17 October 2019
EMA/CHMP/267430/2019
Pharmacokinetics Working Party (PKWP)

Overview of comments received on 'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms' (EMA/CHMP/EWP/280/96 Rev1)

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

Stakeholder no.	Name of organisation or individual
1	European Generic medicines Association (EGA)
2	Jean-Michel CARDOT Laboratoire de Biopharmacie et de Technologie Pharmaceutique
3	CIPLA LTD. India
4	Corporate Product Development Unit Ferrer Health Tech
5	Medicines Evaluation Board, The Netherlands
6	Mr. Prasanna Gudi, QA Manager, RAPTIM RESEARCH, Mumbai, India
7	Mundipharma Research Ltd and Mundipharma Research GmbH
8	European College of Neuropsychopharmacology (ECNP)
9	Bristol-Myers Squibb
10	UCB BioSciences GmbH
11	SciencePharma (Poland)
12	Swissmedic
13	Bayer HealthCare
14	InVentiv Health Clinical
15	Association of Clinical Research Professionals (ACRP)
16	Merck Sharp & Dohme (MSD)
17	Novartis Pharma AG
18	Helmut Schütz, BEBAC – Consultancy Services for Bioequivalence and Bioavailability Studies, Vienna, Austria
19	Pharmascience Inc., 6111 Royalmount Ave, suite 100, Montreal, Quebec, Canada, H4P 2T4
20	AESGP
21	Synthon BV, The Netherlands

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Stakeholder no.	Name of organisation or individual
22	EFPIA – Pär Tellner
23	Francis Micheal, Dr Mohanlal Sayana, Agila Specialities Private Limited, Bangalore
24	EUFEP Network Biopharmaceutics & Bioavailability (Chair: Prof. Dr. Henning Blume)
25	Pharmaceutical Research Institute (Instytut Farmaceutyczny), Warsaw, Poland Piotr Rudzki, Ph.D., Head of Pharmacology Department

1. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
12	22	Comment: Keywords highlight the transdermal route but the other routes covered in lines 83-84 are not explicitly indicated. Proposed change: please add "oral, intramuscular and subcutaneous" as keyword to be considered.
71	22	Comment: The sentence suggests that the guideline only applies to transdermal drug delivery. Proposed change: Please also mention modified drug release following oral, intramuscular and subcutaneous administration.
80-82	15	Comment: This definition does not fit for Transdermal Delivery Systems, as there are no immediate release dermal dosage forms.
85-87	25	Comment: unnecessary information may be deleted to facilitate reading. Proposed change: Prolonged release dosage forms: Prolonged release dosage forms are modified release dosage forms showing a slower release than that of an immediate release dosage form administered by the same route.
86	22	Comment: A slower release may refer to a product with a lag phase in release, rather than a drug product with sustained release. Proposed change: Please replace "slower" by "sustained" or "longer".
88-90	25	Comment: unnecessary information may be deleted to facilitate reading Proposed change: Delayed release dosage form: The release of the active substance from such modified release dosage a forms is delayed for a certain period after administration or application of the dosage. The subsequent release is similar to that of an immediate release dosage form.
92-93	1	Comment: A biphasic release could also be a combination of immediate release (IR) or delayed release (DR) and extended release (ER).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change: **"Biphasic Release:** The first phase of drug release is determined by the immediate **or delayed** release dose fraction providing a therapeutic drug level shortly after administration. The second extended release phase provides the dose fraction required to maintain an effective therapeutic level for a prolonged period."
92-95	7	Comment: We would propose a sight modification to the wording surrounding the definition of 'biphasic'. Unless there is a clear lag-time associated with the onset of release/absorption from the second phase, there will always be some component of the second phase contributing to the plasma profile. i.e. the first phase is not necessarily delivered in isolation. Proposed change: The first phase of drug release is determined by an immediate release (or faster release in relation to the second phase) dose fraction which helps to provide a therapeutic level shortly after administration.
108-111	25	Comment: introduction of bullet point is proposed to facilitate readability Proposed change: There are two main types of transdermal patch systems depending on how the drug substance is dispersed in other patch components: • matrix systems with drug release based on the diffusion of soluted drug substance reservoir systems contain a specific liquid drug compartment with release controlled by a membrane.
110-111	15	Comment: In reservoir systems, drug release is based on diffusion, as well.
113 - 114	16	Comment: The guideline should clearly describe what EMA understands by "a well-defined clinical need" and what level of justification would be needed to show clinical need. When EMA handles different criteria for a modified release (MR) formulation of a new chemical entity or for a MR formulation of a previously marketed immediate release compound, the guideline should state those criteria.
113-114	25	Comment: One of the most important benefits of modified release drug products is an increased patient compliance Proposed change: The development of a modified release formulation has to be based on improvement of patient compliance, a well-defined clinical need and on an integration of physiological, pharmacodynamic and pharmacokinetic

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		considerations.
119	22	Comment: "The choice of active substance contents per unit of the dosage form"; The meaning of the word "unit" is unclear. Does it mean strength, tablet, or something else? Request that an example of a "unit" be given.
125	22	Comment: We would appreciate if clarification that the proposed bullets are only a non-exclusive list of examples is provided in the revised guideline. Proposed change: Please consider adding the word "for example" prior to the bulleted list.
129	22	Comment: "non-oral route of administration (IM/SC and TDDS)"; This is inconsistent with the prior definition given on line 81. Should the prolonged release dosage form be administered by the same route?
134-135	5	Comment: The sentence 'Delayed release… rapid onset of action' seems obvious. Proposed change: It is proposed to omit this sentence.
134-135	22	Comment: Recommend removing the word "generally," as delayed release forms are not adequate for conditions requiring a rapid onset of action. Proposed change: "Delayed release forms are generally not adequate for conditions requiring a rapid onset of action."
141-142	13	Comment: The meaning of 'in conjunction with' is unclear as modified and immediate release formulations are used separately and independently of each other
141-149	22	Comment: The section on the use of the modified release formulation in conjunction with an immediate release formulation is not easy to understand. The bulleted conditions all refer to the use of the immediate release formulation so we would recommend rewording the section as indicated below. Proposed change: "The use of an immediate release formulation in conjunction with administration of a modified release formulation, where appropriate, should be clearly outlined in the following situations".
148	15	Comment: Could you please clarify that these populations are only to be investigated if applicable, e.g. if there is no paediatric waiver.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
155-156	22	Proposed change: Recommend additional wording for clarity. "This guideline is to define the studies necessary to investigate characteristics of modified release (MR) drug delivery systems in humans and to set out…"
162	15	Comment: Please explain abbreviation "MR".
162-168	20	Comment: This paragraph should be placed in the introduction (rather than in the scope) as it explains the general structure of the guideline.
165-166	1	Proposed change: "Application for a modified release formulation of a drug that is authorised as an immediate release formulation **or in the case of an application for an extended release formulation of a drug that is authorised as a different extended release product."**
165-166	13	Comment: It is assumed that this category refers to MR formulations of a drug that is authorised as an IR formulation for the same route of administration. This should be clarified. Furthermore, MR formulations of a drug that is authorised for another route of administration might be considered to be addressed in the guideline as well.
168	13	Comment: While for regulatory experts it might be very clear what is meant with "application according to Article 10(1) or 10(3)", this might not be so clear for other readers. It would be beneficial to provide the full reference or some key word explanation of these application procedures.
173-191	5	Comment: The Guideline on bioanalytical method validation may be added to the list.
202, and 208	6	Comment: For better clarity in understanding. Proposed change: If a new chemical entity is developed to be administered as a modified release dosage formulation for the first time formulation for the first time.
215 - 216	16	Comment: Drug substance characteristics (class of drug/metabolism) are more important factors for causing drug-drug interactions (DDI) than the formulation itself, although it is a necessary need to have an understanding of the impact of formulation release. Often DDI studies are conducted in the early phases of drug development (and as such potentially

