EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2018
EMA/CHMP/648051/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract' (EMA/CPMP/EWP/239/95 Rev.1) †

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

Stakeholder no.	Name of organisation or individual
1	AESGP - Association of the European Self-Medication Industry
2	Dr. Falk Pharma GmbH, Freiburg, Germany (Falk)
3	EFPIA
4	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) AISBL
5	Ferring Pharmaceuticals A/S
6	Reckitt Benckiser
7	Recordati Pharma GmbH
8	Therapeutic Goods Administration, Australia
9	Tillotts Pharma AG
10	Medicines for Europe

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
3	EFPIA welcomes the opportunity to provide comments on the draft "Guideline on equivalence studies for the demonstration of therapeutic equivalence for products that are locally applied, locally acting in the gastrointestinal tract as addendum to the guideline on the clinical requirements for locally applied, locally acting products containing known constituents, CPMP/EWP/239/95 Rev. 1". EFPIA suggest several amendments and/or clarifications to be made in the document. The details are provided in the section for specific comments, whilst the more general comments are presented in the first section of the response. Consistent with increased acceptance of modelling and simulation approaches, it is proposed that the use of in-silico models (e.g. physiologically based pharmacokinetic modelling) be considered as an alternative to human pharmacodynamic studies, local availability studies or other listed data sources. The qualitative and, where appropriate, quantitative choice of excipients should take into consideration disease related sensitivities as well as inherent differences in excipients. For modified release, the use of systemic availability as a surrogate of equivalence should be based on selected tests (those methods with demonstrated in vivo relevance) rather than a wider range of tests, in order to minimise the risk of falsely identifying	General comment for which the content was considered in the updating of the guideline following the public consultation and where applicable specific aspects are addressed in the section on 'Specific comments'

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	inequivalence.	
4	In line with the Legal Basis given in Section 3. (“Legal basis and relevant guidelines”, the guideline shall only apply to Marketing Authorisation Applications submitted in accordance with the Directive 2001/83/EC as amended, under Art. 10(3) (hybrid applications) and may also be applicable to Marketing Authorisation Applications submitted under Art. 8(3) (full applications), Art.10b (fixed combination), Art.10a (well-84 established use applications) of the same Directive, and for extension and variation applications in accordance with Commission Regulations (EC) No 1084/2003 and 1085/2003. Reference to any other types of Marketing Authorisation Applications should be deleted from this guidance (please also refer to our comments to line 141). It remains problematic to ascertain, when “other models” than clinical trials are “adequately qualified”. There is still a lot of room for interpretation left. In particular with regard to “in vivo PK data” it would be helpful to clarify that it refers to human PK data. It is also questionable, whether it is possible to indirectly compare concentrations at the site of action in a scientifically meaningful way, in particular if the concentration of the drug in question in the GI tract is very low. In order to ensure that public health remains adequately protected, demonstrating bioequivalence of undesired systemic drug levels shall always be required to ensure the safety of patients in the EU (please also refer to our comments to the “Equivalence requirements in	General comment for which the content was considered in the updating of the guideline following the public consultation and where applicable specific aspects are addressed in the section on ‘Specific comments’

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	specific situations"). It is our position that it would be useful to introduce the concept that in vitro dissolution studies should be performed jointly with bioequivalence studies in those cases which involve the use of low soluble drug substances. As a matter of fact, properly developed dissolution tests which consider the physico-chemical properties of the drug substance should highlight the differences between test and reference products, if any. Therefore, it would be appropriate to introduce a clear reference to dissolution test performed in adequately chosen experimental conditions, taking into consideration several concentrations of surfactants (i.e. providing sink and non-sink conditions), simulated gastric or intestinal fluid as well as different pH and agitation.	
5	Ferring wish to provide the following general comments to clarify and optimise the draft guideline in its current form: - Gamma scintigraphy is considered to be the golden standard* to capture in vivo disintegration and distribution along the GI. Ferring recommends to implement a methodology including an imaging technique in combination with PK sampling to show the GI distribution for the test formulation and to relate systemic exposure (partial areas) towards location in the GI. - For products showing low bioavailability (e.g. below 5%, see specific comments in next section) Ferring recommends adding measures to capture extent of drug release during GI passage, e.g. faecal sampling.	General comment for which the content was considered in the updating of the guideline following the public consultation and where applicable specific aspects are addressed in the section on 'Specific comments'

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	- Ferring is recommending alignment with US requirements for drugs locally acting in the intestine. The broad variety of locally acting drugs covered by this guideline, especially modified release formulations, are very different in nature and release profiles. Recommendations needs to be general with the single guideline approach. But thereby special cases will not be adequately covered. Ferring recommends product specific guidance like it is done by FDA. * European Journal of Pharmaceutics and Biopharmaceutics 74 (2010) 84-92	
6	The general principles and requirements for demonstrating equivalence in any therapeutic area for products where standard pharmacokinetic studies are not appropriate should be consistent i.e. the requirements should be consistent across all three related guidelines which are currently being proposed for revision: EMA/CHMP/QWP/558185/2014, EMA/CHMP/267194/2016 and this guideline. We have therefore reviewed this draft GI products guideline in the context of the two concept papers released for the above mentioned related guidelines, to ensure any relevant points from these concept papers are incorporated or aligned within this guideline. Specifically, the below points should be considered across all three guidelines: EMA/CHMP/QWP/558185/2014 (concept paper on topical products)	General comment for which the content was considered in the updating of the guideline following the public consultation and where applicable specific aspects are addressed in the section on 'Specific comments'

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	states on line 58: 58 The additional measures of equivalence currently available include in vitro drug release through an artificial membrane and / or human skin membrane to determine the rate and extent of drug release or permeation We agree with this aspect of the topical products concept paper and believe this measure could also be relevant in the context of this draft guideline for GI products i.e. for measuring in vitro drug release across mucosal membranes. This concept should be included into the GI products guideline as a potential method for demonstration of equivalence. EMA/CHMP/QWP/558185/2014 (concept paper on topical products) states on line 67: 67 Method limitations may be addressed by employing a battery of different techniques, but, in any case, this needs to be fully explored and understood to avoid inappropriate use and claims. This wording has not been included in the draft guideline for GI products. We would recommend that the requirement to address method limitations through employing multiple different techniques should apply to GI products as well as topical products, and that the above wording is therefore incorporated into the draft guideline text. EMA/CHMP/267194/2016 (concept paper on orally inhaled products)	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	states on line 86 86 • Given the limitations with imaging studies to conclude on therapeutic equivalence, the current recommendation should be reviewed. We would like to state that we believe imaging studies, while they may have limitations for orally inhaled products, do have usefulness in demonstrating equivalent localisation, deposition and duration of retention at a particular location within the GI tract for GI products. Scinitigraphy imaging has also been successfully used in peer reviewed publications for oromucosal products such as lozenges and throat sprays (Limb et al, 2009). EMA/CHMP/267194/2016 (concept paper on orally inhaled products) states on line 88 88 • The current version states that pharmacokinetics should be studied in the intended patient population. This statement needs to be revised and specific information should be given regarding when healthy volunteers may be used for demonstrating therapeutic equivalence. In line with the Guideline on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) we would like to raise that, in order to reduce variability not related to differences between products, studies should normally be performed in healthy volunteers	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	unless the drug carries safety concerns that make this unethical. Only where the product is expected to have a different impact in the diseased or symptomatic patient vs a healthy volunteer, should any PK or equivalent local availability studies should be conducted in the patient population. In general, for this draft guideline as a whole, we would like to raise that in line with the bioequivalence guideline, where appropriate, studies should be conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC). In line with Directive 2001/20/EC, studies which are conducted in order to ascertain or verify/compare the efficacy or safety of the medicine should be considered as a clinical trial and conducted accordingly. As local availability or other in vivo studies are conducted specifically for this purpose, through demonstration of equivalence with a reference product as pivotal evidence to support the approval of an MA i.e. not simply as part of product development verification or exploratory work, these studies should fall under Directive 2001/20/EC and as such should follow GCP and the Declaration of Helsinki to ensure appropriate validation of the study and protection of the subjects/patients. In line with the requirements for generic registrations to provide data on impurities in their product vs the reference product, including throughout shelf-life of the generic and reference product (Doc. Ref.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	EMA/CHMP/CVMP/QWP/450653/2006 Recommendation on the Assessment of the quality of medicinal products containing existing/ known active substances), we would expect for locally acting, locally applied products this requirement is also met. We would recommend this requirement is laid out clearly within this guideline, in particular the below: “It is expected that the applicant of a generic product justifies why he considers the impurities in his product safe for the intended use and qualified, either by reference to expected similarity with the originator or by other means e.g. compliance with relevant (V)ICH guidelines”.	
7	In general this guideline draft took up the concerns of pharmacists and medical doctors that orally applied, but locally acting products, like the melsamine (5-ASA, 5-aminosalicylic acid, other INN name: melsazine) or budesonide containing products in treatment of inflammatory bowel disease could not easily be compared by a simple dissolution profile. For ensuring the efficacy in patient the method of testing has to be of higher technical and scientific standard. This has to be seen as a good decision. Though a clinical study will be the gold standard in showing efficacy, the need of simplifying the marketing authorisation of further products was necessary. The purposes which are now given in this guideline are in general satisfying. However, there is somehow no trustable and clear line in this draft. As pharmaceutical industry representative I would wish that this	General comment for which the content was considered in the updating of the guideline following the public consultation and where applicable specific aspects are addressed in the section on ‘Specific comments’

