bullet point(s) give examples when no non-acceptable batches are available. The sentence should provide more flexibility. **Proposed change (if any):** Replace by "It should be shown that the dissolution test under the chosen test conditions is able to discriminate between batches with acceptable and non-acceptable in vivo behaviour, **provided the link to the in vivo behavior has been established**." **III. Comment:** The text states that the dissolution test should be shown to be able to discriminate between batches with acceptable and non-acceptable in vivo behaviour. This text seems, like the text at 111, to suggest that a dissolution method needs to be shown to be in vivo relevant / correlated. This may not be the intent. For example it may not be possible to establish an IVIVC to the dissolution test. In such a circumstance, acceptance criteria are set in line with clinical lots (often +/- 10% profile limits on dissolution) without any proof that such	In case there are no non-acceptable batches bullet points 2 & 3 [lines 162 and 166] apply. This could be accepted but means that it has been established which release profile is (non-) acceptable from an in vivo perspective. Therefore that is why it is important to have previously established the link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate.

Stakeholder - page number	General comment (if any)	**Outcome** (if applicable)
<B> 157	limits have in vivo relevance and discrimination of potential impacting factors need to be shown against these limits. **Proposed change (if any):** Revise this text to read "It should be shown that the dissolution test under the chosen test condition is able to discriminate between batches with acceptable and non acceptable **release characteristics.**" ------ **IV. Comment**: For the drug substances where the absorption/permeability is not the same throughout the whole intestinal tract (including colon), the IVIVC is not possible. If the impossibility to perform IVIVC is anticipated for a particular drug substance based on the previous knowledge there should be an option to leave out an IVIVC evaluation. Therefore we propose the following change: Proposed change (if any): Line 157 "Showing discriminatory power may be achieved in one of the following approaches **(as relevant and applicable~~)~~ ~~in order of priority~~**:" ----------	Accepted. "…and non-acceptable **release characteristics.**" [line 156] The different options are deliberately prioritised. This is a stepwise approach.
<B> 166-171	**V. Comment**:	The different options are deliberately prioritised. This is a stepwise approach.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		For the drug substances where the absorption/permeability is not the same throughout the whole intestinal tract (including colon), the IVIVC is not possible. If the impossibility to perform IVIVC is anticipated for a particular drug substance based on the previous knowledge there should be an option to leave out an IVIVC evaluation. Therefore we propose the following change: Lines 166-171 "~~**If neither of the two approaches is feasible**~~, **T**he discriminatory power may **also** be shown by deliberately varying an attribute of the active ingredient (e.g. particle size distribution), composition and/or manufacturing process parameters, in order to produce different in vitro dissolution behaviour, without generating in vivo data for these batches."	
<A> & <B> 160	**52**	**Comment:** "Though" is a typo **Proposed change (if any):** Replace by "**Through**"	Accepted.
<A> 162	**53**	**Comment:** To avoid any confusion or ambiguity, it is recommended to emphasize that the acceptability or non-acceptability of batches refers to their in vivo behaviour. **Proposed change (if any**): Replace by "[…] no batches available **showing unacceptable in vivo behaviour**,	Text reworded.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		[...]”	
<C> 162	**54**	Guidance is missing as to what would be appropriate acceptance criteria when this method is used.	Acceptability means bioequivalent.
<B> 178-184 <H> 182-184	**55**	**I. Comment**: Acceptable batch scale is defined somewhat ambiguously. Current wording refers both to the number of dosage units in a batch or the total mass of a batch. In case a biowaiver is applied to a different strength with differing weight this may lead to confusion on acceptable commercial batch size, therefore it is recommended to re-word this section to be unambiguous. The reference to dosage units is consistent with other guideline. **Proposed change** (if any): Please amend this section so that the number of unit doses is referred to and not the batch mass. **--------** **II. Comment**: The given example leaves some room of interpretation: while we are convinced that no BA-studies are necessary at the scale of 60kg, the issue is more about the final	Comment not clear; not addressed here. This refers to products with full clinical development.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		intended size of 600 kg. Would it be acceptable to obtain approval with only the PK/BA data generated through the PK/BA study (15kg-batch), with no further conditions on the IVIVC level ? Clarification would be appreciated. ----------	
<A> 182-184		**III. Comment:** The example given to illustrate the effect of scale on the decision to perform additional BA studies is not consistent with the guidance. In the example, where no additional BA-studies at a scale of 60 kg are required, the PK/BA studies are conducted at a 15 kg scale, the pivotal clinical trials at a scale of 60 kg and full production scale is intended to be 600 kg. The scale at which the PK/BA studies were conducted (15 kg) is neither the same size as the pivotal clinical studies (60 kg), nor is it 10% of the production scale. There is no guidance as to the requirements for batch size for batches used in IVIVC studies. **Proposed change (if any):** Please clarify the example and provide guidance on the batch size requirements for IVIVC studies, as appropriate. ----------	This refers to products with full clinical development.
<E> 178-184		**IV. Comment**: The example does not make clear what the intention of this paragraph is.	This refers to products with full clinical development.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Proposed change (if any): Clarify and rewrite the paragraph. ---	
<A> 178-181		**V. Comment:** Whenever a sponsor is able to develop a Level A IVIVC, a batch size requirement for bioavailability studies should not be needed. Requiring a minimum batch size is not consistent with the development of a number of small-scale batches of different release rates to develop an IVIVC. Dissolution may be sufficient to link large-scale with small-scale batches under these circumstances. Refer to lines 210-214 which are consistent with this concept. **Proposed change (if any):** Replace by "Bioavailability studies should be performed with batches of 100,000 units or at least 10% of full production scale, whichever is greater, **unless an IVIVC has been established** or pivotal clinical studies have been performed with batches of this size. In this **latter** case, bioavailability studies performed with batches of a smaller scale may be sufficient if these batches have been produced in a manner representative of the full scale manufacturing process."	Batch size requirement refers to bioequivalence studies only.
<A> 178-181		**VI. Comment:** Although reference is made to bioavailability studies, it is not clear whether the guideline is talking about relative BA study or BE study (e.g. for	Batch size requirement refers to bioequivalence studies only.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<C> 173-184		generics). In general, it would be helpful to differentiate between BA studies comparing oral modified release drug product versus an immediate release drug product and bioequivalence studies comparing batches of same product produced with processes differing in scale with a factor of more than 10 or comparing generic and innovator modified release drug products. **Proposed change (if any):** The type of study should be clarified. ---------- **VII. Comment:** Please give a definition of the term "bioavailability study", especially be more explicit about the reference and test treatments wherever this term is mentioned.	Refer to the Bioequivalence Guideline. *See* comment 61.
<A> 163-164, 175 & 338	**56**	**Comment**: The pharmacokinetic parameter the authors refer to are unclear. **Proposed change (if any):** Please clarify the bullet point and add a more complete definition for the term "point estimates."	Point estimate: Mean value T/R
<A> 175 & 338	**57**	**Comment:** Clarification on "other relevant parameters" is required. Cmax and AUC may not be enough to ensure efficacy and safety. Although less critical than for delayed	Examples added.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		release drug products, partial AUCs or modelling and PK simulations may be helpful as well. **Proposed change (if any):** Please clarify and specify what the "other relevant parameters" are.	
<G> 178-184	**58**	**Comment**: How does this section apply to generics? **Proposed change** (if any): Clarification is requested. Proposed to follow the requirements as laid down for immediate-release products in NfG CPMP/EWP/QWP/1401/98 Rev. 1.	Applies equally to generics.
<A> 185-199	**59**	**Comment:** This section only discusses how to perform comparisons and how to apply it when adding additional strengths. **Proposed change (if any):** For aforementioned scenario and similar situations, please include more details about the applications of comparison of dissolution profiles.	Scope: extrapolation of in vivo results to other strengths of the test product.
<D> 186-189	**60**	**Comment: (Sec 2.2 setting of specification /2.1.6)** For establishing dissolution limits for biowaiver of lower strength -Draft guideline does not give information for	Not in the scope of this guideline.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		setting specification of scale up-scale down matrix formulation/ look alike compositions, bio equivalent to innovator and has similarity factor >50, but differs in surface to volume ratio. If Scale down formulation has slight higher dissolution then bio strength, dissolution specification can be different from bio strength. However similarity shall be established. **Proposed change (if any):** Lower strengths either scale up-scale down batches or look alike composition may have different dissolution limits if properly justified by scientific rationale or has similarity factor >50.	
<A> 195	**61**	**I. Comment:** Same as for comment 55 (V) lines 178-181. It is unclear what "the bioequivalence study" refers to.	See comment 55 (V) and new wording [lines 192-195].
<C> 196-199 <E>	**62**	**I. Comment**: According to the current wording, similarity of dissolution profiles may be demonstrated by calculation of a similarity factor. **Proposed change:** Please be more specific if calculation of f2 is acceptable and which conditions apply for the evaluation of f2. ----- **II. Comment**: More guidance on these acceptable	Understanding is correct. See Bioequivalence Guideline. This is not a statistics guideline therefore