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		with an IR formulation) as is also encouraged by regulatory agencies. MSD proposes that the guideline is less stringent on this point and that a possibility to use interaction studies with the IR formulation remains acceptable when justified. Proposed change: Interaction studies and sStudies in special populations should preferably be conducted with the modified release formulation. Interaction studies should preferably be conducted with the modified release formulation, although interaction studies with the immediate-release form could be acceptable with appropriate justification.
217-218 (and 348-350)	7	Comment: We support the proposal to conduct dose-proportionality assessments in multiple-dose studies
219-220	13	Comment: Is a study / are studies performed to select an MR formulation for clinical development from various prototypes sufficient to address this? Proposed change: If yes: …this is generally done through bioequivalence/relative bioavailability studies (eg single dose studies with MR prototypes for selection of candidates formulation)….
219-221	22	Comment: The mechanism behind the different modified release systems is well understood, so the need for investigation of several formulations would add limited information (e.g. HMPC based matrix tablets). Proposed change: Rephrase to "This is generally done through bioequivalence/relative bioavailability studies conducted using different formulations where, for instance, the amount…"
223-241	20	Comment: this section is redundant with section 5.1.4.1 which it cross-refers to. Could not there be a general section on food effect studies with specificities addressed in each of the application types section?
223-241	22	Comment: The section 4.1.1. is a general section about food effect studies and contains paragraphs which are repeated in later parts of the guideline. We would find useful to add a sentence referring to further sections in the document about the dose strengths to be investigated in the food effect studies.
224	5	Comment: IVIVC should be established based on PK studies under fasting conditions. Is it still considered necessary to conduct a study under fed conditions when a IVIVC is used to support changes in formulation to show that dose dumping does not occur?

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
230	7	Comment: Type error Proposed change: ...important from a safety perspective...
233	1	Proposed change: "If there is a **clinically significant** food effect on the MR formulation additional study(ies) with an oral solution can be considered, to evaluate if the food effect is related to the formulation or to the drug substance. In this situation, a single dose 4 way crossover study; MR fed and fasted + oral solution (or immediate release (IR) formulation if a solution is not feasible) fed and fasted can be conducted.
239	17	Comment: Regarding "studies of the effect of different kinds of food", the message on different kinds of foods can be interpreted in different ways- either caloric value or nutritional composition needs to be mentioned. Proposed change: It is suggested that the sentence is rephrased as "studies on the effect of different kinds of food composition i.e. caloric content of food, nutritional composition of food".
239	22	Comment: The term "marked" is unclear. Proposed change: Recommend rewording to "clinically relevant" to emphasize the clinical relevance of the food effect. "In case there is a marked clinically relevant food-effect, additional food-interaction studies might be needed..."
248-249 and 261-262	13	Comment: The draft guideline requests to determine the rate limiting step that determines systemic availability. While appreciating the value of knowing this, experimental accessibility might be difficult to achieve. It would be beneficial to better understand from this guideline the importance of this information for a regulatory approval of a product. Furthermore, what has to be shown in vivo in humans and for what information in vitro data are sufficient?
Lines 248-249 Lines 261-262	24	Comment: The requirement "Studies should be conducted to evaluate drug transport characteristics and the rate limiting step that determines systemic availability" is not precise/clear as there are no validated and commonly accepted study design conditions established to answer these questions. Proposed change: In-vitro and / or in-vivo investigations should be realised which allow certain conclusions upon drug transport characteristics and the rate determining step that determines systemic availability.
253	5	Comment: Is IVIVC possible for transdermal formulations? No information on this was found in appendix II.

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253	13	Comment: While the draft guideline states that "aiming to establish an IVIVC is advisable" for TDDS, no specific guidance is provided in Appendix II what should be considered for an IVIVC with TDDS. Are there successful applications and regulatory acceptance of TDDS IVIVC available? If that is the case, more guidance concerning the IVIVC for TDDS should be provided in Appendix II. Otherwise, deletion of this request in line 253 might be considered.
253-254, 265-266	22	Comment: Please add which kinds of food should be tested, or a reference to a food effect guideline.
253	24	Comment: The statement "Aiming to establish an IVIVC is advisable" does only make sense, if rate of absorption is relevantly influenced by the formulation. Proposed change: Aiming to establish an IVIVC is advisable if the rate of absorption is determined by the formulation characteristics.
255-258	7	Comment: We note the proposal to conduct studies to investigate the influence of sauna and sun cream on transdermal patch adhesion. Further clarity is requested on whether these should be PK studies (the text appears under a PK heading). We also request further details on these aspects, such as the duration of sauna exposure and the amount and type(s) of sun creams to be investigated.
255-258	7	Comment: If no PK data are intended to be gathered in sauna and sun cream studies, then we would propose that for clarity, these requirements are moved to the quality guideline on modified release transdermal products.
256	1	Proposed change: '.... patch adhesion and, in general the **influence of common human behaviours** ~~**sauna and sun cream**~~ on the patch adhesion (see also Guideline on quality of transdermal patches EMA/CHMP/QWP/911254/2011) should be investigated."
256	15	Comment: Please require phototoxicity testing conditional, as indicated in ICH S 10. Reference to ICH S 10 should be added.
256	15	Comment: "…the effect of sauna and sun cream…" The aforementioned listing is not identical to Guideline 911254 Proposed change: Please rephrase, "... and, in general, the effects of conditions of everyday activities (see also Guideline

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		911254) should be investigated."
256	22	Comment: Dose proportionality issues can be described and/or explained; they cannot be addressed. "In case of several multiple dose strengths, dose proportionality issues should be adequately discussed addressed."
256-258	24	Comment: Trials investigating conditions of sauna on patch adhesion are difficult to realise and, in case of narrow therapeutic range drugs, ethically critical; furthermore, a standardisation of "sun cream" investigations is difficult considering the different type of products on the market. Proposed change: Waiver of such requirement – or: "if an applicant desires to allow sauna and use of sun cream in the SmPC this needs to be justified with adequate data".
261	22	Comment: In view of the challenges to standardize the conditions for sauna or application of sun cream, we would like clarification whether to test for these conditions is deemed necessary or could be otherwise justified. Clear instructions in the Product Information Leaflet, as in current practice, are an alternative that in our opinion would lead to a reasonable way to waive such studies. Proposed change: The use of transdermal drug products in the sauna or in conjunction with sun cream should be demonstrated by experimental study data or otherwise justified. The Product Information Leaflet should provide clear instructions on the use in the sauna or with sun cream.
261-262	22	Comment: "...to evaluate drug transport characteristics..." may be misunderstood as investigating only the effect of defined transporters on drug absorption from the IM/SC depot Proposed change: "... to evaluate drug absorption characteristics from the IM/SC depot..."
261-266	22	Comment: The referred investigations can be conducted in non-clinical studies, which is not clear for the current wording. Proposed change: Rephrase to "Studies should be conducted to evaluate drug transport characteristics and the rate limiting step that determines systemic availability i.e. drug release and/or other formulation related particularities. This evaluation can also be conducted through non-clinical studies."
263-265	22	Comment: The statement about the interplay between the active substance, the formulation and the skin (lines 247-248 in