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	guideline gives more likely one clear way of testing such a product. This draft now might leave the assessors in an uncertain situation and increases workload and bureaucratic effort in both parts of the business: the competent authority and the European pharmaceutical industry. Changes and more clear ways are strongly recommended. Otherwise it is more likely possible that outcome of a marketing authorisation application would be dependable from whom it is reviewed and how he/she is interpreting this quite flexible guideline. To guarantee a fair, easy and transparent process, we would strongly advise to keep up to one way and one or two possible methods of testing and to describe these procedures more detailed. Many thanks.	
8	The document covers a wide range of product types and provides high level guidance. Consideration could be given to developing addenda to provide more detailed advice based on specific product characteristics (e.g. the approach to non-solution drugs that are not systemically absorbed). Differences in excipients may result in differences in the safety and tolerability of a product. Although mentioned, the guidance places insufficient emphasis on the importance of demonstrating the similarity of the safety and tolerability in circumstances where excipients differ but systemic levels are measurable, and as important elements to consider in any equivalence study. Sponsors should carefully consider the product characteristics, mechanism of action, underlying disease being treated, validity of any invitro or invivo studies, and the effects of any excipients or differences in dose delivery systems in the development of their	General comment for which the content was considered in the updating of the guideline following the public consultation and where applicable specific aspects are addressed in the section on 'Specific comments'

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	generic product. The absence of clinical studies needs to be justified. The TGA would recommend a pre-submission meeting. When using in vitro methods and/or pk data as a surrogate for therapeutic equivalence of locally acting products, the choice of batches for the Test and Reference Products needs to be justified. The variability of the critical quality attributes of the products should therefore be taken into account. In relation to simple chemical entities in simple dosage forms, it may be sufficient to test only two batches of Test Product and two batches of Reference Product to determine the variability of each. However, for more complex chemical entities or dosage forms (e.g. sevelamer which is a complex 3-dimensional polymer), in vitro data on a larger number of batches of both Test and Reference Products is required to determine the variability. In such cases it may be appropriate that the in vitro equivalence studies be performed using outlier batches of both the Test and Reference Products rather than a representative batch of each. It is suggested that words to the above effect be added to Section 4.2 or possibly amended into Section 4.3.3.	
9	We appreciate and support this guideline as it will facilitate the development of high quality locally applied, locally acting (LALA) gastrointestinal products. It will also facilitate a uniform regulatory view within the EU. The draft reflects to a great extent the special requirements / special physiologic situation of LALA gastrointestinal modified release products. To also achieve here the same quality	General comment for which the content was considered in the updating of the guideline following the public consultation and where applicable specific aspects are addressed in the section on 'Specific comments'

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	level we propose some additions / modifications - see specific comments.	
10	Medicines for Europe welcomes the Guideline on equivalence studies for the demonstration of therapeutic equivalence for products that are locally applied, locally acting in the gastrointestinal tract as addendum to the guideline on the clinical requirements for locally applied, locally acting products containing known constituents. Medicines for Europe is positive on the further clarification the guideline provides on the requirements that need to be fulfilled to waive clinical trials with clinical or pharmacodynamic endpoints in the demonstration of therapeutic equivalence for locally applied, locally acting gastrointestinal products and on the necessary in vivo bioequivalence studies and in vitro equivalence tests. Medicines for Europe would like to highlight that the current scope does not refer to the legal basis under Art. 10(1) (generic application). We would like to propose to add generic applications to the scope as they will be applicable in cases where equivalence can be demonstrated only by a BE study or BCS biowaiver.	General comment for which the content was considered in the updating of the guideline following the public consultation and where applicable specific aspects are addressed in the section on ‘Specific comments’