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
196-199		methods and criteria may be provided to assist non-statistics assessors. **Proposed change** (if any): Rewrite paragraph, or add addendum with additional explanation.	outside of the scope.
<A> 206-207	**63**	**I. Comment:** Please indicate the typical requirement for maximum variability allowable. This guideline should seek harmonisation with FDA's guidance for extended release oral dosage forms (1997) in the coefficient of variation (CV) for mean dissolution (n=12) profiles of a single batch should be less than 10%. **II. Comment:** Does variability of data include both in vitro variability as in vivo variability? It is appropriate to emphasize to avoid any confusion. **Proposed change (if any):** Replace by "The **in vitro and in vivo** variability of data should …"	Only reporting of variability is required and possible discussion. Both *in vitro* and *in vivo* is meant.
<A> 208-209	**64**	**Comment:** The statement "[…], the less confidence can be placed on the predictive power of the correlation." is inaccurately describing the intended message. **Proposed change (if any):** Replace by "[…], the less	Comment taken into account. Text has been reworded.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		confidence can be placed **in the model parameters' estimates and the higher the uncertainty in the model-predictions for in vivo behaviour becomes**."	
<B> 210 -212	**65**	**Comment**: This section should address the possibility to waive in vivo data for biostudies during scale-up on the basis of an established level A IVIVC (e.g. if batch size < 100.000 is used in the biostudy or in case of scale-up by more than factor 10) **Proposed change** (if any): Please amend section accordingly.	See previous comments regarding batch size. Bioequivalence study is always required with a batch size representative for commercial scale. *Refer also to lines [222-223].*
<C> 213, 270, 315 & 320	**66**	**Comment** Please provide reference to the definition of Level A, Level B and Level C IVIVC in Annex 2.	Accepted.
<C> 216-245	**67**	**Comment** The way the term "formulation" is used in these paragraphs might be misleading, as an IVIVC is usually only developed for one type of formulation. **Proposed change** (if any): Use the term "batch" instead of "formulation".	Actually it is meant different formulations.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 216-217	**68**	**Comment:** The current wording for the sentence is confusing. **Proposed change (if any):** Replace by "A Level A IVIVC is established based **on** for example ~~on~~ a deconvolution [...]l	Accepted.
<C> 218	**69**	**Proposed change (if any**): Please delete "and not Cmax and AUC".	Accepted.
<A> 221-223	**70**	**Comment:** The statement may need some modified wording for clarity and further guidance about the use of Unit Input Response (UIR) throughout the development is desired in the context of this must-consideration. **Proposed change (if any):** Replace by "(2) a single IVIVC model must be applicable to all formulations **and within the established ranges of the critical product attributes of those formulations used for IVIVC model development and validation, and should preferably be extendable to other formulations with a similar release mechanism.**"	Addressed by rewording.
<A> & <C>	**71**	**I. Comment**: Since it is acknowledged that formulation	It is understood that the IVIVC formulations