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		the section on transdermal drug delivery also holds for intramuscular depot formulations where the interplay with the muscle environment can be relevant. Proposed change: add language:" the kinetics of intramuscular depot formulations is determined by the interplay between the active substance, the formulation and the muscle tissue.
Section 4.3, line 263	22	Comment: The referred pharmacokinetic investigations should be conducted for a compound which is well known from an oral treatment. Proposed change: Rephrase to "Pharmacokinetic investigations for a compound which is well known from an oral treatment should comprise single-dose and multiple-dose investigations…."
265	13	While an IVIVC for e.g. s.c. implants is justified and can be achieved, i.m. depot formulations include oily solutions. It is assumed that for these an IVIVC is not requested. This might be clarified with an updated wording of this section.
265	22	Comment: The Guidance states that "IVIVC is advisable" for IM/SC depots. "Advisable" might be interpreted as required. Unfortunately, IVIVC is often difficult to achieve, particularly for more complex dosage forms and routes of administration. Thus, caution is advised. The potential benefits of the depot formulation may far outweigh having an IVIVC. Proposed Change: Aiming to establish an IVIVC is advisable replaced by: An IVIC approach may be helpful (please see Appendix 2).
265	24	Comment: An advice to establish an IVIVC does only make sense if adequate/meaningful in-vitro testing procedures are available. This is not the case in the majority of i.m./s.c. forms, especially for oily solutions and often only of very limited value for implants. Proposed change: Meaningful in-vitro dissolution procedures should be established whenever possible. Relationship of such procedure with in-vivo data should be investigated.
261	20	Comment: "...to evaluate drug transport characteristics..." may be misunderstood as investigating only the effect of defined transporters on drug absorption from the IM/SC depot

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change: "... to evaluate drug absorption characteristics from the IM/SC depot..."
266	5	Comment: For depot formulations: What is the required duration of a single dose study? Intended treatment period (e.g. 3 months) ? + some time after treatment? And when removal of the implant is possible?
275	15	Comment: At the end of line 275, please add "... or metabolism." (mentioning of metabolic profile in line 288f.)
276-286	25	Comment: In case of active substance with well established use clinical studies with pharmacokinetic endpoints seem to be sufficient to assure patient safety and clinical efficiency (similar to bioequivalence studies). Conducting of unnecessary clinical trials seems to be unethical and leads to additional costs of pharmaceutical industry, which are shifted to the patients or lead to the cancelation of innovative drug form development projects by medium and small companies. Therefore, pharmacodynamic or clinical efficacy/safety studies should be required only in certain cases. A possibility of performing such a studies as post-marketing authorisation studies (Phase 4 trials) is proposed. Proposed change: Re-writing of the paragraph.
279	1	Proposed change: Therefore additional clinical data will generally be required, **if not justified otherwise, i.e. if bioequivalence is not confirmed for relevant PK parameters."**
280-282	7	Comment: This sentence might benefit from being re-worded as it becomes difficult to follow and lacks clarity at the end. Proposed change: Consider splitting into two sentences. For example: Whenever the strength of the new modified release formulation differs from those approved for the immediate release product, this difference and the possible resulting different dosage regime has to be highlighted very clearly in the SmPC, PL and labelling. This is an important routine risk minimisation measure to avoid medication errors.
281	22	Comment: Bioavailability is a better definition when referring to AUC. "...different extent of absorption bioavailability)."
283-284	6	Comment: Not always possible for the MR formulation to perform better than the IR formulation with regards to benefits / safety / risks. Proposed change: The applicant has to prove that the benefits of the new formulation at least outweigh or equal the potential risks linked with this product in comparison to the immediate release one.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
283-284	20	Comment: the sentence seems incomplete. Proposed change: the applicant has to prove that the benefits of the new formulation outweigh the potential risks of medication errors.
285	5	Proposed change: Please modify: ….in appropriate SD and MD pharmacokinetic, pharmacodynamic…
287	7	Comment: Type error Proposed change: ...the formulation are given...
291-292	22	Comment: Regimen is spelled incorrectly. "...different dosage regime regimen..."
292	13	Comment: An MR form for a drug marketed as IR form could be developed for a different indication than already marketed. In this case the total systemic exposure of MR and IR may be different. Proposed change: Statement should be adapted to reflect this situation
294-295	6	Comment: For better understanding of which one to compare. Proposed change: The marketed immediate release product of the same active substance in the same dosage form (route of administration) should serve as the reference product.
295-297	22	Comment: "Toxicological, pharmacological or clinical tests to define the intrinsic properties of the active substance are not required assuming..." The statement is unclear. Request clarification of the identity of intrinsic properties. Request that this sentence be rewritten to more clearly specify assumptions.
295-297	25	Comment: The sentence is of a general nature and should be placed in the paragraph similar to par 2. General considerations in the former guideline issued in 1999. Proposed change: Introduce novel paragraph "General considerations".
303	22	Comment: The text is considered misleading, as often the final market formulation (colour, markings) may not be used in PK and therapeutic studies. To reflect this it would be more appropriate to modify the text on this point.

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		Proposed change: Suggested modification of this text to "The formulation used in the pharmacokinetic and therapeutic studies should be representative of (or "suitably equivalent to") the final market formulation. Differences between this formulation and the final market formulation should be justified considering the differences and their potential impact on release characteristics and bioavailability of the products."
306	1	Comment: Please adapt the wording in accordance with the Note for Guidance on Bioequivalence for immediate release to ensure clarity and consistency.
306-307	7	Comment: Propose re-wording for clarity Proposed change: The conclusions of the studies are based on concentration measurements of the active substance and/or metabolite(s), occasionally in conjunction with determination of an acute pharmacodynamic effect.
306-307	25	Comment: It is not clear when studies have to be based on concentration measurements of the active substance and/or metabolite(s). Proposed change: Clarification or reference to bioequivalence guideline is needed.
308	25	Comment: The sentence is of a general nature and should be placed in the paragraph similar to par 2. General considerations in the former guideline issued in 1999. Proposed change: Introduce novel paragraph "General considerations".
309-311	1	Proposed change:"In case of no accumulation (i.e. insignificant levels at the end of the dosing interval **based on the criteria outlined in section 6.1**) multiple dose studies are not required as steady state is **effectively** achieved after a single dose."
309-314	1	Proposed change: Move 309-311 to after line 314.
309	20	Comment: If the linear absorption and elimination are confirmed in IR formulation and linear kinetics is expected (i.e. no flip-flop) in MR, it should not be necessary to conduct multiple dose studies. For instance, in Japanese guideline for the evaluation of MR formulation, multiple dosing study is required when the compound shows nonlinear kinetics, narrow therapeutic range, or severe AE. Otherwise, it says prediction via simulation from single dose data is enough.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
309	22	Comment: In case of linear PK of the active substance (assessed with the IR form) AND homothetic (=quantitatively proportional between the dose strengths, same dissolution profile…) MR formulation (e.g. multi-particulate dosage form), why would a dose linearity study be necessary?
310-311	12	Comment: The sentence "In case of no accumulation (i.e. insignificant levels at the end of the dosing interval) multiple dose studies are not required since steady state is achieved after a single dose" should be deleted. The issues addressed in Section 5.1.1 show how important multiple dose data are for a new MR formulation.
310-311	19	Comment: Is accumulation assessed similarly as defined on lines 593-595? If accumulation is not observed then waiver of steady state studies is possible and the steady-state studies recommended in sections 5.1.1, 5.1.2 and 5.1.3 no longer apply? Please clarify.
310	20	Comment: "(i.e. insignificant levels at the end of the dosing interval)" sounds ambiguous. Proposed change: "(i.e. BLQ at the end of the dosing interval or accumulation ratio predicted from half life is 1.0)"
310	22	Comment: If the linear absorption and elimination are confirmed in IR formulation and linear kinetics is expected (i.e. no flip-flop) in MR, is it really necessary to conduct multiple dose studies? For instance, in Japanese guideline for the evaluation of MR formulation, multiple dosing study is required when the compound shows nonlinear kinetics, narrow therapeutic range, or severe AE. Otherwise, it says prediction via simulation from single dose data is enough.
310-311	25	Comment: According to the principles of pharmacokinetics in case of no accumulation steady-state cannot be reached. "Insignificant levels" should be defined as an numeric value if possible. Proposed change: In case of no accumulation (i.e. AUC(0-τ) > 90% AUC(0-∞) after single dose insignificant levels at the end of the dosing interval) multiple dose studies are not required since steady state is achieved after a single dose.
313-314	1	Comment: Please adapt this section for new MR formulations of authorised IR products in accordance with chapter 6, lines 554-555 (generic MR products). Please clarify that the multiple dose bioequivalence study has to be performed under the SmPC labelled condition only. If the product should be taken under fasting conditions or irrespective of food intake, the multiple dose study should be