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 4-9	3	Comments: While it is understood that the title of the parent guideline (CPMP/EWP/239/95) cannot be altered at this time, the title of the proposed guideline is cumbersome. By inference, if the product acts locally in the gastrointestinal tract, it will have been applied locally. As such, it is recommended that this be simplified. Proposed change (if any): Guideline on equivalence studies for the demonstration of therapeutic equivalence for products that are ~~locally applied,~~ locally acting ~~in the~~ gastrointestinal tract medicines, as addendum to the guideline on the clinical requirements for locally applied, locally acting products containing known constituents	Accepted. With minor linguistic modifications
Lines 45-47	3	Comments: See comment for Lines 4-9. Proposed change (if any): This guideline refers to medicinal products that are ~~applied locally and intended to exert their effect~~ locally ~~within the~~ **acting** gastrointestinal (GI) tract **medicines**. The assumption is that systemic action, if any, would be considered as an undesired effect.	Not accepted. In this case an extensive explanation is preferred to avoid misinterpretations.
Line 46	2	Comments:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Even if this guideline applies in general to drugs acting (somewhere) locally in the gastrointestinal tract, most products and drugs have therapeutically relevant effects only at specific defined sites / sections in the gastrointestinal tract. This should be indicated. Proposed change (if any): …at specific site(s) in the GI tract.	This sentence has been added in section 4.1.
46-47	6	Line 46 states: “The assumption is that systemic action, if any, would be considered as an undesired effect.” Comments: This statement is too general and does not necessarily reflect the complex nature of some locally acting products, which is some circumstances may have both local and systemic effects, depending on route of administration, format, mode of action of the active ingredient etc. Where active ingredients have both systemic and local action. It should be clarified whether this guideline covers both local and systemic action, or if systemic action should be addressed solely through reference to the standard bioequivalence guideline. Our view is that the applicant should have to design a programme of studies that consider both local and	Not accepted. The proposed text does not address the concern expressed: “in some circumstances some locally acting products may have both local and systemic effects”. In these cases, systemic contribution should be assessed according to the existing guidelines for systemically acting drugs and the local contribution based on this guideline. In some cases PK BE studies or a waiver could address both at the same time.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		systemic action, and that this should be considered within the scope of this guideline i.e. the applicant should consider PK from a safety (one sided) and/or true (systemic) bioequivalence point of view, and apply the principles in the bioequivalence guidelines for design of the PK study, in line with CPMP/EWP/239/95 final and CPMP/EWP/4151/00 Rev. 1 If there is evidence of systemic absorption demonstrated via a PK study, then the guideline should mandate a subsequent safety evaluation study if this data is not available for the bioequivalent reference product(s). Proposed change (if any): “The assumption is that systemic action, ***if there is any evidence that the product could also be absorbed systemically***, would be considered as an undesired effect, ***except in specific circumstances where systemic action is known, considered and justified within the clinical programme***”	
48-50	6	Comments: "known constituents" and “known active substances” are both referred to. “known” needs to be defined. Our position is that the definition of known constituents and known active substances should be aligned with the concept of a European Reference product	Not accepted. “Known” refers to drugs already in the market and this term is already in the guideline for which this guideline is an addendum since 1995.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Addition of definition or clarification on “known” actives.	
Line 50 - 54	2	Comments: Adequate qualification of any method/model is indicated as precondition for their use in place of clinical trials. Unfortunately, no adequate specification of the adequate qualification is given in the guideline. It should be indicated that for all methods and models used in place of clinical trials, all parameters with relevant impact on transit, release and dissolution in vivo should be adequately reflected by the method / the model. Omitting relevant parameters should cannot be accepted.	Partly accepted. Some of the proposed text has been included in section 4.2 since it can be considered as part of the sound justification required by the guideline.
Line 52-54	3	Comments: It is proposed that consideration be given to accepting the application of *in-silico* models (e.g. physiologically based pharmacokinetic modelling) in the context of equivalence studies for products acting locally in the GIT, provided these are adequately validated using existing data. Proposed change (if any): Depending on the situation, human pharmacodynamic (PD) studies, local availability studies or, where appropriate, even animal, ~~or~~ *in vitro* ***or in silico*** studies may be considered, provided that the respective methods/models are adequately qualified.	Not accepted. The proposed in-silico models based on modelling and simulation are not validated presently. These tools are recognised as valuable tools for the sponsors’ decisions, but not yet for regulatory decisions. Once they were considered as validated, they could be used as demonstration of therapeutic equivalence, but it does not seem necessary to include them in this guideline since other present or future existing guidelines on M&S or PBPK would be more appropriate.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 54	1	Proposed change (if any): Add examples, e.g. described in EU pharmacopoeia, to clarify the meaning of “adequately qualified”.	Not accepted. The Applicant / sponsor should justify the applicability/suitability of the employed method. The inclusion in the EU or any other pharmacopoeia could be used for that justification, but this will be a case by case decision.
Line 54	3	Comments: Clarification is requested regarding criteria used to determine if the respective models/methods are "adequately qualified".	Not accepted See a previous response on a similar comment.
Lines 55-58	1	Comments: Antacid products may contain 2 or more locally applied, locally acting substances, including e.g. combinations with alginates or simethicone. Proposed change (if any): “It has been shown…. products containing the same active substances”.	Accepted.
Line 60	2	Comments: It should be indicated more clearly what is meant with ”…at the site of action…” (as proposed). Proposed change (if any): “...at the specific site(s) of primary therapeutic requirement…”	Partly accepted. ‘Specific’ and ‘sites’ have been included in the text as proposed.
Lines 60 - 62	2	Comments: Falk welcomes the requirement of the demonstration of *in vitro* assays to reflect the *in vivo* situation. However, all parameters that have been shown to be	Partly accepted. The text “all parameters with relevant impact on in vivo transit, release and dissolution” was included in part 4.2.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		relevant for the *in vivo* situation (concerning transit, release, dissolution, absorption) need to be considered in the *in vitro* assays (as described e.g. in Garbacz & Klein JPharmPharmacol 2012;64:944-968). It needs to be defined how the availability of the drug at the site of primary therapeutic requirement ('site of action') can be demonstrated convincingly. To assess the release and/or drug availability at a specific site in the gastrointestinal tract, imaging or scintigraphic methods and/or direct measurements of luminal or mucosal concentrations (e.g. by biopsies) at the site of primary therapeutic requirement should be used. Proposed change (if any): The requirements how to demonstrate the site of drug release and the site(s) of its local availability *in vivo* should be defined precisely. This could be done in the "site specific sections" of the guideline (i. e one of the 4.3. sections), as e.g. for non-solution products acting locally in the mouth (lines 197-198).	It is not agreed that only imaging or scintigraphic methods or direct measurements of luminal or mucosal concentrations (e.g. by biopsies) at the site of primary therapeutic requirement should be used. In vitro methods and indirect measurements might also be valid methods as explained in the present text of the draft guideline. It is not possible to give precise description of requirements for all possible drugs products acting locally in the GI tract.
Lines 62 - 65	2	Comments: Falk supports the notion that similarity of drug release and availability at the site of action (preferred: at the site of therapeutic requirement), are the major factors to determine the comparability of clinical responses of locally applied medicinal products with local effects in the gastrointestinal tract containing the same substance. As drug release and availability depend on	Partly accepted. It is not possible to give precise description of requirements for all possible drugs products acting locally in the GI tract. However, the text: "taking into consideration all parameters with relevant impact on in vivo transit, release and dissolution" has been included to remind this claim of this stakeholder.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		many parameters, it is crucial to identify and define all conditions and parameters that have an impact on the release and local availability *in vivo*. In an adequate *in vitro* tests all relevant parameters in this respect need to be considered.	
Lines 65-67	1	Comments: Please add examples in the following sentence: "Therefore**, in those cases where the *in vitro* tests or pharmacokinetic (PK) studies reflect *in vivo* drug release and availability at the site of action**, clinical trials could be waived". Proposed change (if any): …e.g. shown by measuring pH increase in the stomach or oesophagus...	Not accepted. The proposed text seems to refer to a PD in vivo study in humans (out of the scope of this guideline) and the original sentence only refers to in vitro and PK studies.
Lines 65-67	2	Comments: The present statement appears for several reasons not sufficiently precise. See proposed changes. Proposed change (if any): …in those cases where *in vitro* tests in combination with PK studies have shown to allow sound conclusions on the *in vivo* drug release and its local availability…	Not accepted. The proposed text implies that in vitro data alone or PK data alone is not enough for demonstration of equivalence. This is contrary with the guideline thinking.
Lines 65-67	3	Comments: The sentence does not clarify that *in vitro* or *in vivo* conditions need to replicate disease state. Proposed change (if any):	Not accepted. The in vitro methods or PK method do not need to reflect the disease physiology but simply the in vivo performance of the product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Therefore, in those cases where the in vitro tests or pharmacokinetic (PK) studies reflect in vivo drug release and availability at the site of action, **reflective of disease physiology,** clinical trials could be waived.	
Lines 68 - 60	2	Proposed change (if any): The types of studies required to demonstrate equivalence should be decided <u>also</u> taking into account the specific characteristics of the dosage form.	Accepted.
Lines 73-74	2	Proposed change (if any): The choice has to be fully justified considering all relevant parameters having an impact on impact on the release and local availability *in vivo.*	Accepted. With minor linguistic changes.
Line 78	3	Comments: Clarification is requested regarding the term “chemical entities”. For example, clarification is required on whether this includes synthetic peptides. If not, it would it be preferable to refer to these “small molecules” instead.	Not accepted. Small peptides are included if chemically synthesised. The term “chemical entities” has been selected correctly.
Lines 81-83	3	Comments: In line with the parent guidance CPMP/EWP/239/95 and Section 4.2, the guideline is understood to mainly apply to abridged applications including 10(1) generics as well. Proposed change (if any): This guideline applies mainly to **abridged** Marketing Authorisation Applications for human medicinal products submitted in accordance with the Directive	Not accepted. This guideline does not apply to generic medicinal products as defined in the European Legislation (i.e., Directive 2001/83/EC) because these generic medicinal products are limited in the EU to systemically acting product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		2001/83/EC as amended, under **Art. 10 (1) (generic applications) and** Art. 10(3) (hybrid applications).	
81-83	4	Comments: The scope of application of the guideline should be more clearly defined. Proposed change (if any): Delete “mainly”, i.e. This guideline applies to Marketing Authorisation Applications for human medicinal products 81 submitted in accordance with the Directive 2001/83/EC as amended, under Art. 10(3) (hybrid 82 applications).	Not accepted. The scope is not only hybrids, but also line extensions, variations, well-established use applications, fixed combinations and full applications
81-86	10	Comments: Legal basis under Art. 10(1) (generic application) is missing in this section in cases where equivalence can be demonstrated by a BE study or if a waiver approach can be used. Additionally, according to line 141 generic applications are explicitly included in the scope of this guideline. Proposed change (if any): Also include legal basis under Art. 10(1) (generic application) in this section in cases where equivalence can be demonstrated only by a BE study or BCS biowaiver.	Not accepted. Please see previous responses on the explanation about the EU legal basis and why generic products are only those with systemic action in the EU.
Lines 110-138	5	Comments: Section ‘4.1 Types of locally acting, locally applied gastrointestinal products’ provides a good classification for the different types of locally acting gastrointestinal products. No reference to or use of this section is	Not accepted. It is used in subsections of section 4.3.1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		however applied during the remaining guideline. Consequently, the section appear redundant for the overall purpose of the guideline. Proposed change (if any): Delete section 4.1	
111-112	10	Comments: Drugs acting locally in oesophagus can't be classified in any category. Proposed change (if any): Please add a new category or add an explanation how such products should be classified.	Accepted. It has been included with the stomach.
N/A	9	General comments: In the document, there is use of general terms such as "same", "similar" and "major" which have a wide range of interpretation. Where ever possible, more precise language should be used.	Not accepted.
Lines 113-114	2	Comments: Add the oesophagus as an additional site of action (between line 113 and 114).	Accepted. But it has been included in the line of the stomach as proposed by another stakeholder to avoid many bullet points.
113-114	4	Comments: It is not clear that the sub bullets "a. Drugs that have a pharmacological, intracellular target" and "b. Drugs that have a target in the lumen or at the membrane surface", as well as being applicable in "1.c) In the intestine (e.g. anti-inflammatory and anti-motility agents", are also applicable in "1.a) In the mouth and/or throat (e.g. local analgesics or anaesthetics)" and in "1.b) In the stomach (e.g. antacids)".	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Move the 'target' sub-bullets to a separate item, No. 2, and re-number the subsequent bullets, i.e.: "2. According to the target, e.g.: a) Drugs that have a pharmacological, intracellular target b) Drugs that have a target in the lumen or at the membrane surface 3. According to their mechanism of action, e.g.:" …and so on	
113-117	9	Proposed change (if any): After a) thee should be a new line numbered: Esophagus	Accepted. It has been combined with the stomach for simplicity.
Line 114	1	Comments: Add "oesophagus" Proposed change (if any): b) In the oesophagus and stomach (e.g. antacids)	Accepted.
Lines 115	2	Comments: Given the large extension of the intestine and the specific characteristics of its sections, defined, separate subsections for the intestinal sections should be indicated. Proposed change (if any): c) in the proximal sections of the small intestine; d) in the distal sections of the small intestine; e) in the	Partly accepted. All these subsections of the intestine have been included but in the same bullet point.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		colon; f) in the rectum.	
Lines 116 - 117	2	Comments: In many cases, e.g. for mesalazine, the drug targets both intracellular, as well as luminal / membrane surface targets (see Campregher & Gasche BestPractResClinGastroenterol 2011;25:535-546; Xue et al. AlimentPharmacolTher 2012;36:813). Proposed change (if any): add a line c. Drugs acting at multiple sites.	Accepted.
129	4	Comments: “, e.g.” is missing at the end of the sentence. Proposed change (if any): 4. According to their pharmaceutical form, e.g.:	Accepted.
134	4	Comments: Replace “drug” with “drug substance” and “, e.g.” is missing at the end of the sentence. Proposed change (if any): 5. According to the state of the drug substance in the dosage form, e.g.:	Accepted.
137	9	Comments: Cream and ointment are not appropriate terms for a GI medicine. Proposed change (if any): Delete and replace by **gel**	Accepted. The section has been corrected and slightly modified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
140-142	4	Comments: According to section 3., generic applications are not in scope of this guideline, therefore reference to these should be removed. Proposed change (if any): General assessment of equivalence applies to locally applied, locally acting GI products to be approved either as a hybrid or as a reformulated product, i.e. therapeutic equivalence should ensure equivalence in terms of efficacy and safety.	Accepted.
Line 144	2	Comments: The “sound justification and appropriate qualification” should be indicated more precisely: Proposed change (if any): …sound justification and appropriate qualification, taking into consideration all parameters with relevance to the in vivo situation.	Accepted. The proposed text has been extended with “relevant impact on in vivo transit, release and dissolution” as proposed previously by this stakeholder, since it is more informative than simply “the in vivo situation”.
144	4	Comments: To ensure consistency of approach, it would be useful to understand the criteria to qualify as ‘sound justification and appropriate qualification’.	Not accepted. In a general guideline it is not possible to cover all the possible cases. The justification is case by case depending on the product.
144-147	4	Comments: The guideline should state a minimum level of validation required rather than leave this open to interpretation, loosely referring to ICH Q2 (R1).	Accepted. The proposal has been considered in a slightly modified text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): The following sentence should be added to the end of paragraph, line 147: "At the minimum any *in vitro* method used has to be robust, reproducible, sensitive and specific for the purpose for which it is intended."	
144-147, 243-245	6	Line 144 states "provided they have a sound justification and appropriate qualification. In vitro test(s)/model(s) should be validated (e.g. in line with ICH Q2 (R1)) before use" Line 244 states "methods should use widely accepted apparatus or, if a new method is used, should be suitably validated." Comments: The level of validation required is not clear. Clarity is required as to whether the method should be published and peer reviewed, validated according to "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009) and/or approved by an authority. Proposed change (if any): More clarity should be provided on the required level of suitable validation. Our proposal would be that any new method must be validated according to both the	Partly accepted. The Guideline on bioanalytical method validation is not applicable in this field as it only refers to the measurement of drug levels in biological matrices. However, the first paragraph of section 4.2 has been slightly modified and completed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Guideline on bioanalytical method validation and, where appropriate, via peer reviewed publication.	
Line 147	2	Comments: (as in line 144) Proposed change (if any): add: …sound justification for the chosen in vitro test(s)/model(s), particularly indicating of having considered all parameters of relevance in the in vivo situation should be provided.	Not accepted. This text was already included in the prior sentence.
Lines 148-150	2	Comments: It appears generally questionable if the demonstration of higher sensitivity of an alternative method (compared to an adequate clinical trial) is reasonable - or rather indicates e a general disregard of the high level of complexity and variability of the in vivo situation. Randomized, controlled clinical trials will obviously remain the gold standard. Therefore, the meaning and the objective of the demonstration of a superior sensitivity in vitro is inherently artificial and therefore questionable. Nevertheless, if alternative approaches, such as in vitro models shall be used to show comparable release characteristics, it has to be demonstrated that they reflect the in vivo situation, considering all parameters that are relevant for transit of the product and the release and the dissolution of the drug in the in vivo situation.	Not accepted. We agree that the clinical trials remain the gold standard but in vitro methods can be more discriminative or sensitive simply due to the flat dose-response curve of some drugs. In this regard, the guidelines do not require demonstration of higher sensitivity in the alternative method but similar or higher, not lower. This is essential to accept an alternative method. The text referring to “comparable release characteristics, it has to be demonstrated that they reflect the in vivo situation, considering all parameters that are relevant for transit of the product and the release and the dissolution of the drug in the in vivo situation.” has already been considered in previous comments and it is not considered necessary to be repeated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): add: In order to claim that an alternative model is reflecting in vivo drug release and availability at the site of action, the applicant should discuss the relevance of all parameters of the in vivo situation for the transit of the product and the release and dissolution of the drug and demonstrate that all relevant parameters have been considered adequately in the alternative model.	
148-150	4	Comments: The sensitivity of any alternative model should more accurately be stated as “higher or **equivalent**” rather than “higher or similar” as in the current wording. For example, it is very difficult to replicate and compare the gut micro-environment to an artificial *in vitro* situation. It is also difficult to predict local concentrations that would be seen at the site of action *in situ* to those used *in vitro. In vitro* tests provide useful complimentary/supporting data, but are no substitute for bioequivalence studies. Proposed change (if any): In order to claim that an alternative model is reflecting in vivo drug release and availability at the site of action, the applicant should justify the relevance for the therapeutic effect and the higher or equivalent sensitivity based on their own experimental data or literature data	Not accepted. The sensitivity in this sentence refers to the ability to detect differences. It should not be understood that the in vitro test conditions have to replicate the in vivo conditions and that it is necessary to compare the gut micro-environment to an artificial *in vitro* situation. It does not need to predict *in vitro* the local concentrations that would be seen at the site of action *in situ.* As such, although similar and equivalent can be considered as synonymous, the last might be understood as a formal comparison, which is not intended here.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
151-152	10	Comments: *[…] The sensitivity of the PK endpoints … based on literature data or on a pilot study.* Clarification would be needed about the determination of the sensitivity. Would that type of study (e.g. PK dose proportionality) needed by default unless there is good data from the literature? Proposed change (if any): To define better the additional study/pilot.	Not accepted. Based on the new wording of the guideline "The sensitivity of the PK endpoints/in vitro methods following administration of different doses of the reference product should be well established, e.g. based on literature data or on a pilot study" and later "if absorption is not saturated (demonstrated e.g. by means of a dose-proportionality study)". Therefore, if there is no good literature data an e.g. PK dose proportionality study is needed.
153-156	10	Comments: Could you please define the term “sensitive”? Normally the highest strength is regarded as the most sensitive. Clarification would be helpful. Proposed change (if any): To include a definition of the term “sensitive”.	Not accepted. It is not considered necessary since it is explained in Introduction: "During recent years the assessment of locally applied and locally acting products has evolved. It has been shown that alternative models (including in vitro and in vivo methods) may have a higher sensitivity than traditional clinical and PD endpoints to detect possible differences between medicinal products containing the same active substance". In this context, to show that PD or clinical endpoints are less sensitive it has to be shown a flat dose response curve, i.e., when doubling the dose the repose is not doubled but much less. For example when comparing acarbose product the blood sugar levels are not reduced to a half when administering double dose.
Line 160	2	Proposed change (if any): The approach taken should be fully justified with	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		regard to reflecting all relevant parameters in the in vivo situation in the specific patients.	
162-166	4	Comments: The wording 'the products possess similar critical quality attributes and are qualitatively and quantitatively similar' is too vague and subjective. Proposed change (if any): For instance, the requirements for demonstration of in vivo PK bioequivalence may be waived under a specific set of circumstances when, for example, the test and reference products are a solution, the products possess equivalent critical quality attributes and are qualitatively and quantitatively equivalent, and the method of administration is the same.	Not accepted. The words similar and equivalent are synonymous and the term similar is preferred for in vitro methods (for example dissolution profiles are compared with a similarity factor). In this case, "similar" has been defined with an acceptance range of 10% by default in this guideline. Regarding the comparison of the excipient composition the word similar has been used traditionally in EMA documents like the Guideline on the investigation of bioequivalence
166-170	4	Comments: In order to ensure that public health remains adequately protected, demonstrating bioequivalence, within the usual acceptance criteria, of undesired systemic drug levels shall always be required to ensure the safety of patients in the EU. Please also note that this guideline is about products acting locally in the GI tract. Therefore, how can a PK bioequivalence study looking at the profile of a drug '*mainly absorbed from the site of action*', i.e. systemically distributed, be used to indicate therapeutic equivalence of a locally-GI-acting product?	Not accepted. Equivalence in the safety aspects with the usual acceptance range (non-inferior safety) is already required in this draft guideline. This is similarly defined in the guideline on the investigation of bioequivalence. Therefore, this guideline is not changing any criterion in this field. In certain cases the measurement of systemic exposure is not necessary if it can be assumed that it will be equivalent (e.g. BCS biowaivers), which is a criterion similar to the one existing already in the Guideline on the investigation of bioequivalence. A PK bioequivalence study looking at the plasma profile of a drug '*mainly absorbed from the site of action*', i.e.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): In order to address systemic safety, even if clinical equivalence is demonstrated with a PD approach, data on the extent of absorption is required. This requires a bioequivalence study, where the 90% confidence interval range for the ratio test/reference of the PK parameters of interest shall not exceed the upper limit of the acceptance range as described in the guideline on the investigation of bioequivalence.	systemically distributed, can be used to indicate therapeutic equivalence of a locally-GI-acting product because it gives information on how the drug is released from the dosage form and becomes available at the site of action. The local efficacy and safety depend on the drug availability at the site of action.
Lines 171 - 173	2	Comments: It appears questionable if with locally applied products containing drugs with local action in the gastrointestinal tract PK bioequivalence studies, i.e. studies on the systemic availability of a drug are principally relevant for the demonstration of therapeutic equivalence even if the drugs are absorbed (also, but not exclusively)) from the site of action. This is all the more true if a drug after its absorption is subject to multiple steps of metabolism in sections of the gastrointestinal tract with largely differing metabolic capacities before it appears in the systemic compartment (e.g. for budesonide, Seidegard et al. EurJPharmSci 2008; 35(4):264-270;Seidegard et al. EurJPharmSci 2012; 46(5):530-536). In addition, at least in the case of certain drugs (e.g. 5-aminosalicylic acid), plasma concentrations of drugs acting locally in the GI tract represent only a proportion of the	Not accepted. It is the present state-of-the-art to use partial AUCs to identify the absorption from the different sections of the small intestine, colon or rectum. This is not a new requirement in this field as can be seen at for example: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM426317.pdf and https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384149.pdf. Therefore, it is considered that additional studies, such as imaging, scintigraphic studies or direct quantitative demonstration of the local availability (e.g. by biopsies) are not necessary. Quantitative evaluation of the proportion of systemically available drug / metabolites is considered adequate to allow reliable conclusions on the availability at a specific local site.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		absorbed drug as another proportion of the absorbed drug is re-secreted form the mucosa into the GI-lumen (Goebell et al. Gut 1993;34:669-675; Zhou et al. DrugMetabDisp 1999;27(4):479-485). Therefore, evaluation of quantitative aspects only based on plasma concentrations is clearly not adequate for such kind of drugs. Taken together, without additional studies, such as imaging, scintigraphic studies or direct quantitative demonstration of the local availability (e.g. by biopsies), quantitative evaluation of the proportion of systemically available drug / metabolites is not adequate to allow reliable conclusions on the availability at a specific local site. Proposed change (if any): Delete this sentence.	
174-176, 189-193	6	Line 174 states: “Ideally, the same excipients and amounts used in the reference products should be selected for the test products. Differences in inactive ingredients, whether known or unknown, may require additional comparative tolerability studies.” Line 189 states “excipient composition should be critically reviewed since excipients may affect local residence time … An equivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by	Not accepted. The acceptance level of change depends on each type of product and excipients. It is not possible to give general guidance applicable in all cases.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		reference to other data…" Comment: Discussion around excipient composition and justification is helpful, but further guidance around level of acceptable changes would be useful here e.g. Doc. Ref. CPMP/EWP/4151/00 Rev. 1 where it is clearly laid out what the requirements are in terms of pharmaceutical equivalence Proposed change (if any): Additional clarification around what the requirements are in terms of pharmaceutical equivalence for excipients	
Line 176	3	Comment: Clarification is requested regarding whether "additional comparative tolerability studies" refers to *in-vivo* nonclinical or clinical studies or both.	Not accepted. It is the responsibility of the Applicant to justify the use of non-clinical models. Non-clinical studies are not excluded by default. If clinical tolerability studies are conducted it is not necessary to ask for non-clinical studies.
Lines 177 - 178	2	Comment: It should be indicated that the justification of the applicability of an *in vitro* method should primarily address having taken into consideration all parameters of the *in vivo* situation with relevance for transit of the product and release and dissolution of the drug in the *in vivo* situation. Proposed change (if any): ...if justified with regard to having taken into account all parameters of the *in vivo* situation that are relevant for transit, release and dissolution.	Accepted.
Line 178	3	Comments:	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Products acting locally in the intestine: Excipient composition might also need to be carefully reviewed for compounds targeting colon locally e.g. Crohn's disease. Subjects with Crohn's disease might have a different reaction (sensitivity) to drug excipients compared to that of healthy subjects.	Although line 178 is not related to excipients, this comment has been included in the previous paragraph.
187	4	Comments: In order to ensure that public health remains adequately protected, demonstrating bioequivalence, within the usual acceptance criteria, of undesired systemic drug levels shall always be required to ensure the safety of patients in the EU. Proposed change (if any): If the test product is a solution at time of administration and contains an active substance in the same concentration as an approved solution, studies supporting equivalent efficacy may be waived. In those cases where some degree of drug absorption and systemic bioavailability is observed, a bioequivalence study is required in order to address systemic safety.	Not accepted. Oral solutions with the same or sufficiently similar excipients can be considered to provide the same local availability. Therefore, there is no need to require studies, since waivers have been always applied. This is not a new requirement. Similarly, the systemic exposure would be equivalent. In fact oral solutions can be waived for systemically acting products. It would be inconsistent to require PK BE safety studies in locally acting products.
Line 192	3	Comments: This line refers to amounts of excipients only. It is more appropriate to refer to it is amount and/or nature of excipient if different excipients. Proposed change (if any): …, unless the differences in the amounts ~~of these~~	Partly accepted. The words have been modified to "qualitative and/or quantitative composition" because nature could be misunderstood.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and/or nature of excipients can be adequately justified…	
Line 195	3	Comments: Clarification is requested regarding which type of equivalence studies are required i.e. efficacy, safety or pharmacokinetic.	Accepted**.** When the guideline refers to equivalence studies, they are studies with PD or clinical (efficacy) endpoints. Safety studies are named as tolerability studies. Safety parameters are included as secondary parameters in all efficacy studies. PK studies are named as bioequivalence. In vitro studies are also equivalence studies, but the term in vitro has always been added. The term bioequivalence has been reserved for PK studies only. The term therapeutic has been added for clarification.
197-205	6	Line 201 states “with sampling of saliva is a possible approach despite its inherent variability…”. Comments: The bioequivalence guideline allows for widening of confidence intervals for cmax for known variable actives. This should be acceptable in instances where the intra-subject variability of saliva concentration exceeds 30% in line with the bioequivalence guideline. If the API and excipients are known ingredients with historical evidence on safety, then such products should be applicable for a safety study waiver if the upper limit of 90% CI is not within 120%, and accordingly should be applicable for an efficacy waiver if the lower limit of 90% CI is below 80%.	Not accepted. It is not necessary to give this information because cross-reference to the guideline on the investigation is already included in the guideline, therefore, it can be easily deduced.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Reference to the acceptability of potentially widening the CI for cmax, if saliva concentration intra-subject variability exceeds 30%, should be included. Reference to the conditions required to be met for a safety or efficacy study waiver should also be included within this section.	
206-213	6	Line 207 states “it is possible to assess indirectly the local availability or the amount released by assessing the amount remaining in the dosage form at selected time points..”. As discussed in the general comments, with reference to EMA/CHMP/QWP/558185/2014 (concept paper on topical products) line 67:“*Method limitations may be addressed by employing a battery of different techniques, but, in any case, this needs to be fully explored and understood to avoid inappropriate use and claims*”. We believe there should be a requirement to address method limitations through employing multiple different techniques to demonstrate local equivalence. The method described above, which is essentially in vivo dissolution, and does not take into account factors such as local absorption rates, impact of excipients on absorption, retention at the mucosal membrane etc. This method should therefore not be used in isolation	Not accepted. It is not agreed to require by default additional studies if the applicant / sponsor justifies: - The drug is not absorbed systemically. - Excipients do not affect absorption. or alternatively it can be assumed that if the drug is released from the dosage form at the same rate and excipients do not affect absorption, both test and reference will be absorbed systemically and retained in the membrane in the same way since these steps will depend on the drug and not on the dosage form. On the contrary, if the excipients are different additional studies are required for demonstration of equivalent efficacy and safety.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		as a demonstration of equivalence In addition, if the applicant is limiting solely to generation of local data (by a surrogate study such as this) the application should have to provide evidence of the fact that the active only acts locally. As discussed in the general comments, the study itself should also be conducted according to GCP. Proposed change (if any): “it is possible to assess indirectly the local availability or the amount released by assessing the amount remaining in the dosage form at selected time points... ***However, this method is not sufficient in isolation as a demonstration of equivalence. Additional data taking into account other relevant factors such as local absorption rates, impact of excipients on absorption, retention at the mucosal membrane, should also be provided within any application***”.	
Line 226, 206-213	3	Comments: Clarification is requested regarding the meaning of ‘for the time being’, and how this relates to Lines 206-213, where clearly “currently used” methodologies are applied for dissolution profile similarity.	Accepted**.** Line 226 refers to in vitro methodology. Lines 206-213 refer to in vivo dissolution methodology. The text “in an in vivo study” has been added for clarification.
228	4	Comments: In order to ensure that public health remains	Not accepted. See comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		adequately protected, demonstrating bioequivalence, within the usual acceptance criteria, of undesired systemic drug levels shall always be required to ensure the safety of patients in the EU. Proposed change (if any): In those cases where some degree of drug absorption and systemic bioavailability is observed, a bioequivalence study is required in order to address systemic safety.	
Lines 229 – 239	2	Comments: For non-solutions products that are not measurable at the site of action (!) and without measurable systemic levels (!), clinical or PD equivalence studies are indicated to be required. As this affects primarily efficacy, it should be non-inferiority studies, in place of equivalence studies. Proposed change: Replace ‘equivalence’ by ‘non-inferiority’	Not accepted. This guideline is an addendum to an existing guideline. The requirement of equivalence studies was defined in that guideline.
230	4	Comments: There is no section addressing products acting locally in the oesophagus. This omission should be addressed.	Accepted. The oesophagus has been included in the section about the stomach.
Line 231	2	Comments: Add a complete section of products acting locally in the oesophagus, with subsections according to the section for products acting locally in the stomach.	Partly accepted. The oesophagus has been included in the section about the stomach.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 247-248	1	Comments: "…some degree of drug absorption and systemic bioavailability…". Does this sentence refer to the difference between absorbable and non-absorbable antacids?	Not accepted. That sentence is in a different paragraph and it refers not only to antacids.
247-248	4	Comments: The principle that 'in those cases where some degree of drug absorption and systemic bioavailability is observed, a bioequivalence study is required in order to address systemic safety' should not be unique to non-solutions acting locally in the stomach. It should be a general principle for all sites of action and all pharmaceutical forms throughout the GI tract.	Partly accepted. The need of PK safety data is already mentioned in section 4.2: "even if clinical equivalence is demonstrated with a PD approach, data on the extent of absorption may be required, or their lack should be justified. If this requires a bioequivalence study, then the 90% confidence interval range for the ratio test/reference of the PK parameters of interest should not exceed the upper limit of the acceptance range as described in the guideline on the investigation of bioequivalence." For solutions, a biowaiver could be possible. If not equivalence studies are required. These studies would address the safety profile. For products acting in the mouth or throat the in vitro methods that are used to waive efficacy studies are considered enough to waive safety studies. If drug levels are similar at the site of action in the mouth and throat there is no reason to believe that absorption and systemic exposure can be significantly different. However, if absorption in the mouth is assessed with PK studies the decision tree indicates that studies without charcoal blockade are needed for safety. The same has been now clarified in the text. For products acting in the intestine, PK efficacy studies are