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
230 – 239		changes can significantly alter the drug product, should the types of product tested in an IVIVC study or for dissolution specification settings be restricted to adjustments of processing parameters and formulation adjustments that would be deemed acceptable within current scale-up and post approval change guidelines? This would focus the IVIVC clinical study on potential manufacturing variability or formulation changes that could realistically be envisioned during future commercial manufacture, rather than on very different formulations which are unlikely to be commercially manufactured. If this clarification is not made, then how would the investigator determine when the formulation had been adjusted too much, to change the release mechanism? **Proposed change (if any):** Please provide a clarification on this point. --------- **II. Comment:** We would suggest adding a concluding statement at end of the paragraph for clarification sake. **Proposed change (if any):** Please add the following sentence: "**In other words, it is important that the intended target formulation is appropriately**	should be reflective of the potential manufacturing variability or formulation changes that could realistically be envisioned during future commercial manufacture. *[see lines 238-247].* Accepted.
<A> 240-245			

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		bracketed."	
<A> 247, 270	**72**	**Comment**: Redundant sentence in lines 247 and 270. **Proposed change (if any):** Deletion of one of the sentences.	Deleted from line 270.
<A> 252-253 <G> 252-253	**73**	**I. Comment**: The FDA guidance for extended release oral dosage forms (1997) suggests that "the last time point should be the time point where at least **80%** of drug has dissolved. If the maximum amount dissolved is less than 80%, the last time point should be the time when the plateau of the dissolution profile has been reached." We would suggest the following proposal to allow further harmonisation. **Proposed change (if any):** Replace by "[...] (generally ~~more than 85% dissolved i.e.~~ Q=80%). **If the maximum amount dissolved is less than 80%, the last time point should be the time when the plateau of the dissolution profile has been reached.**" --- **II. Comment**: The third dissolution point is proposed to be at more than 85 % (i.e. Q=80 %) dissolved. This is not in line with what is required acc. to Ph. Eur. 5.17 (i.e. more than 80 %). Also, Ph. Eur. does not apply the Q+5 % requirement for prolonged release dosage forms (See Ph. Eur. 2.9.3, Table 2.9.3.-2).	Accepted. As above

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 252-253		**Proposed change (if any**): Change the bracketed text in line 248 to: *"(generally more than 80 % dissolved)."* ------ **III. Comment**: The previous guideline did require the last time point when more than 80% is released. This draft requires the third point to be set when at least 85% have been released. Proposed change (if any): ...generally more than 80% released...	As above.
<A> 254-256	**74**	**Comment**: The meaning of a variable lag-time should be clarified and more importantly, the meaning of what is an acceptable lag-time (e.g., less than 2 hours?) **Proposed change (if any):** Include examples of acceptable methods to determine lag-time (e.g., extrapolation of slope to x-axis intercept).	The following text has been included in the guideline: *"The method to determine the lag time is up to the applicant".[line 257]*
<D> 261-262	**75**	**I. Comment:** Tolerance limits may be derived from the spread of in vitro dissolution data of batches with demonstrated acceptable in vivo performance. (bio batches)- Specifications should be established on clinical/bioavailability lots. Widening specifications based on scale-up, stability, or other lots for which bioavailability data are available is recommended.	Rejected. See comments 40, 51 & 113

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<D> 261-264, 270-271		**Proposed change (if any):** Tolerance limits may be derived from the spread of in vitro dissolution data of batches (both initial and stability samples) with demonstrated acceptable in vivo performance. (bio batches). ------ **II. Comment:** BE for IVIVC and Side batches (for Non IVIVC) - 90% CI outside limit of 80-125%. However prediction of subject can be submitted for successful bio equivalence. To elaborate it further the ratio for C_{max} and AUC shall be in the range of 80-125%. However 90%CI can be predicted based on number of subjects. **Proposed change (if any):** Criteria for acceptable in-vivo performance for side batches are not explained in current guidance. The acceptable in-vivo performance based on current bioequivalence guidance (90% confidence interval for pharmacokinetic parameters (Cmax and AUC) 80-125% will be challenging. We would like to propose concept for predictive BE instead of bioequivalence for side batches or T/R (80-125) to conclude acceptable in-vivo performance for side batches. ----------	The recommendations of the PK GL are valid for MR products. Rejected.
<A> 262		**III. Comment:** Clarification is required on the type of batches meant under 'bio-batches': batches included in bioequivalence studies and/or batches used in clinical trials	Refer to Glossary.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		with demonstrated safety and efficacy? **Proposed change (if any):** please clarify. ----------	
<C> 263-264		**IV. Comment:** For the side batch concept, please specify test and reference treatment of a corresponding bioequivalence study. **--------**	Rejected.
<A> 263-264		**Comment:** The so-called side-batch concept with demonstrated bioequivalence between batches at the proposed upper and lower limit of the dissolution range is very strict. **Proposed change (if any):** Replace by: […] bioequivalence of the proposed upper and lower limit of dissolution against a clinically relevant target."	Rejected.
<A> 265-268	**76**	**I. Comment**: The FDA guidance for extended release oral dosage forms (1997) specifies that the difference between any time point cannot be greater than 25% instead of ± 10%. We would suggest the following proposed change to allow further harmonisation. **Proposed change (if any):** Replace by "Normally, the permitted range in release at any given time point should not exceed **a total variability of 25%** ~~a total numerical~~	Rejected.