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		performed in fasted condition only. The daily pre-dose meal in a multiple dose bioequivalence study under fed condition only needs to be high fat, high calorie content on the day of PK profiling. During the accumulation period, we propose in accordance with our comment and arguments on line 606 that subjects can receive standardised, normo-caloric meals throughout the study including the day of profiling unless different meal conditions are requested by the SmPC.
313	20	Comment: If the SmPC recommends the specific dosing condition regarding food intake (fasted or fed) of IR, it should not be necessary to compare PK of MR with IR under the condition SmPC recommends.
313	22	Comment: "(i.e. insignificant levels at the end of the dosing interval)" sounds ambiguous. Proposed change: "(i.e. BLQ at the end of the dosing interval or accumulation ratio predicted from half life is 1.0)
313-314	22	Comment: If the SmPC recommends the specific dosing condition regarding food intake (fasted or fed) of IR, is it necessary to compare PK of MR with IR under the condition SmPC recommends? Proposed change: Specify the dosing condition (fasted/fed) to be tested in comparison with IR.
313-314	24	Comment: It should be clearly stated that the steady state study should be conducted under conditions of normal use of the product is, i.e. the steady state study does not need to be conducted in the fasted state if this is not the normal use.
314	1	Proposed change: "Rate and extent of absorption from a modified release formulation should be evaluated by comparison with an immediate release formulation following single dosing and generally also repeated dosing **unless there is no drug accumulation (line 310)**."
Line: 314	22	Comment: Suggest removing "repeated dosing." Generally multiple-dose studies are not as sensitive as single-dose studies with respect to BE evaluations. "Rate and extent of absorption from a modified release formulation should be evaluated by comparison with an immediate release formulation following single dosing and generally also repeated dosing."

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315	1	Proposed change: "The pharmacokinetic parameters of interest ~~**may be**~~ for single dose studies **may include** AUC(0-t), AUC(inf)), residual area, Cmax ,Tmaxx and Tlag (if justified)l and for multiple dose studies AUC(0-Tau), Tmax,ss Cmax,ss and Cmin, ss ~~**and**~~ **or** fluctuation. The pharmacokinetic parameter(s) chosen as primary for the comparison, i.e. the parameter(s) considered most likely to reflect efficacy and safety should be justified."
315-316	6	Comment: The ratio of AUC 0-t / AUC 0-∞ (and its variability among subjects) will provide better evaluation of the estimated last sampling time, which can be adjusted in further studies. Proposed change: The pharmacokinetic parameters of interest may be for single dose studies AUC(0-t), AUC(0-∞), residual area, Cmax , tmax and tlag and AUC0-t / AUC0-∞
315-316	22	Comment: Residual area=AUCext? Does it mean extrapolated area? Please define.
315-316	25	Comment: In case of oral dosage forms AUC(0-72h) may be considered to replace AUC(0-∞) – as described in Bioequivalence guideline. Proposed change: The pharmacokinetic parameters of interest may be for single dose studies AUC(0-t), AUC(0-∞), residual area, Cmax, tmax and tlag and for multiple dose studies AUC(0-τ), tmax,ss, Cmax,ss, Cmin,ss and fluctuation. In case of oral dosage forms AUC(0-∞) and residual area may be replaced by AUC truncated at 72h, AUC(0-72h).
317-318	13	Comment: It is not clear what is really meant with the sentence "… the parameter(s) considered most likely to reflect efficacy and safety should be justified." Are assumptions sufficient or data requested on basis of the IR formulation? The request should be more precise.
320	1	Comment: For demonstration of the modified release characteristics comparison of Cmax and Tmax parameters between the MR and the IR formulation should be sufficient. Proposed change: Please delete this paragraph.
325-327	1	Proposed change: "Fluctuation in drug concentrations should be studied following repeated dosing. Unless otherwise justified, the modified release product should produce similar or less fluctuations as the immediate release product **for the same dosing frequency**".

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325-327	7	Comment: We note that the fluctuation in plasma concentrations associated with a modified release dosage form should be similar to or less than that associated with the immediate release product. Although the dosing interval associated with the modified release form is generally fixed, there are occasions when the immediate release product is recommended for 4- or 6-hourly administration. This variation may have a significant impact on fluctuation of the reference product. Should more than one IR regimen be investigated? Proposed change: Unless otherwise justified, the modified release product should produce similar or less fluctuation than the immediate release product dosed at the recommended least-frequent dosing interval.
328-330	7	Comment: We would propose that the time to steady state after switching from an IR to prolonged release preparation be addressed using simulations based on the immediate release data plus those data gathered as part of the multiple dose PR assessment.
332-334	1	Comment: The need for multiple dose study should be explicitly excluded in cases where there is no accumulation (see also line 310). Proposed change: "If the active substance and the MR formulation (see section 5.1.3) exhibit linear pharmacokinetic 332 properties it may be sufficient to compare the modified release formulation and the immediate release 333 formulation after single and multiple dose administration at one dose level (**i.e. if there is significant drug accumulation).**"
332	22	Comment: We would recommend adding elimination half-life in the list of single dose PK parameters to be reported. Proposed change: Individual and mean values of the elimination half-life should be submitted for single dose studies.
332-334, 335, 338-339	24	Comment: "Linear pharmacokinetics" should be substituted by "dose proportionality in exposure".
333-334	22	Comment: Linear PK is related to the substance and not to the formulation. Proposed change: If the active substance in IR and MR formulation.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
333-334	22	Comment: The phrase "This also applies if the composition of the strengths is not quantitatively proportional." is unclear. Recommend rewording to clarify meaning. This paragraph pertains to linear and non-linear PK. An example that is clearly presented can be found in Section 5.1.4 (lines 371-377.)
334	22	Comment: Multiple dose studies in healthy volunteers need not be repeated with IR formulations. Data obtained with the MR formulations at steady state, along with the single dose IR and MR data should be sufficient to assess PK of the new MR formulations. Proposed change: Change line 333-334 to "If the active substance and the MR formulation (see section 5.1.3) exhibit linear and stationary pharmacokinetic properties it may be sufficient to compare the modified release formulation and the immediate release formulation after single dose administration at one dose level. Multiple dose studies at one dose level will be necessary for dosage forms demonstrating significant accumulation."
335-339	22	Proposed change: If the active substance in IR and MR formulation
339	5	Comment: And single unit dosage formulations?
340–344	18	Comment: Of a questionable value, especially if other development goals (e.g., "flatter profile", less frequent administration) are met. Proposed change: Remove entirely (preferred) or point out that a one-sided test for non-superiority of inter-subject variances is required.
341-344	12	Comment: This paragraph should either be more precise (e.g. for which PK parameters the variability of the modified release formulation should not exceed that of the immediate release formulation) or it should be deleted. In its current form it is not very helpful.
343-344	1	Comment: Variability is not a criterion, nor part of the rationale for the development of a modified release product. Proposed change: Please delete section 5.1.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
343-344	22	Variability is related to PK parameters not to the formulation Proposed change: The variability for of the modified…that for of the IR formulation.
343-344	22	Comment: Whilst we agree that variability of the modified release formulation should preferably not exceed that of the immediate release formulation, we would argue that due to the complexity of MR formulations and the variability in human physiology involved in drug absorption, variability for MR products is more likely to exceed variability of the immediate release product.
343-344	24	Comment: Reduction of inter-subject variability is not typically an essential goal of MR formulation development. Thus, requirements should not be defined for this parameter. Proposed change: Inter-subject variability after administration of IR and MR forms should be compared and adequately justified in terms of potential clinical consequences.
344	5	Comment: And when no data are available on IR formulations?
345	22	Comment: "The variability of the modified release formulation should preferably not exceed that of the immediate release formulation." What if it does exceed the variability of the immediate release formulation? It is likely variability in absorption may be greater.
348-349	1	Proposed change: "Dose proportionality should be evaluated by means of a single dose **study. As an alternative a multiple dose study could be used if there is significant drug accumulation.** ~~**and multiple dose study where.**~~ **T**he PK parameters of interest of all the strengths/doses are compared after dose adjustment."
Line 348-350	13	Comment: Will the same approach be applied for the determination of dose proportionality as proposed for IR formulations (EMA Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *, 20 January 2010, p. 11/12), i.e. dose-adjusted mean AUC(0-∞) (after single dosing) and/or mean AUC(0-τ) (after multiple dosing) should not deviate by more than 25%?
348	20	Comment: Which method should be used to demonstrate dose proportionality? Proposed change: We suggest the following addition: "Whenever there are several strengths or when several single units