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			also PK safety studies and there is no need to conduct separate studies. For products acting in the rectum the same requirement has been included.
249	4	Comments: A BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. This is presumably restricted to Class III drug substances as these have limited absorption. Perhaps the guideline should be more explicit in this area?	Not accepted. Class I drugs could be used for local action in the mouth, throat, oesophagus, stomach and proximal sections of the GI tract. The text of the guideline should not be restricted.
Lines 257 – 258 Lines 257 - 258	2	Comments: For non-solutions, without a valid in vitro tests, equivalence studies are indicated to be required. As this affects primarily efficacy, it should be non-inferiority studies, in place of equivalence studies. Proposed change (if any): Replace ‘equivalence’ by ‘non-inferiority’	Not accepted. This guideline is an addendum to an existing guideline. The requirement of equivalence studies was defined in that guideline.
Lines 261-263	3	Comments: The document should include consideration of both the type and the amount of the excipient that may affect GI transit. For example, based upon the dose administered, the excipient sorbitol may have a minimal or significant effect on GI transit. Proposed change (if any): ‘In addition, particular consideration should be given to	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the amount and type of excipients that may affect GI transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), in vivo solubility (e.g. co-solvents) or stability of the active substance.'	
Lines 264-265 & 313	3	Comments: Decision tree line 313 is not fully aligned with the text for the "Solutions". Lines 264-265 refer to bioequivalence studies if some degree of systemic bioavailability is observed. See also comment for Lines 261-263. Proposed change (if any): Specify in the box "Are **amount and/or type of** excipients similar **and no systemic bioavailability observed?"**	Not accepted. The space in the decision tree is limited and it is not possible to include too much text.
264-265	4	Comments: In order to ensure that public health remains adequately protected, demonstrating bioequivalence, within the usual acceptance criteria, of undesired systemic drug levels shall always be required to ensure the safety of patients in the EU. Proposed change (if any): Bioequivalence studies based on systemic exposure shall be employed to compare test and reference products if some degree of systemic bioavailability is observed in order to address systemic safety.	Partly accepted. The text has been modified to express that "Bioequivalence studies based on systemic exposure might be employed to compare the efficacy and safety of test and reference products if some degree of systemic bioavailability is observed" for solutions. For non-solutions it is already mentioned "If the conditions to apply for a BCS biowaiver are not fulfilled and some degree of systemic bioavailability is observed, bioequivalence studies based on plasma levels usually in fed and fasting state could be used as a surrogate of equivalence in efficacy and systemic safety".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 266-271	3	Comments: These (*in vitro*) models must be validated with regards to the clinical conditions. Proposed change (if any): … dissolution profiles in the physiological pH range are similar. **These models must be validated such that they are discriminative under clinical conditions.**	Not accepted. That requirement has already been defined in the previous sections of the guideline (see section 4.2).
Lines 269 to 271	3	Comments: *In-vitro* studies based on their binding capacity are considered acceptable surrogates for the assessment of efficacy, as long as excipients are not critical and disintegration and dissolution profiles in the physiological range are similar. Clarification is requested as to which are the criteria to define the excipients as being not critical or similar. Also, if the excipients are critical, the acceptable amount of these should be clarified. It is requested that these be included in the document with references. Furthermore, some of the compounds may not be dissolved, dissolution test may not need to apply. Proposed change (if any): "... as long as excipients **do not have significant negative impact on *in-vitro* equilibrium and**	Not accepted. The guideline is a general guideline that applies to multiple types of products and excipients. It is not possible to give guidance or limits for every single excipient and product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		dynamic binding (not critical) and disintegration and **/ or** dissolution profiles in the physiological range are similar.	
271	8	Comments: sevelamer does not dissolve Proposed change (if any): and disintegration and dissolution profiles in the physiological pH range (as appropriate) are similar.	Accepted.
Lines 277-278	3	Comments: It would be helpful to include limits of “very rapid dissolution” and “rapid dissolution”.	Not accepted. This is already defined in the guideline on the investigation of bioequivalence, which is cross-referenced in this guideline.
Line 279-280	5	Comments: In Section ‘4.3.3 Products acting locally in the intestine’ it is stated that: *“if conditions to apply for a BCS biowaiver are not fulfilled and some degree of systemic bioavailability is observed, bioequivalence studies based on plasma levels usually in fed and fasting state could be used as a surrogate of equivalence in efficacy and systemic safety*” Ferring recommends to define a limit of e.g. 5% to clarify meaning of ‘some degree’ of bioavailability Proposed change (if any): *“if conditions to apply for a BCS biowaiver are not*	Not accepted. There are systemically acting products whose bioavailability is less that 5% and PK BE studies are feasible. As long as absorption is not saturated the PK BE studies can be conducted and reflect the release from the dosage form and the availability in the GI tract.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		fulfilled and some degree of systemic bioavailability is observed (above 5%), bioequivalence studies based on plasma levels usually in fed and fasting state could be used as a surrogate of equivalence in efficacy and systemic safety"	
280-282	4	Comments: It should be clarified that 'bioequivalence studies based on plasma levels usually in fed and fasting state' refers to studies in humans. Proposed change (if any): If the conditions to apply for a BCS biowaiver are not fulfilled and some degree of systemic bioavailability is observed, bioequivalence studies in humans based on plasma levels usually in fed and fasting state could be used as a surrogate of equivalence in efficacy and systemic safety because the site of action is the site of absorption for drugs acting inside the gastrointestinal membrane.	Partly accepted. It has been included in section 4.2 that is a general section and therefore, it will apply to all sections.
Lines 281-282	2	Comment: The site of absorption is not necessarily the site of therapeutically relevant action as also healthy mucosal / epithelial sections may absorb the drug and the proportions of drug absorbed at healthy sites contribute to plasma levels without being relevant for therapeutic effects. E. g., considerable proportions of mesalazine are released by many preparations already in GI-sections proximal to the colon and are absorbed very efficiently in the small intestine. As	Not accepted. The Lines 281-282 refers to immediate release products and the example of mesalazine refers to modified release products. The sites of absorption and the site of action can be different in patients but they are located closely. The absorption in healthy subjects will occur always in healthy mucosal / epithelial sections to give comparative information on the in vivo release and the time and site of local availability. If the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		transit is highly variable and there are large differences with respect to permeability in different intestinal sections (i.e. in the small intestine and in the colon) a close correlation between local availability and plasma levels cannot be generally assumed, and the same is true for the correlation of plasma levels and efficacy (Christensen et al. AlimentPharmacolTher 1990;4(5):523-533). Proposed change (if any): …could be used as a surrogate of systemic safety, but as a surrogate of efficacy only if the site of action is identical to the site of absorption for drugs acting inside the gastrointestinal membrane.	time and site of local availability is equivalent for test and reference products they can be assumed to be therapeutically equivalent. It is agreed that PK bioequivalence studies are not able to give information on the local availability in absolute terms, but as the problem is comparative, it is not necessary to know the absolute values of local availability.
285-287	4	Comments: The following change is proposed in order to duly take into consideration those cases where the drug site of action differs from the site of absorption. Proposed change (if any): It can be assumed that when the rate and extent of absorption of the drug is comparable, distribution of drug within the different zones of the intestine is comparable. Only if the site of absorption corresponds to the drug site of action (i.e small intestine), plasma levels can be considered a surrogate marker of equivalence in efficacy and systemic safety. In case the drug site of action differs from the site of	Not accepted. It is already been explained in the guideline that when the site of action (mouth or stomach) is different to the site of absorption (intestine) the PK BE studies are not surrogate for efficacy. In the case of the intestine the partial AUCs can be used to identify the sections of AUC that corresponds t the site of action, if necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		absorption, a bioequivalence study (both in fed and fasted state) could be not adequate based on plasma levels as a surrogate of equivalence in efficacy and systemic safety.	
289	9	Comments: The term permeability in this context is wrong. Proposed change (if any): Replace by **permeation**	Not accepted. In the context of intestinal absorption the term permeability is considered correct based on the BCS.
290	4	Comments: In order to ensure that public health remains adequately protected, demonstrating bioequivalence, within the usual acceptance criteria, of undesired systemic drug levels shall always be required to ensure the safety of patients in the EU. Furthermore, specific requirements are proposed in cases where the locally acting drug is intended for use in a GI condition where the intestinal permeability could be altered with an impact on systemic exposure parameters. Proposed change (if any): In those cases where some degree of drug absorption and systemic bioavailability is observed, a bioequivalence study is required in order to address systemic safety. In case the locally acting drug is intended for use in a gastrointestinal disease in which intestinal permeability could be altered with an impact on systemic exposure parameters (i.e. increase in Cmax and AUC), a bioequivalence study in healthy	Not accepted. The requirement of PK BE studies for safety is already included in the guideline. Regarding the need of studies in patients, the use of healthy volunteers is considered enough to assess how the products release the drug in vivo. The increased or decreased permeability in disease state will affect the absolute values of the rate of absorption, but as the issue at stake is the comparison between test and reference in relative terms, the use of healthy volunteers is considered acceptable.