Stakeholder - page number	General comment (if any)	**Outcome** (if applicable)
<D> 265-268	~~difference of ±10%~~ of the labelled content of active substance ~~(i.e. a total variability of 20%: a requirement of 50 thus means an acceptable range from 40-60%)"~~ --- **II. Comment** Normally, the permitted range in the release at any given time point may exceeds a total numerical difference of ±10% of the labelled content of active substance (i.e. a total variability of 20%: a requirement of 50±105 thus means an acceptable range from 40-60%, unless a wider range is supported by a bioequivalence study or a validated IVIVC. **Proposed change (if any):** In certain cases, reasonable deviations from the ± 10 % range can be accepted provided that the range at any time point does not exceed 25%. ± 10% Limits for dissolution may be revised as ± 12.5 %. This is also in accordance with US FDA guideline for dissolution. Specifications greater than 25% may be acceptable based on evidence that lots (side batches) with mean dissolution profiles that are allowed by the upper and lower limit of the specifications are bioequivalent. ---	Rejected.
<A>	**III. Comment:** To avoid misunderstanding, repeat that	Rejected. Text is clear as is.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
266 – 267		the variability relates to labelled content. **Proposed change:** Replace by "[…] (i.e. a total variability of 20% of labelled content: a requirement of 50±10% **of labelled content** thus means an acceptable range from 40-60%)"	
<B> 267-268	**76**	**Comment**: Section 'a. No IVIVC' provides guidance on how to set specifications if no IVIVC has been established; it means that a wider acceptance range is not supported by a validated IVIVC. **Proposed change** (if any): "[…] unless a wider range is supported by a bioequivalence study ~~**or a validated IVIVC**~~"	Accepted as editorial.
<E> 269-298	**77**	**Comment**: It would be extremely helpful to have illustrations how this exactly works. **Proposed change** (if any): Add an addendum with an example or illustrations of these proceedings.	Refer to Annex 2 of this guideline.
<C> 272-275	**78**	**Comment**: The sentence is difficult to understand. **Proposed change** (if any):	Accepted.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Dissolution profiles are generated from the proposed limits using the established IVIVC that preferably includes an appropriate mathematical ~~function~~ description of the in vitro dissolution behaviour (e.g. Weibull function, Hill, etc as justified by the behaviour of formulations tested during product development), or, normally less usefully, based on release at different time points	
<C> 275-280	**79**	**Comment**: It is not clear for which reason the calculated plasma concentration profiles of the reference formulations are needed as the acceptance criteria is based on comparison between the profiles predicted for the lower and upper specification limits (see lines 286-290).	Bioequivalence requires always a reference.
<C> 277, 279	**80**	**Proposed change** (if any): Use the term "batch" instead of "formulation".	Rejected.
<B> 278, 284, 288, 290	**81**	**Comment**: In order to achieve a consistent interpretation of the guideline it is important that terms and reference to pharmacokinetic parameters is done in a harmonised way throughout the guideline text. **Proposed change** (if any): Line 278 '[…] The corresponding Cmax and **the selected** AUC **parameter** value […]'	Accepted.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Line 284 '[…] based on confidence intervals around the mean Cmax and **the selected** AUC **parameter** […]' Line 288 '[…] i.e., the difference between the Cmax and **the selected** AUC **parameter** for the mean in vivo concentration […]' Line 290 '[…] than 20*% between the predicted Cmax and **selected** AUC **parameter** for the upper and lower dissolution specifications […]'	
<A> 281-282 287-290	**82**	**Comment:** The guiding principle of specification setting is that all batches within the lower and upper dissolution specification limits should be BE to one another is very strict. **Proposed change (if any):** Replace by "The guiding principle of specification setting is that **any set of batches within the lower and upper dissolution specification is expected with a high probability to be bioequivalent to one another if tested. Efficacy and safety considerations by the sponsor may justify wider limits, and bioequivalence with the clinical target might be justified**."	Rejected. The guiding principle of specification setting is that all batches within the lower and upper dissolution specification limits should be **bioequivalent to one another**.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 281-282	**83**	**I. Comment**: It is noted that the document as positioned (i.e. in the subsection related to setting specifications where an IVIVC has been established) is correct, though would not be possible under other circumstances. **Proposed change (if any):** Please replace as follows: "The guiding principle of specification setting (for the dissolution test)_ **provided that a IVIVC has been established**_ is that all batches within the lower and upper dissolution specification limits should be bioequivalent to one another." **II. Comment:** We have concerns around BE comparisons at the dissolution extremes to justify dissolution specifications (*versus* BE comparison of the extremes vs the middle), since we believe these to reduce the probability of success. **Proposed change (if any):** We would recommend including the drivers behind the proposals (especially whether they are to address a theoretical risk or actual issues observed).	Rejected. The **guiding** principle of specification setting is that all batches within the lower and upper dissolution specification limits should be **bioequivalent to one another**. Rejected. The **guiding** principle of specification setting is that all **batches** within the lower and upper dissolution specification limits should be **bioequivalent to one another**.
<A> 282-291	**84**	**I. Comment:** This test is quite complex and seems to be at odds with the position in the EU BA/BE guidance, where	It is noted that the text here is about the case where a level A IVIVC is established.

Stakeholder - page number	General comment (if any)	**Outcome** (if applicable)
	limits of 80-125% for PK parameter equivalence are provided. Clarification is required for selecting 20% in difference between upper and lower limit. Clarification is also required with regard to the reference [what is considered as reference (=100%)]. **Proposed change (if any):** Please consider if this text is aligned with the EU BA/BE guideline. Also, It would be very helpful to have some more specific guidance around acceptance ranges, incl. whether there is an expectation to use the CI for the reference to then predict what the point estimate for the IVIVC mean prediction would be.	The guiding principle of **specification** setting is that all batches within the lower and upper **dissolution specification limits** should be bioequivalent to one another.
	II. Comment: If you consider the following case, how would you set dissolution specification: A bioequivalence study was performed comparing the innovator and generic product. The bioequivalence of the generic product to the innovator was successfully demonstrated. However, the Cmax ratio of the generic/innovator product was for example 110%. • Should the dissolution specification of the generic product be set in a way to assure bioequivalence **compared to the generic product,** i.e. Cmax in the range 90-110% compared to the generic biobatch product ?	It is noted that the text here is about the case where a level A IVIVC is established. The guiding principle of **specification** setting is that all batches within the lower and upper dissolution specification limits should be bioequivalent to one another.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 288-290		• Or should the dissolution specification be set in a way to assure bioequivalence **to the innovator product**, i.e. Cmax in the range of 90-110% compared to the innovator biobatch product ? **Proposed change (if any):** Please clarify. --- **III. Comment :** The statement as written is unclear **Proposed change (if any):** Replace by "[...] for the mean in vivo concentration-time data predicted **for batches at the extremes of the dissolution specification** must be less than ..."	Rejected. See above.
<A> 298	**85**	**Comment:** The present document does not include the use of predictive mathematical models as supplemental data to strengthen an IVIVC/R or for comparing in vitro dissolution profiles in the case where the statistical analysis, i.e., f2 test, is limited by the data. A mechanistic model may also be of value when the IVIVC does not fully meet all requirements. For example, if the predicted AUC or Cmax based on a conventional IVIVC is greater than 20% of the observed values, a predictive absorption model may show that the in vitro dissolution profile is still within the range of acceptance based on AUC and Cmax values, and the associated variability of these values, as shown	Taken into account. [Refer to lines 196-199].