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		can be taken simultaneously to achieve the desired dose, dose proportionality for different strengths / doses of the modified release formulations should be adequately addressed" e.g. by visual inspection of graphically presented plasma concentration vs. time data.
348-350	22	Comment: It is suggested that a single dose study of dose-proportionality is sufficient and there is no need to subject healthy volunteers to longer term exposure when there is no additional information gained. One could also consider a multiple-dose dose-proportionality study (only) in cases where the IR formulation indicated nonlinear kinetics (e.g. Michaelis-Menten), however the necessity of the study might be obviated if the results could be predicted based on results from earlier studies and the IR formulation. Further, it is unclear as to why dose-proportionality of generic formulations is not required (single dose) – see comment on section 6 below (line 547). Proposed change: Dose proportionality should be evaluated by means of a single dose study where the PK parameters of interest of all the strengths / doses are compared after dose adjustment. A multiple dose study may be considered in cases where the IR formulation exhibited non-linear kinetics.
348-350	24	Comment: In case that dose proportionality has been shown in single dose studies and furthermore, other phenomena like auto-induction or auto-inhibition can be excluded by an adequate multiple dose study at the highest dose, additional dose-proportionality investigations are not considered necessary. Proposed change: Dose proportionality should be evaluated by means of a single dose study where the PK parameters of interest are compared after dose adjustment. If pharmacokinetics is not time-linear, dose proportionality should be investigated in a multiple dose setting.
349	13	Comment: It is not clear what a multiple dose study adds once dose-proportionality has been demonstrated after single dose administration. This may be useful only when pharmacokinetics are not time-linear (auto-induction or inhibition). In this case dose proportionality should only be investigated at steady-state. Proposed change: Dose proportionality should be evaluated by means of a single dose and multiple dose study where the PK parameters of interest of all the strengths/doses are compared after dose adjustment. If pharmacokinetics are not

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		time-linear, dose proportionality should be investigated in a multiple dose study.
349	17	Comment: Evaluation of dose proportionality after single and multiple dose. Can the dose proportionality of MR after multiple doses be assessed by means of simulations using single dose data rather than conducting a separate study?
349	20	Comment: If dose proportionality and dose strength equivalence were demonstrated after single dosing, it is unlikely to obtain differing results after multiple dosing unless there is reason to believe that a drug follows nonlinear PK. Proposed change: "... by means of a single dose study where the PK parameters of interest..."
349-350	22	Comment: If dose proportionality and dose strength equivalence were demonstrated after single dosing, it is unlikely to obtain differing results after multiple dosing unless there is reason to believe that a drug follows nonlinear PK. Proposed change: "... by means of a single dose study where the PK parameters of interest..."
352, 371-377	10	Comment: If the different formulation strengths are qualitatively the same but not exactly proportional (which should be often the case for single unit formulations), is it compulsory to check the food effect on different strengths or could evaluation of the highest strength be enough? Same question if a level A IVIVC has been developed?
353	1	Proposed change: "The influence of food on the bioavailability of oral modified release formulations must be investigated **in a single dose study.**"
355	25	Comment: Unnecessary information may be deleted. Content of the meal is described in lines 357-359. Proposed change: high-fat high-calorie meal immediately before dosing
362	13	Proposed change: delete 'that'
362-364	22	Comment: In case of dose-proportional exposure and the absence of time-dependent pharmacokinetics for the drug substance formulated as an immediate release drug product, clarity is desired why a dose proportionality study after multiple dosing is required. This is also in contradiction with lines 332-334 where only one dose level is mentioned in case

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		of linear pharmacokinetics. Proposed change: Dose proportionality should be evaluated in a single dose study, at least at the highest and the lowest dose level using bracketing criteria of proportional product composition. Partial AUC analysis and population pharmacokinetics modelling and simulation may waive dose proportionality studies following multiple dosing.
365	1	Proposed change: "If there is no **clinically significant** food effect on the immediate-release formulation, a 2-way cross-over study comparing 365 the modified release formulation in fasted and fed states could be sufficient (given that other studies 366 compare the modified release and the immediate release formulations under fasting conditions)."
365-370	13	Comment: Given that food effect studies with high-calorie / high-fast meals are performed under strictly standardized conditions, a historical comparison of IR and MR data would appear sufficient also in the case of a clinically significant food effect. A direct comparison of the MR and the IR forms in a separate 4-way crossover study under fasting and fed conditions will not provide additional knowledge. Proposed change: The general recommendation should be, to perform a 2-way cross-over study for the MR form, regardless of whether or not there was a food effect for the IR form.
368-370	17	Comment: If the significant food-effect on IR form is already known, there should be no need to study the IR formulation as proposed here in a 4-way crossover study. Proposed change: consider removing the need of studying IR formulation under fed and fasted conditions, when the food effect on this formulation is already known.
368	20	Comment: If the food effect is already quantified with IR formulation, it sounds redundant to test it again in a 4-way cross-over study (even if there is a significant food effect). Thus regardless the impact of food effect with IR formulation, 2-way cross over sounds enough to quantify the food effect of MR formulation.
368	22	Comment: The food effect from an intramuscular formulation may not be known, if the compound is new and the modified-release formulation is decided based upon non-clinical pharmacology. The linkage to the immediate release formulation should, hence, be reconsidered.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change: To remove this paragraph.
368	22	Comment: If the food effect is already quantified with IR formulation, it sounds redundant to test it again in a 4-way cross-over study (even if there is a significant food effect). Anchoring the evaluation of food effect for the MR formulation based on the food effects for IR product is not necessary. Thus regardless the impact of food effect with IR formulation, 2-way cross over sounds enough to quantify the food effect of MR formulation. Proposed change: Suggest removing the following text "If there is a food effect on the MR formulation additional study (ies) with an oral solution can be considered, to evaluate if the food effect is related to the formulation or to the drug substance. In this situation, a single dose 4 way crossover study; MR fed and fasted + oral solution (or immediate release (IR) formulation if solution is not feasible) fed and fasted can be conducted."
370	5	Comment: Is a food effect study for MR required when IR tablet should be administered under fasted conditions?
371-374	19	Comment: In this sentence, reference in regards to the number of studies required for food-effect assessment is only made to multi-particulate dosage forms. For the other dosage form, e.g. single unit formulation should the requirements be as per Appendix III of this document? Can you please clarify in a revised document.
371-374	22	Comment: Investigation of the food effect of an intramuscular formulation seems to be added experiments without added value. If it's already known that the immediate release formulation has a food effect, why repeating that investigation? Proposed change: Rephrase to a suggestion rather than a recommendation.
374-377	7	Comment: We note the recommendation to conduct food-effect studies at the highest possible dose, and agree with this in principle. However, for some products (e.g. strong opioid formulations) it seems excessive to expose healthy volunteers to particularly high doses, simply to investigate a food effect. It is hoped that a clinical justification, leading to the investigation of lower doses, thus minimising the level of risk to the volunteers, would be acceptable.
378-380	1	Proposed change: Delete the recommendation 378-380 and replace with "**The assessment of food effect will be made based on AUC and Cmax alone**".
378-380 (and	7	Comment: We support the recommendation to introduce shape analyses (via partial AUC's) into food effect and other