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		subjects only may not be considered sufficient and a study in patient population should be performed.	
291 and following section	9	Absorption kinetics may be different in damaged mucosa and normal mucosa (e.g. due to mucosal retention of the active substance). The draft does not address in this section if PK in patients are needed or healthy subjects are sufficient. Proposed change (if any): Clear guidance	Not accepted. The guideline on the investigation of bioequivalence is cross-referred in this guideline. Therefore, the same requirements apply. In principle, studies in healthy volunteers are acceptable because the question at stake is a comparison between test and reference in relative terms to assess how the product is released and becomes available at the site of action. It is not essential to know the absolute values of the amount absorbed of both products. Whatever it is, it can be assumed that it will be equivalent.
Lines 291-293	2	Comments: The site of absorption is not necessarily the site of therapeutically relevant action as also healthy mucosal / epithelial sections may absorb the drug and the proportions of drug absorbed at healthy sites contribute to plasma levels without being relevant for therapeutic effects. E. g., considerable proportions of mesalazine are released by many preparations already in GI-sections proximal to the colon and are absorbed very efficiently in the small intestine. As transit is highly variable and there are large differences with respect to permeability in different intestinal sections (i.e. in the small intestine and in the colon) a close correlation between local availability and plasma levels cannot be generally assumed, and the same is true for the correlation of plasma levels and	Not accepted. See previous comment.