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		from virtual trial simulations. **Proposed change (if any):** 2.2.c. Supportive Evidence of an IVIVC In addition to a level A IVIVC, *in silico* models that provide a mechanistic understanding of *the in vivo* dissolution and absorption process may be accepted as evidence to support a biowaiver application in limited situations with adequate justification. These situations may include cases where the acceptability of the *in vitro* dissolution data based on statistical comparison, for example the f2 test, is found to be borderline and inconsistent with *in vivo* clinical data. The use of models and simulated data would also support biowaivers where the predicted AUC or Cmax based on a conventional IVIVC is greater than 20% of the observed values. A predictive absorption model may be used to show that the *in vitro* dissolution profile is still within the range of acceptance based on AUC and Cmax values, and the associated variability of these values, as shown from virtual trial simulations[1,2]. The justification of the *in silico* simulations must demonstrate the model is adequately predictive, i.e., sufficient to cover the range of data under question, and should include observed clinical data and appropriate	

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		statistical methods for comparing simulated to observed data as part of the justification. 1. Crison, John, R., Timmins, Peter, Keung, Anther, Upreti, Vijay, V., Boulton, David, W., Scheer, Barry, J. 2012. Biowaiver Approach for Biopharmaceutics Classification System Class 3 Compound Metformin Hydrochloride using In Silico Modeling. J. Pharm Sci 101(50):1773-1782. 2. Homsek, Irena, Paojcic, Jelena, Dacevic, Mirjana, Petrovicm Ljiljana, Jovanovic, Dusan. 2010. Justification of metformin hydrochloride biowaiver criteria based on bioequivalence study. Arzneimittelforschung. 60(9):553-559.	
<A> 300-301	**86**	**Comment:** Reference to guidance documents is rather non-specific. **Proposed change (if any):** Please give detailed references, e.g.: ICH Q8R2	Rejected. Reader should be familiar.
<A> 301-302	**87**	**Proposed change (if any):** Amend the wording with: "Particular attention should be paid to the control of **critical quality attributes** that are required for the control of drug release". Additional note: please give examples of expected CQAs.	Text reworded.
<B>	**88**	**Comment**:	