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
798-805)		bioequivalence assessments
378	22	Comment: Recommend removing "only if the products are proportional in composition." If dissolution profiles are similar, is there a need to conduct food effect studies at the low and high doses regardless of proportionality in composition? "...the food effect can be investigated for one of the strengths only if the products are proportional in composition (e.g. multi-particulate dosage forms or proportional tablets), having the same manufacturing process, exhibit linear pharmacokinetics and their dissolution profiles are similar in a range of dissolution media."
Section 5.1.4.1, 378-380	22	Comment: It is unclear as to how the agency expects comparison of shapes of curves and what would constitute an important difference. Proposed change: Please either add clarity to comparison of shapes of curves and what constitutes an important difference or remove this expectation.
378-380	24	Comment: It is often the case that food significantly alters the shape of the curve. A statement "verify that the shape is not significantly altered" is misleading and may be understood as requirement to establish strict acceptance criteria. This is not appropriate, especially as individual profiles need to be inspected (mean curves not representative in most cases). Proposed change: For the assessment of food effect besides AUC and Cmax, it may also be valuable to compare modified release characteristics by the shape of the concentration-time profiles which should not be significantly altered.
379	5	Comment: Visual check of shape only or also statistical evaluation? Do we need criteria for non-equivalent shape of the curve?
386-387	22	Comment: The text states "if the formulation or the manufacturing process is changed during development, a new evaluation of the food effect for the final formulation may be needed." It is appreciated that such changes need to be risk assessed for their impact on the evaluation of food effect, but it is also noted that some changes to formulation or manufacturing process are much less likely to impact on the need for further evaluation than others. It would be useful perhaps to be clearer on what changes need this consideration and what changes do not, even in 'in principle' terms. Proposed change: Consider changing this text to "If the formulation or the manufacturing process is significantly changed (i.e. in such a way as to potentially affect release characteristics) then a new evaluation of the food effect of the final

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		formulation may be needed. For less-significant changes (e.g. changes to manufacturing site) a new evaluation of the food effect would not be expected.
387	1	Proposed change: "If the formulation or the manufacturing process is changed during drug development a new evaluation 386 of the food effect for the final formulation may be needed, **unless otherwise justified**."
391-393	17	Comment: More clarity is required around this statement on different type of administration. Would submitting a biowaiver for BE studies after showing equivalence in in vitro dissolution justify the absence of a BE study?
394, 395-399	10	Comment: Can some of the assessments be done "in silico", eg by using relevant software such as GastroPlus? For example to evaluate the potential influence of a decrease or increase in transit time due to disease state or concomitant medications?
395-397	1	Comment: This paragraph is not in line with recommended approaches as described in the immediate release dosage forms bioequivalence guideline. Investigation of the modified release formulation concomitantly with another substance should be optional. Proposed change: Please replace this paragraph with the proposed one below, in line with the guideline for immediate release products "**Medicinal products that according to the originator SmPC are to be used explicitly in combination with another product (e.g. certain protease inhibitors in combination with ritonavir) may be studied either as the approved combination or without the product recommended to be administered concomitantly. Co-administration of drugs that are included in the combination should be optional."**
395	7	Comment: Rewording suggestion Proposed change: If an oral modified release formulation is to be often co-administered with...
395	13	Proposed change: - delete 'be' ; - the term 'often' is unclear. Instead of using the term 'often' e.g. indications should be given where it is recommended to investigate concomitant active substances affecting GIT physiology.
395-399	24	Comment: The term "is often co-administered" is vague and should be defined more precisely, e.g. in case of combination therapy recommended by therapeutic guidelines or in case of high probability of co-administration in the indication.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
396	5	Comment: Or pH stomach…
398	22	Comment: "...additional in vitro dissolution testing showing equivalence between the closed and the opened formulation is necessary." Closed and open in vitro dissolution comparison for a capsule seems unnecessary or should be justified. Recommend defining closed and open formulation.
Lines 400-414	22	Comment: The guideline stresses that additional testing of the performance of the oral modified release formulation may need to be performed in "patients with markedly altered gastrointestinal function". Some examples of this condition would be helpful, as 'markedly altered GI function' is not a commonly utilized clinical description.
406	5	Proposed change: Please modify: If dose dumping is observed under certain (worse case) conditions (e.g. much higher….
410	13	Comment: Quantitation criteria are missing with regard to "much higher peak exposure".
410-414	13	Comment: The required investigation of food effect provides the respective data for the posology to be used in the subsequent clinical trials, and the outcome thereof with respect to efficacy/safety will finally determine the label proposal. The meaning of this paragraph is therefore unclear.
413	22	Comment: It could be helpful to consider providing some guidance on the level of change that would be considered as unacceptable early release (aka. dose dumping) or the risk assessment principles that would lead to such a determination. A cumulative assessment of the PK data across single- and multiple-dose studies may help elucidate potential problems of dose dumping, and this should be considered before further investigation/ reformulation. Proposed change: Please consider clarifying changes in PK that would be considered unacceptable early release or adding some risk assessment principles that might be considered ahead of reformulation.
413	22	Comment: "...product failure,..." It is difficult to characterize variability of product failure. Please provide additional guidance.
415, 425-427	10	Comment: What is "a reasonable amount of alcohol"? This should be quantified as interpretation of "reasonable" may lead to very different volumes/ results. Furthermore, it is required "on an empty stomach". In real life, if people take their medications with alcohol, it is most

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		likely to happen in the evening or maybe at lunch time, hence the "fasting" will no longer persist. Hence it should be specified since how long the stomach should be empty.
416	5	Comment: It may be helpful if some examples of substances and excipients which are sensitive to alcohol are given here.
419-422	9	Comment: Per the Quality of Medicines Questions and Answers issued by QWP (*), guidance was provided on the methodological requirements to perform in vitro testing to determine the effect of alcohol on the modified-release oral products. It is suggested that the same consideration be incorporated into the current guidance to add clarity and promote consistency. (*) See "Specific types of product - Need for in vitro dissolution studies with alcohol for modified-release oral products including opioid drug products"
419-428	11	Comment: "Reasonable" amount of alcohol to be administered during in vivo studies should be defined in the guideline by indicating volume and concentration.
419	13	Comment: The experimental conditions for the in vitro testing of the impact of alcohol need to be defined, e.g. % alcohol, temperature, pH etc.
Line 419 - 424	16	Comment: The wording in these lines is very vague. It is not clear what would be considered a high versus a low concentration or what the definition is of a short versus a long period. MSD recommends that EMA aligns the wording in the guideline with the FDA wording, as the wording in the FDA guidance is more descriptive. We also suggest that the guideline states that EMA encourages a discussion of results prior to reformulation in order to avoid an additional burden of in-vivo studies.
419-422	21	Comment: Investigation on release properties in combination with alcohol (dose dumping) - The guideline only indicates general terms as 'high / low content alcohol'. It is not clearly identified which percentage needs to be used when investigating the alcohol effect. Is that up to the applicant to justify? For example, the relevant FDA guidelines are clearer concerning that (e.g. "Quality by Design for ANDAs: an Example for Modified Release Dosage Forms"). - The guideline only indicates general terms as 'short and long period of time'. It is not clearly identified which period on