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		efficacy (Christensen et al. AlimentPharmacolTher 1990;4(5):523-533).	
Lines 291-305	3	Comments: Clarification is requested regarding whether the definition of “modified Release” products in this section also includes “enteric coated” drug products and, if so, whether the same conditions apply.	Not accepted. The definition of “modified release” is made in the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). In addition, and since in the present document there are only two sections - immediate release and modified release- delayed release has to be included in the modified release group.
293	9	Proposed change (if any): delete “because the systemic absorption occurs at the site of release.” Replace by: “**if the systemic absorption starts at the same site and has the same absorption kinetics**.” Rationale: Some modified release products have both a pH trigger and sustained release properties. The proposed change reflects this.	Partly accepted. It is agreed that some modified release products are gastro-resistant to have a pH trigger to start release and later they are prolonged release. However, the present sentence is also correct because systemic absorption occurs at the sites of release, as soon as it starts to be released by the pH trigger and during the whole period of the prolonged release. Therefore, the proposed text is added into the exiting one.
Lines 293 - 311	2	Comments: Generally, PK evaluation of partial AUCs should be mandatory for pharmaceutical substances acting locally in the distal small and/or large intestine with a well-justified definition of the segments for which partial AUCs are assessed. Definition of the intestinal segments should be based on individual scintigraphic findings to allow appropriate assignment of partial AUCs to the respective GI segments.	Not accepted. It is agreed that scintigraphic studies can be useful to identify the cut-off points of partial AUCs, but it is not the only methodology and, therefore, it is not necessary to include in the guideline the requirement of scintigraphic studies as mandatory. It is the responsibility of the applicant / sponsor to justify the selected cut-off points.
293-294	9	Comments:	Not accepted.