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
303-304		The draft guideline seems to systematically request the establishment of a link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate. This approach implies that an IVIVC would be required as a general requirement. Experience shows this is not always relevant and it should therefore not be required in all cases. (See similar comments on lines 72-73, 346-347, 373/374) **Proposed change** (if any): Please amend as follows: "Pharmaceutical development should establish**, where relevant and necessary**, the link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate.	*See comments 6, 26, 99 & 106*
<A> 305-307	**89**	**I. Comment:** The text states that, under an enhanced development approach, the dissolution test can be met by real time release testing. What testing is envisaged ? Is this testing of some other parameter than dissolution ? (presumably, as dissolution is a destructive test). **Proposed change (if any):** Consider exemplifying / clarifying what RTRT might support dissolution test assurance. **II. Comment**: In the case where, in an enhanced pharmaceutical development environment, the release of	Could be a combination of other parameters- on a case-by-case basis. Refer to Real Time Release Testing Guideline. Could be a combination of other parameters- on a case-by-case basis.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		drug from an MR dosage form can be evaluated not by dissolution but by alternative controls (e.g. controls on the release controlling excipient, manufacturing parameters or critical drug substance attributes), perhaps a dissolution acceptance criterion may not need to appear in the control strategy (even as a 'will meet if tested' RTRT like requirement)? **Proposed change (if any):** Consider whether the text reflects that there are some instances when a dissolution test may not be required. **III. Comment**: In section 2.3, it is very encouraging to see "real time release testing" has been encompassed in the draft guidance. However, further guidance should be included. **Proposed change (if any):** When the manufacturing process for a drug product is changed from batch to continuous, it would be helpful to also have guidance indicating if comparison of dissolution profiles, coupled with an existing Level A IVIVC and verified drug release rate prediction algorithm/calibration model could serve as a sufficient data package for the agency to grant biowaivers.	Could be a combination of other parameters- on a case-by-case basis.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> 307-309 378	**90**	**Comment:** Does the scale impact refers to the algorithm which mechanistically links all relevant process parameters, material attributes and intermediate product attributes with the drug release rate? Does this sentence include the requirement to verify the predictability of drug release rate based on input parameters-driven algorithm in case a RTR testing approach is selected? **Proposed change (if any):** please clarify	Yes.
<A> 311-313	**91**	**Comment**: It would be helpful if more details/definitions on "**the significance of the change**" could be provided.	This is in the scope of variation regulation and variation classification guideline.
<C> 313	**92**	It is not clear, which "bioavailability/bioequivalence data" are referred to in particular. Please specify.	The sentence refers to variations to approved products and is considered self-evident.
<B> 313-314	**93**	**Comment**: The requirements for the variations to products should in our opinion take due account of the classification and requirements for the documentation according to the Commission Regulation (EC) No 1234/2008 of 24 of November 2008 ('the variations regulation') and the corresponding guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and	Reference is made to the variation regulation and variation classification guideline.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		veterinary medicinal products. For the variations in which the justification for absence of BA/BE data is not requested in the above mentioned Guideline reference should be made to this Guideline without any need for additional justification. **Proposed change (if any):** "If bioavailability/bioequivalence data have not been submitted their absence should ~~**always**~~ be justified **in accordance with the requirements of the Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products."**	
<A> 315-319	**94**	**Comment:** Please define the term "shape parameter." Since this is not a pharmacokinetic parameter, please specify the type of information that is expected. Alternatively, coupled IVIVC-PK simulations may be adequate to show that the shape of the single dose PK profile ensures appropriate bioavailability or bioequivalence at steady state for the formulations in the comparison. **Proposed change (if any):** Please clarify and include detailed guidance regarding shape parameters.	The term "shape parameter" is deleted.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<B> 317-319	**95**	**Comment**: The acceptance criteria for AUC and Cmax values calculated based on a level A IVIVC, are not detailed; the difference should not be larger than 20%. Please clarify for variations whether the selected AUC parameter (eg, AUC(0-inf) or AUC(0-t)) has to meet acceptance criteria in case of such comparisons. Cross reference to earlier guideline sections might help clarify the specifications setting process. **Proposed change** (if any): Please amend section accordingly.	The guiding principle of specification setting is that all **batches within the lower and upper dissolution specification limits should be bioequivalent to one another**. *Refer also to lines 281-291.*
<C> 323	**96**	**Comment**: Section 3 "Delayed release dosage forms": further guidance is missing on how similarity of dissolution profiles should be compared (using e.g. a similarity factor). EMA/618604/2008 Rev. 5, Section 3 gives a more detailed description, is this in accordance with QWP? Please be more specific	Guidance in the quoted document as updated is valid.
<A> 333-334	**97**	**Comment**: It is not clear to which paragraph 2 the text is referencing. **Proposed change (if any):** Please provide a more descriptive reference.	Comment noted, reference amended.
<C>	**98**	**I. Comment**: It is mentioned that besides PK Parameters	Examples included.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
337-338 <A> 337-338		like (AUC0 → t(last), AUC0 → ∞, Cmax, also other "relevant PK parameters" should be given. Since AUC and Cmax values seem to be most appropriate to describe a MR dosage form, could you please specify which other PK parameters should be given in this regard? ------ **II. Comment:** Clarification is advocated about the "other relevant pharmacokinetic parameters". Partial AUC to reflect the shape of the drug concentration-time curve is particularly important for delayed release dosage forms. **Proposed change (if any):** please provide clarification.	*See comment 57.*
<C> 346-347 <B> 346-347	**99**	**I. Comment**: It is not clear why Pharmaceutical development should establish this link and not other functions like clinical PK or Pharmacometrics. **Proposed change**: ~~Pharmaceutical development should establish the~~ <u>The</u> link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate <u>should be established</u>. --------- **II. Comment**: The draft guideline seems to systematically request the establishment of a link from pharmacokinetic parameters	*See comments 6, 26, 88 & 106.* *See comments 6, 26 & 88 & 106.*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		through in vivo drug release to in vitro dissolution rate. This approach implies that an IVIVC would be required as a general requirement. Experience shows this is not always relevant and it should therefore not be required in all cases. (See similar comments on lines 72-73, 303-304, 373-374) **Proposed change** (if any): Please amend as follows: "Pharmaceutical development should establish**, where relevant and necessary**, the link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate.	
<F> 352-354	**100**	**I. Comment**: Residence time would depend upon size. This may be an issue for larger tablets, but not for small ones. **Proposed change** (if any): The development of **large** single unit non-disintegrating gastroresistant dosage forms ~~is generally discouraged~~ for gastroresistant products **should be approached with caution** since their residence time in the stomach ~~is~~ **may be** unpredictable and in general longer than disintegrating dosage forms which contain multiple units of pellets. -------	*See comment 9.*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<C> 352-356		**II. Comment**: The guideline seems to actively discourage the use of a single unit non-disintegrating gastro resistant dosage forms due to the perception of a higher risk of dose dumping and/or erratic PK profiles. It is recommended that the guideline focus on methods to characterise the potential for dose dumping and/or erratic PK profiles, rather than discouraging a particular type of dosage form. It is worth mentioning that there are already many restrictions on the application of single unit non-disintegrating dosage forms including tablet/capsule size, selection of polymers, inherent PK variability due to drug substance permeability/metabolism, etc. ------	This understanding is correct. *See comment 9.*
<A> & <C> 352-356		**III. Comment**: Single vs. multi unit dosage forms – Single unit non-disintegrating gastro resistant dosage forms continue to be utilized by the industry and in specific cases are more appropriate than multi-unit dosage forms Whilst multi-unit dosage forms may offer advantages with respect to dose dumping, the manufacturing process may be more challenging to control so thought needs to be given to the reason for the delayed release and the most appropriate dosage form designed to meet the QTPP.	See above.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Proposed change (if any): **1)** Consider including guidance on how an investigator could evaluate the risk of dose-dumping, such as studying the impact of compressive forces mimicking the stomach contractions (i.e. housekeeper wave) during in-vitro dissolution testing. **2)** Consider including some guidance on understanding the repeat dose PK profiles versus single dose PK profiles to determine if erratic concentration profiles truly occur when the patient takes the medication as prescribed. For example, if the drug product is dosed fasted and the drug substance has a half life that is significantly longer than the average fasted state gastric emptying time (which dictates the onset of absorption). It would be expected that gastric emptying time variability would not significantly impact the repeat dose PK variability.	
<F> 357-362	**101**	**I. Comment**: If the gastro-resistance is to protect the drug substance from low pH, this is less of an issue as the food would have some effect. Proposed change (if any): ------	Comment considered but no changes are proposed.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<A> & <C> 357-362		**II. Comment**: For the impact of meals on drug product, only the pH is mentioned, however, in the literature it has also been cited that in the fed state, significantly more mechanical, compressive forces can be applied to the dosage forms. **Proposed change (if any):** Include recommendations on other physiological aspects (in addition to pH) that can change when the drug product is dosed with a meal rather than in the fasted state.	*See revised text.*
<A> & <C> 357	**102**	**Comment:** This is the first time "SmPC" is used in the document **Proposed change (if any):** Consider adding the acronym to the glossary.	It is added.
<E> 361-362	**103**	**Comment**: It may be mentioned that pH 6 may be achieved for a short period of time. Proposed change (if any):	In the vast majority of cases it is pH 3-5 therefore this is kept in the text.
<C> 366-367	**104**	**Comment**: More guidance on a close to neutral medium would be appreciated.	Reference to Ph. Eur. Is deleted. No further change is proposed.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Proposed change (if any): ...and one to ensure that the majority of the active substance has been released in a (near) neutral medium (pH 6.8)	
<A> & <C> 368	**105**	**Comment:** Is this comment referring to a single dissolution test that begins at low pH and buffer is added after ~2 hrs to then determine the drug release profile at high pH? **Proposed change (if any):** Please provide more clarity on what this means and it would be useful to explicitly state if a single dissolution method that starts at low pH and changes to high pH is preferred because it is perhaps more bio-relevant or if two separate dissolution methods are preferred for each pH or if there is no preference.	It is up to the applicant to show suitability of method.
<C> 373-374 <B> 373-374	**106**	**I. Comment**: For a delayed release formulation it may be difficult to establish a link between in vivo absorption and in vitro release over time as gastric emptying is variable. --- **II. Comment**: The draft guideline seems to systematically request the establishment of a link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate.	*See comments 6, 26, 88 and 99.* *See comments 6, 26, 88 and 99.*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		This approach implies that an IVIVC would be required as a general requirement. Experience shows this is not always relevant and it should therefore not be required in all cases. (See similar comments on lines 72-73, 303-304, 346-347) **Proposed change** (if any): Please amend as follows: "Pharmaceutical development should establish**, where relevant and necessary**, the link from pharmacokinetic parameters through in vivo drug release to in vitro dissolution rate.	
<B> 376-378	**107**	**Comment**: In the case of delayed release dosage forms, from the pharmaceutical development point of view it is quite unrealistic to verify the whole design space at full commercial scale. This would imply the realization of numerous full scale batches, i.e. translating into time, material and energy intensive experiments while it is possible to obtain enough relevant information in a sufficient extent from the experiments on pre-industrial, mostly pilot scale, the latter already involve an aspect of scale-up effect with regard to laboratory scale, which is also in agreement with the ICH Topic Q 8 (R2) Pharmaceutical Development, Step 5, NOTE FOR GUIDANCE ON PHARMACEUTICAL DEVELOPMENT	Requirement for verification at the full commercial scale remains. Sufficient guidance is provided elsewhere, e.g. in ICH Q8 and ICH Points to Consider. No further need for specific guidance on scale-up for modified release dosage forms.