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		time are relevant? Is that up to the applicant to justify? - In-vivo investigation should compare the systemic exposure when the MR product is ingested with a reasonable amount of alcohol on an empty stomach. What is reasonable? Is it up to the applicant to justify 'a reasonable amount'?
Line 419:	22	Comment: Clarification is desired about the dosing recommendation to avoid a prolonged residence in the stomach. For example, dosing in fasting conditions instead of intake of fed condition? Proposed change: The possibility of unintended increase exposure and the associated safety risk should be described in the SmPC.
Section 5.1.4.3, 419-422 and Section 6.9, 816-821	22	Comment: The draft text states "for such formulations, in vitro studies of the release in alcohol solution should be performed." We agree, however, the text lacks clarity and specificity as to what studies should be conducted. Proposed change: Consider adding more clarity as to the expected design of such in vitro studies with alcohol, for example, the specific alcohol concentrations and dissolution media to be evaluated.
419-424	24	Comment: The conditions of in-vitro testing for potential influence of alcohol on drug release should be defined. Furthermore, acceptance criteria need to be defined. Proposed change: Conditions specified in the Q&A document should be suggested, i.e. 5%, 10% and 20% of ethanol. The duration of testing should be limited the (maximum) duration of gastric residence in fasted state, i.e. 2 hours. Acceptance criteria should be defined in line with the specifications for batch release.
420 423	13	Comment: The terms 'accelerated' as well as 'high or low alcohol concentration' should be quantified in terms of eg 'increase in % dissolved at time n' and '% alcohol content', respectively. Likewise, the conditions of an in vivo study should be detailed in terms of proposed alcohol dose and concentration
420	22	Comment: It would be valuable if the guideline could indicate what type of in vitro data the authorities would like to see to assess the risk for ethanol induced dose dumping. Proposed change: A suggested testing programme would be 5-40% ethanol in pH 1.2 for 2 hours covering the most challenging practically possible situation.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
420-424	22	Comment: We find the section about low or high alcohol concentrations for a short period of time or at lower alcohol concentrations over a longer period of time is very vague. Also the requirement for a mandatory reformulation appears to be too strict. An in vivo interaction study with alcohol should be acceptable independent of the in vitro study outcomes. Proposed change: We would recommend aligning with FDA proposals as follows: in vitro dissolution testing using various ethanol concentrations 40%, 20%, 5% for 2 hours".
422 and 429	24	Comment: The statement "the alcohol effect cannot be avoided by reformulation", needs to be specified.
423–428	18	Comment: In vivo studies – especially with high volumes and concentrations of alcohol administered on an empty stomach – are highly unlikely to be approved by any European ethics committee. The attitude of "Well, perform the study in the US or Canada instead" is considered hypocritical. Proposed change: Drop in vivo studies.
425-428	1	Comment: This section lack specificity and should describe more clearly how such studies should be performed. For clarity, we suggest EMA to consider a separate appendix or guidance document to specifically address how to conduct alcohol interaction studies. In particular, the following elements need to be clarified: - It is stated that "The *in vivo* investigation of alcohol induced dose dumping should compare the systemic exposure when the modified release product is ingested with a reasonable amount of alcohol on an empty stomach." This is ambiguous and needs to be supplemented with proposals on volume, composition and concentration of alcoholic drink. These investigations should be ethically justified; explicit guidance will be required to design the studies with alcohol consumption. - For the in vivo investigation it should be clearly defined in the guidance what is the reasonable amount of alcohol to be ingested on an empty stomach. - What are the criteria for declaring absence of alcohol-induced dose-dumping, when the individual ratios were assessed?

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
425-428	7	Comment: 'A reasonable amount' of alcohol should be better defined. Proposed change: Earlier studies have been conducted with 120 ml or 240 ml of 40% ethanol. We recognise that these levels of alcohol ingestion are high, but if in vitro experiments have failed to identify or characterise the extent of alcohol-vulnerability, the in vivo test needs to represent a significant challenge.
425-426	24	Comment: If in-vivo studies are requested at all, the amount of alcohol co-administered with the product should be defined. The suggested "reasonable amount" allows a broad range of interpretation.
426	22	Comment: The text states that a product should be reformulated if accelerated active substance is observed in vitro. The text does not clarify what degree of change might be acceptable (and this should be added). Also we consider that some products should be considered acceptable without re-formulation based upon use of an alcohol contra-indication on the label. The text goes on to state "only in those cases where it can be justified that an in vitro alcohol interaction cannot be avoided by reformulation, could an in vivo study be accepted in order to substantiate that such an interaction is unlikely to occur in vivo." This is not considered to be appropriate – if a product can be shown to be suitable for use in an in vivo study there should be NO need for reformulation. We recommend this section also be further clarified to indicate that if accelerated release is NOT observed in vitro, a clinical alcohol study would not be expected. Proposed change: Recommend the text is changed to "Where significantly accelerated active substance release (i.e. no longer meets products release test) is seen in vitro in alcohol solution, the product should be considered to have a significant shortfall in its performance that will need to be managed either evaluation in vivo, reformulation or where reformulation is untenable or, where the product risk / benefit analysis would support, by product labelling. We also recommend this section also be further clarified to indicate that if accelerated release is NOT observed in vitro, a clinical alcohol study would not be expected.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
430-431	7	Comment: Slight re-wording proposed. Proposed change: Contraindicating alcohol is generally not considered sufficient to address a formulation interaction with alcohol.
434	25	Comment: The sentence is of a general nature and may be deleted or placed in the paragraph similar to par 2. General considerations in the former guideline issued in 1999. Proposed change: Delete the sentence or introduce novel paragraph "General considerations".
435	6	Comment: Washout duration becomes very important when a MR formulation has an extended estimate of AUC 0-∞ Sample size calculation, though done routinely for IR products, sometimes becomes challenging when intra-subject variability is not fully known for MR products, or simply cannot be polated based on IR product data. Proposed change: Under "Other points to consider" a brief relevant description about the following points can be added – 5.1.5.5 Washout period in case of more than 1-period study 5.1.5.6 Sample size; especially when comparing MR with an IR formulation in a cross-over design.
436, 437-439	10	Comment: Can some of the investigations (special populations) be made "in silico"?
437-439	1	Comment: It is unclear as to what the expectation is for considering the listed special patient groups. Routine completion of PK studies in these special patient groups is impractical. In vitro testing including dissolution data in various physiologically related conditions and clear understanding of pharmacokinetics of the drug in different subject populations should suffice to support the MR formulations in the listed special patient groups. Proposed change: Please clarify the regulatory expectations as to special populations.
437	5	Comment: 'Vegetarian' is no special patient population in routine PK investigations for e.g. new drugs. Why is it for MR products? If no specific reason, it is proposed to omit this population here.
437-439	7	Comment: More guidance on the design of studies examining once-daily products in the specified populations would be welcome. For example, would food effect studies be expected in each of the vegetarian, paediatric and elderly patient