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		Partial AUC assessment is the most sensitive tool to show *in vivo* performance of formulations. It allows for the evaluation of pharmacokinetic similarity in terms of drug amount absorbed at the desired site of action and thus should be highlighted in the text. Proposed change (if any): Change: "Partial AUC assessment can help to distinguish…" to "Partial AUC **is currently the most sensitive pharmacokinetic read-out parameter and therefore assessment is critical to** distinguish absorption caused by…" Rationale: Clarification and clearer guidance.	The comment is agreed but it is not necessary to highlight that partial AUC is the most sensitive parameter. The guideline is sufficiently clear in this respect: " Partial AUCs (early and late partial AUCs as defined by predefined, well justified cut-off points) should be used as primary PK endpoint in both types of single dose studies, even in case of significant accumulation when a multiple dose study is required."
Lines 299-301	3	Comments: With an increasing number of tests, there is also an increasing risk of falsely identifying inequivalences. As such, it is proposed that the "battery of state-of-the-art experiments" be restricted to those methods with demonstrated *in vivo* relevance rather than all methods. Proposed change (if any): test and reference exhibit similar *in vitro* dissolution profiles in ~~a battery of state-of-the-art~~ experiments **using methods with demonstrated in vivo relevance** (not only in the QC media and buffers at pH 1.2, 4.5 and 6.8, but also *in*	Not accepted. It is agreed that the larger number of tests, the larger probability of a false negative outcome but, as this is a matter of randomness, the sample sizes of in vitro tests can be increased as much as necessary to avoid the false random outcomes. In addition, in most cases in vivo predictive dissolution test have not been identified (due to absence of an IVIVC). The Applicant / sponsor can always justify that there is no need to use several in vitro tests if one of them has been shown to be predictive of the in vivo behaviour based on an IVIVC. This text of the guideline refers to the other cases where no in vitro dissolution test has been shown to be predictive. In

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		vitro methods simulating intraluminal pH-conditions and residence times in the human GI tract, etc.	those cases several in vitro dissolution methods are necessary to show that no difference can be detected in the in vitro behaviour. The Applicant / sponsor has to justify the number of in vitro conditions tested. Obviously the conditions / methods selected by the sponsor should be those with more in vivo relevance.
Lines 299 - 304	2	Comments: Not only the pH conditions, but also a multitude of additional parameters with in vivo relevance for transit, release, dissolution and absorption should be reflected in an in vitro model (Ibekwe et al. PharmRes. 2008;25(8): 1828-1835; Garbacz & Klein 2102 JPP 2012;64: 944-968). Falk welcomes the notion that QC media and buffers are not considered to be sufficient and more discriminating methods such as the reciprocating cylinder apparatus are given as one example of systems that are able to better reflect the in vivo conditions. In addition, it should be specified to use biorelevant media. Given the relevance of ionic strengths and buffer capacity on the release characteristics observed with different media, e.g. phosphate buffers and bicarbonate-buffers, also the choice of buffers should be justified (Fadda et al. IntJPharmaceutics 20009; 382:56-60; Garbacz et al. EurJPharmSci 2014a; 51:224-231). Moreover, it was clearly shown - at least for monolithic	Partly accepted. The text has been revised.

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		formulations - that mechanical forces are also of relevance for drug release and so, also the mechanic stability of a product should be taken into account (Koziolek et al. JPharmSci 2014; 57:250-256; Garbacz et al. EurJPharmSci 2014; 57:264-272; Garbacz et al. JPharmPharmac 2014; 67:199-208). Proposed change (if any): (lines 301-302) …e.g. tests with biorelevant media in bicarbonate buffers and adequate ionic strength in the reciprocating cylinder apparatus… Add: The mechanic stability of the product should be demonstrated adequately.	
299	9	Comments: The term “similar” is vague and wide open to interpretation for the applicant and the reviewer. Some clarification is desirable.	Not accepted. In this specific case it refers to dissolution profiles, which are compared according to the f2 similarity factor. Therefore, if the f2 similarity factor is >50 the profiles are similar.
301	9	Comments: For *in vitro* dissolution tests to be meaningful they need to simulate *in vivo* conditions. A consideration of gastro-intestinal (GI) physiology reminds us that luminal fluids are buffered by bicarbonate, furthermore phosphate levels are very low (Basit 2005). The most commonly used dissolution media are those which include phosphate species (Merchant 2014). In a study by Andreas et al., (2015) investigating biorelevant dissolution methods, the	Accepted.