Stakeholder - page number	General comment (if any)	**Outcome** (if applicable)
	(EMEA/CHMP/ 167068/2004) which states that a design space can be developed at any scale. A thorough investigation of process and formulation parameters in a pilot scale offers a quality insight into product behaviour under real scale production conditions. In a number of cases the size of pilot scale usually corresponds to minimal industrial scale. These trials are thereupon combined with only few full commercial scale experiments to examine the extent of scale-up effect or to confirm the expected. Our experiences show that this approach supported by comprehensive material knowledge, process expertise and intense analytical activity, including real time release testing, sufficiently build a reliable picture of delayed release product produced at industrial scale. It is however of great importance to test the most important i.e. critical parameters, that influence critical quality attributes, which are responsible for the delayed release, in a full industrial scale. These critical parameters are previously well defined and argumentation in a scope of risk analysis. **Proposed change (if any):** "As the principle for controlling the drug release in a delayed release dosage form may be susceptible to scale-up effects, it is particularly important that **the critical quality attributes (defined in pilot scale) of the** design space **are** verified at the full commercial scale."	

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<E> 320-321	**108**	**Comment:** Definitions of level A, level B and level C IVIVC have not yet been explained.	See Annex 2.
<A> & <C> 376-378	**109**	**Comment**: The susceptibility of delayed release dosage forms to scale up effects is dependent on the dosage form selected. For example, the scale up of coating of single unit tablets is well understood and is based on sound engineering principles so verification of design space at scale may not be necessary. **Proposed change (if any):** Need to encourage a risk based approach including consideration of the need to verify the design space at commercial scale.	Outside the scope of this guideline. Details in other specific guideline. *See comment 107.*
<A> 379	**110**	**Comment:** numbering error **Proposed change (if any):** Replace by chapter **3.4**.	Amended.
<E> 382-383	**111**	**Comment:** In this section, it should specifically be stated that the in-vitro comparison performed at pH 4.5 and pH 6.8 after initial storage for 2 hours in the acidic medium, should also be done after initial storage for 2 hours at pH 3-5 if the SPC requires the co-administration with food or does not exclude the co-administration with food.	Yes, understanding is correct.
<B>	**112**	**Comment**:	Accepted as: "Profiles of release after gastro-