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		authors concluded that the use of dissolution tests with sequential exposure to biorelevant dissolution media were able to forecast differences between formulations and to reflect the trends observed in *in vivo* studies for food effects. The importance of ionic composition when determining drug release profiles (buffer salts and their concentration) was also highlighted in a study by Fadda and Basit, 2005. During GI transit, solid dosage forms are also exposed to mechanical pressure caused by GI motility events. Tablets and capsules >8 mm need an empty stomach to pass the pylorus. In a normal daily eating cycle they can be retained in the stomach for 24 hours. Bortolotti (2000) has reported antral pressure up to 96 mm Hg. Trials have demonstrated that dissolution testing is heavily influenced by mechanical pressure (Garbacz 2015). Bacterial enzymes and available liquid in the colon can be a further factor influencing *in vivo* release. As a result of the aforementioned, the following change is proposed. Proposed change (if any): Change: “but also *in vitro* methods simulating intraluminal pH-conditions and residence times in the human GI tract,” to: “but also *in vitro* methods simulating intraluminal pH-conditions, **ionic buffer strength, biorelevant buffer composition, mechanical stress** and	

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		residence times in the human GI tract," Rationale: Equivalence under these conditions is more predictive for *in vivo* and ensures quality beyond composition and testing the mono-factorial influence of the pH gradient.	
Lines 306-309	2	Comments: Falk supports the requirement of PK/bioequivalence studies in fasting and fed state. However, in addition to single dose studies, multiple dose studies should be performed in any case to demonstrate or to rule out systemic accumulation of a drug released by a new preparation. In addition, PK studies should be performed with patients in each claimed indication to be as close as possible to the therapeutic situation, as also the conditions in section of the gastrointestinal tract which appear primarily unaffected may not correspond to that of controls (Rao and Read ScandJGastroenterol 1990; 25(suppl 172):22-28; Hebden et al. APT 2000 ;14(2):155-161). Proposed change (if any): (lines 307-309) Pharmacokinetic bioequivalence should be demonstrated in single and multiple dose studies in fasting and in fed state in patients for each claimed indication.	Not accepted. The need of multiple dose studies is defined in the existing guidelines. It is not necessary for immediate release products or delayed release products. In the case of prolonged release products it would depend on the existence of accumulation or not. The need of patients is not agreed because the PK bioequivalence studies are intended to compare the in vivo release and local availability of the product and this behaviour can be compared in healthy volunteers. Only in very specific cases where the release depends on the gastrointestinal conditions that occur only in patients the use of patients would be necessary. As explained above it is not a measurement of plasma concentrations in absolute terms in the patient population, but a comparative exercise on the in vivo product release and local availability.
307-308	9	Comments: Single dose studies can be the administration of single	Not accepted. The strength to be tested is discussed in section 4.4.

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		or multiple units. The most discriminative is multiple units and therefore we propose the following change. Proposed change (if any): Change: “Bioequivalence should be demonstrated in single dose studies in fasting and fed state” to: “Bioequivalence **of the highest labelled dosage strength** should be administered in single dose studies in fasting and fed state” Rationale: Equivalence under these conditions is more discriminative and adequately reflects the clinical treatment situation.	Section 4.4 explains that bioequivalence should be shown with the most sensitive strength to detect possible differences. The same rules as for systemically acting drugs apply since the guideline indicates: " Additional strengths may be waived from this *in vivo* demonstration ("additional strength biowaiver") if certain conditions are met as described in the ‘Guideline on the investigation of bioequivalence’". The highest strength is usually employed according to the above mentioned guideline and the guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms. This reference has been included for clarification in section 4.4.
Line 305; lines 309 - 311	2	Comments: In general, use of partial AUCs is considered a valuable approach to match systemic drug concentrations to drug absorption form specific gastrointestinal sections. However, in the present draft guideline, no guidance is given how to separate partial AUCs. The separation of partial AUCs should be based on findings from studies to justify the cut-off points, e.g. imaging or scintigraphy studies. Moreover, similarity of tl_{ag} and t_{max} values, overall local and systemic exposition by measuring concentrations and amounts in urine and faeces are considered very important to conclude on local availability. Proposed changed (if any): Appropriate rules or	Partly accepted. It is the responsibility of the applicant / sponsor to justify the cut-off points of the applied product. It is not possible either to pre-define in the guideline the cut-off points (because they are product-specific) or to define a single methodology like scintigraphic studies. Certainly, for certain products similarity in tmax and tlag is important as already mentioned in the existing guidelines and it is not necessary to repeat the same in this guideline because cross-reference to these other guidelines is already included. Measurement in urine is not considered necessary if plasma concentrations are measured. However, It is agreed that concentrations in faeces may be useful in certain cases and the paragraph: “Comparison of drug levels in faeces may be

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		methods to allow the adequate separation of partial AUCs need to be defined considering all relevant parameters on the chronological course of systemic concentrations.	necessary in certain cases." was added in the text.
312	4	Comments: In order to ensure that public health remains adequately protected, demonstrating bioequivalence, within the usual acceptance criteria, of undesired systemic drug levels shall always be required to ensure the safety of patients in the EU. Proposed change (if any): In those cases where some degree of drug absorption and systemic bioavailability is observed, a bioequivalence study is required in order to address systemic safety.	Not accepted. See response in previous comments.
Line 313	5	Comments: Section 4.3.3 Decision tree for products acting locally in the gut Figure appears to be suboptimal. If you have a solution, first point is: 'Are excipients similar?' If answer is ´no' next question is: 'Is there a valid in vitro test?' If answer is yes, reader is once again faced with the question: 'Are excipients similar?' Proposed change (if any): Update figure	Accepted.
313	9	Comments: Transit of the dosage form through the GI tract and to	Accepted.

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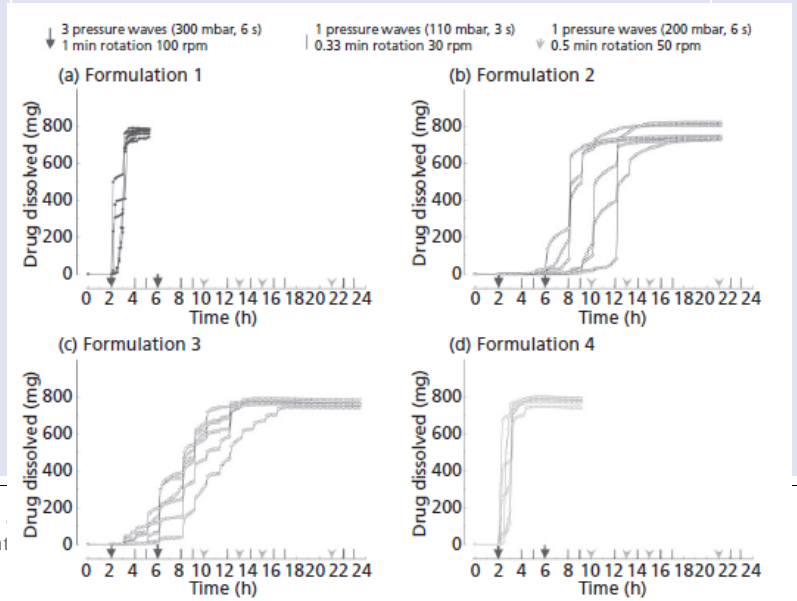
		the area of inflammation is a complex and highly variable process. Gender differences in transit time, metabolic capacity and gut flora are well-described. As demonstrated in the publication by Garbacz 2015, mechanical stress simulated *in vitro* results in highly variable dissolution profiles of modified release formulations (see Figure 1 below). Release kinetics of modified release formulations cannot be comprehensively assessed *in vitro.* Therefore, it is essential to assess similarity / potential differences between formulations through bioequivalence studies. **Figure 1** Dissolution profiles of mesalazine 800 mg modified release tablets in the stress test apparatus, 37.5°C and 1160 ml fill volume. Given are individual profiles, formulation numbers as well as the timing and fortitude of the stress phases are indicated by labelling (Garbacz 2015)  	

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		Proposed change (if any): For the "Decision tree for products acting locally in the intestine", the following is proposed – see **graph on separate page**): Rationale: As excipients are just one component of product quality (others are quantities of excipients and the manufacturing process) *in vitro* tests only are not sufficient to ensure similar to equal *in vivo* performance. Furthermore, the definition of similarity of excipients is virtually impossible given the many factors influencing *in vivo* release. Additional comment: The arrow from ***SOLUTION-ARE EXCIPIENTS SIMILAR –NO*** should -for clarity- go directly to ***MEASURABLE SYSTEMIC LEVELS.***	
315	4	Comment: The intestine and the rectum are not mutually exclusive, the rectum is part of the intestine. Please ensure there is no conflicting guidance in the Section 4.3.3 as far as it concerns products being developed for use in the rectum, or for use in the rectum + rest of the intestine (or large intestine).	Accepted.
337	4	Comments: In order to ensure that public health remains adequately protected, demonstrating bioequivalence, within the usual acceptance criteria, of undesired systemic drug levels shall always be required to ensure	Not accepted. The guideline already indicates in this section that "In those cases where systemic bioavailability is observed, a PK bioequivalence study is required in order to address systemic safety."

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		the safety of patients in the EU. Proposed change (if any): In those cases where some degree of drug absorption and systemic bioavailability is observed, a bioequivalence study is required in order to address systemic safety.	
347-349	4	Comments: It should be clarified that 'bioequivalence PK studies' and '*in vivo* PK data' refer to human PK. Proposed change (if any): In those cases where the reference product has different strengths and equivalence is shown by means of *in vivo* studies (e.g. human bioequivalence PK studies, i.e. pharmaceutical quality data + *in vivo* PK data), bioequivalence should be shown with the most sensitive strength to detect possible differences.	Accepted.