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
382-383		The current proposed wording of the draft guideline does not sufficiently reflect the inherent variance in testing. **Proposed changes** (if any): "Profiles of release after gastro-resistance testing **of the changed formulation should ~~of course be unchanged~~ be similar to that of the test batch used in the bioequivalence or pivotal clinical study."**	resistance testing should ~~**of course**~~ be unchanged."
<A> 387-388	**113**	**Comment:** Clarification is required about the term "showing acceptable performance".	*See comments 40, 51 & 75.*
<B> 387-389	**114**	**Comment**: The definition of the term 'biobatch' should be completed so as to allow for batch sizes below 100.000 units, in which case this would be the full production scale. This type of cases allowed for immediate release products (reference is made to point 4.1.2 b. of the Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). **Proposed changes** (if any): Add sentence: "**In situations where a commercial batch is of a size smaller than 100,000 units, a full production batch is required."**	*See previous comments in this regard.*
<C>	**115**	Convolution is not mentioned in the text.	Included in the definition of deconvolution.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
395-401			
<B> 401 <A> 401 and 409	**116**	**I. Comment**: The equation is not properly formatted; the interval for the integral should be placed correctly. **Proposed change** (if any): Please ensure the equation appears as intended in the final guideline. ------ **II. Comment**: We would suggest using the following format for the integrals. **Proposed change (if any):** $c(t) = \int c_g(t-u) r_{abs}(u)\, du$	Amended. Amended.
<F> 410	**117**	**Comment**: The definition of delayed release is time-based only, whereas the description of such products at Lines 323 et seq is pH-based. **Proposed change** (if any): Either modify the definition, or add a specific definition for gastro-resistant dosage forms	Refer to Ph.Eur.
<A> & <B> 418	**118**	**Comment**: Minor typo to correct	Amended.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Proposed change (if any): Change *"top"* to *"to"*	
<I> 422-424	**119**	**I. Comment**: MDT is calculated from the formula $MDT = \frac{\int_0^\infty (M^\infty - M(t))dt}{M^\infty}$ as indicated only when M∞=dose. When M∞<dose then the mean dissolution time is infinite and the abovementioned formula corresponds to the mean saturation time instead. (Rinaki E., Dokoumetzidis A., Macheras P. The mean dissolution time depends on the dose/solubility ratio. Pharm Res 20: 406-408, 2003). **Proposed change** (if any): Add phrase at the end "…when M∞=dose, while when M∞<dose, MDT is infinite and the abovementioned formula corresponds to the mean saturation time (Rinaki E., Dokoumetzidis A., Macheras P. The mean dissolution time depends on the dose/solubility ratio. Pharm Res 20: 406-408, 2003). -------	Formula amended.
<A> 423-424		**II. Comment**: We would suggest using the following format for the equation. **Proposed change (if any)**: $MDT_{vitro} = \frac{\int_0^\infty (M_\infty - M(t))dt}{M_\infty}$	Amended.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
<B> 423		**-----** **III. Comment**: The equation is not properly formatted, the interval for the integral should be placed correctly, the key for interpreting the symbols used is missing (e.g. M^{∞}, M(t)), a fraction bar is missing. **Proposed change** (if any): Please ensure the equation appears as intended in the final guideline	Amended.
<A> & <C> 452-453	**120**	**Comment:** The sentence defining sink conditions could be misinterpreted. Stated in this fashion the focus is on the final amount of drug release at the end of the test. This is likely to be controlled by the dosage forms release profile rather than a definition independent of the dosage form and only dependent on drug substance properties. If there is a "dose dumping" event in-vitro, the actual saturation concentration of the drug substance may prevent it from being fully realized. For example, if only 10% of the drug is typically released from the dosage form after 2 hrs in acid and the saturation solubility of the drug substance occurs when 30% of the drug is released in this media, you will never detect a higher release than 30% at 2 hrs and most likely even less drug will be solubilised than the saturation concentration depending on the kinetic solubility. Using sink conditions described in this fashion,	No difference is seen in the proposal.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		you may underestimate dose dumping potential. **Proposed change (if any*):*** Replace by *"Sink conditions: the volume of medium at least three times that required in order to form a saturated solution of drug substance."*	
<E> 480-481	**121**	**Comment:** Section II is also going to be revised? Because in the old guideline 'validation'of ivivc was discussed : predicatibility internal and external which is rather important.	Yes it is being revised.
<A> 481-484	**122**	**Comment:** In case of generic drug development there is usually available literature data about pharmacokinetic properties of the drug after intravenous administration or after oral solution administration or after immediate release formulation administration. Therefore, there is no need to perform pharmacokinetic evaluation of the "appropriate reference formulation" – such as an iv or oral solution. We believe that two or more modified release formulations with sufficiently different dissolution profiles are enough to establish level A IVIVC. **Proposed change (if any*):*** Delete "and an appropriate reference formulation (for the purpose of deconvolution)"	It is noted the sentence starts with *"Generally,…"*. If it is done differently it should be justified.
<A> 499-501	**123**	**Comment**: The wording is confusing and need clarification.	Accepted.

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Proposed change (if any): Replace by "Generally, level B and C correlations are not useful for supporting major variations in the composition or manufacturing process of the product but ~~in setting specifications,~~ multiple level C correlations could be supportive **in setting specifications".**	
<A> 502-506	**124**	**Comment**: The long sentence is difficult to understand. **Proposed change (if any):** Replace by: "A multiple Level C correlation should be based on at least three time points of the dissolution profile. A multiple point Level C correlation may be used to justify a biowaiver, provided that the correlation has been established over the entire dissolution profile with one or more pharmacokinetic parameters of interest. This could be achieved by correlating the amount dissolved at various time points with C_{max}, AUC, or any other suitable parameter."	Rejected.
<A> 506-508	**125**	**Comment**: Lines 506-508 and 511-512 *[nb lines 511-512 does not exist any as it has been deleted following this comment)* are duplicates. Moreover, the verbiage 'likely to be feasible' (lines 507-508) is deemed to be more appropriate than 'is feasible'.	Accepted "*…is feasible".* *Lines 511-512 deleted.*

Stakeholder - page number		General comment (if any)	**Outcome** (if applicable)
		Proposed change (if any): Delete lines 511-512: "It should be noted that …..of a Level A correlation is feasible."	
<A> 519-521	**126**	**Comment**: The methodology of predictability analysis of an IVIVC is missing in NfG section II (CPMP/EWP/280/96 Corr.) **Proposed change (if any):** Limits for internal and external prediction errors should be defined.	This will be added in the updated version of the PK guideline.

Please add more rows if needed.