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		populations?
437-439	7	Comment: The inclusion of 'vegetarians' as a sub-population will be operationally difficult without further clarification of how vegetarian is defined and how long vegetarian status has to be maintained before entering a trial. Would a screening test be expected to confirm vegetarian status? If not then this entry criteria would be difficult to control and standardise, and could be interpreted differently. Proposed change: Further clarification on the intended subgroup would be welcomed.
437-438	13	Comment: While the objective of the requested consideration of different physiological conditions is clear, the expected consequences of these considerations for development studies remain unclear. It would be beneficial to clarify whether it is intended to address these aspects in vitro or whether it is expected to include such special populations/conditions also in clinical in vivo studies.
437	17	Comment: It is not clear why "Vegetarians" are classified as special populations in this section? There doesn't seem to be any published data to indicate absorption of MR dosage forms is different in vegetarians.
437-439	19	Comment: In this section, the vegetarian patient population is recommended to be taken into consideration when designing oral once daily MR formulations. Can you please elaborate on this recommendation?
437	22	Comment: What does "reasonable amount of alcohol" mean in "The in vivo investigation of alcohol-induced dose-dumping […] empty stomach"? Proposed change: "[…] a reasonable amount of alcohol (approximately XX ml, minimum of XX g absorbed) on an empty stomach. The composition of the drink should be described with regard to alcohol content (% volume, grams). The results of the study […]."
437	22	Comment: Recommendation on evaluating impact of vegetarian diet is vague and does not provide clear guidance. It is unclear why, when (and what) additional studies with vegetarian food are necessary. Proposed change: Change this text to "Different physiological conditions (e.g. altered transit times, pH, food intake) in paediatric and elderly patients (or in patients routinely taking antacids) should be taken into consideration especially when

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		designing oral once daily MR formulations.”
437-439	25	Comment: renal / hepatic failure may be added Proposed change: Different physiological conditions (e.g. transit times, pH, food intake) in vegetarian, paediatric and elderly patients should be taken into consideration especially when designing oral once daily MR formulations. Influence of renal or hepatic failure should be assessed as described in appropriate guidelines.
440-442	23	Comment: How the effect of different sites of application of SC/IM depot formulations shall be investigated? What is agency’s stand? Do you mean to say that we need to have a separate study to prove that both test and reference products are comparable? Proposed change: As the test and reference products are comparable in one site shall be extrapolated to the other sites, agency shall remove the further evaluation at the other site.
444-446	23	Comment: In case of SC/IM depot formulations, it should be investigated that not only the plasma levels are within the therapeutic concentrations at the end of the dosing interval but also how the plasma levels decrease after removal of the depot formulations. Proposed change: When the test product Cmax and AUC are comparable to the reference product, these pharmacokinetic profiles ensure that the drug distribution and elimination are similar to each other in a broader perspective. In view of this, agency shall remove the evaluation about how the plasma levels decrease after removal of the depot formulations.
448-450	24	Comment: In case that the modified release product intends to mimic the performance of an immediate release product given several times per day, the criteria for acceptance of bioequivalence should be clearly defined, e.g. concerning the necessity to demonstrate BE for every Cmax and partial AUC.
449	5	Proposed change: Please modify: In these cases the plasma concentration time profile of the modified release preparation should be…
449 and 486	13	Comment: Although this is a rare situation it would be interesting what the metrics for equivalence in Cmax would be for such a situation given the multiple peaks

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
449-450	25	Comment: it is not clear what does "equivalent" mean in this sentence. Proposed change: In these cases the modified release preparation should be bioequivalent with the immediate release formulation given in the dose schedule that is imitated.
451-461 and 696-708	20	Comment: There is significant redundancy in the two sections Proposed change: Combine information into one section
451-461 and 696-708	22	Comment: We would recommend deleting the word "rarely" because multiphasic modified drug products are developed. The requirement to be bioequivalent may hold for AUC but necessarily for the shape of the plasma concentration-time curve. Referring to other sections such as 5.2. about therapeutic studies or investigational data of the relationship between the shape of the concentration-time profile and the pharmacodynamics is desired.
452-461	5	Comment: It may be mentioned that single unit formulations are not advised/preferred due to the drawbacks indicated in this section.
5.2 Therapeutic studies 463-479	22	Comment: There is significant redundancy in the two sections Proposed change: Combine information into one section
463-479	25	Comment: The requirement for clinical efficacy and safety trials with exception only in certain cases may lead to limiting competitiveness between pharmaceutical companies and sets marketing-barrier for innovative forms. It is proposed to change this principle: PK data is generally sufficient and therapeutic studies are required only in certain cases, possibly as post-marketing studies. (See also comment to the lines 276-286). Proposed change: Re-writing of the paragraph.
468-471 and 480-496	20	Comment: The two sections are redundant and 'exceptional cases' is unnecessarily restrictive. Proposed change: delete 'exceptional cases' from the sentence and move paragraph to section 5.2.1
Lines 468-471	22	Comment: These lines should be deleted or substantially revised to reflect that therapeutic studies should usually not be needed, although there may be exceptions, as opposed to the currently presented approach where waiving studies is the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		exception. Safety and efficacy data are not necessary if equivalent PK data are obtained from the new modified release formulation. If traditional BE/BA cannot be used to demonstrate equivalence then sponsors should be able to satisfy the requirements using a study which demonstrates therapeutic equivalence or, if well-established correlative biomarkers are available, a PD study which shows biomarker equivalence. Proposed change: 'As a principle, comparative clinical efficacy and safety data are not needed in addition to PK data for modified release products developed after the immediate release formulation, unless adequately justified. As the efficacy and safety of the immediate release product is known, the major issue would be to demonstrate that the new modified release formulation is as safe and effective as the existing formulation. Although a modified release drug is likely to have a different rate of absorption from immediate release and that demonstration of BE on Cmax (equivalent rate of absorption) with immediate release form may be difficult to demonstrate, additional therapeutic studies should generally be considered unnecessary if a strong rationale based upon known therapeutic levels of drug, PKPD models, and PK simulations at steady state can be provided. Additional benefits of the new formulation should be shown or justified, if claimed. However, in exceptional cases, iIf the assessment of concentration-effect relationship indicates that there is a well-defined relationship between plasma concentration(s) of the active substance /active metabolite(s) and clinical response, clinical trials may be considered unnecessary.'
470-471	1	Proposed change: "In this case the same or a better level of efficacy and safety has to be concluded from PK~~**/PD**~~ studies."
482	1	Proposed change: "However, therapeutic studies might be waived **when one of the following conditions is met**:"
Section 5.2.1, lines 482-496	22	Comment: The guidance offered in these lines appears to suggest that if appropriately justified and if applicable, additional clinical studies may not be needed. However the expectations in the last sentence are considered to be unclear "In this case the same or a better level of efficacy and safety has to be concluded from PK/PD studies". Proposed change: Suggest modifying the text to "However, in exceptional cases, if the assessment of concentration effect relationship indicates that there is a well-defined relationship between plasma concentration(s) of the active substance(s) / active metabolite(s) and clinical response, clinical evaluation may be considered unnecessary. The altered PK profile of an MR product (e.g. lower fluctuation or significantly reduced Cmax whilst maintaining equivalent AUC) may offer the same or better safety and / or efficacy. This may be concluded based on modelling and simulation of the concentration-response

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		results from the IR program.”
482-496	22	Comment: It would help the reader if it was clarified that therapeutic studies may be waived in the three different situations. The guideline may unintentionally be interpreted as all three conditions / situations must apply in order to qualify for a waiver.
484, 488, 495	25	Comment: Symbols Cmax,ss and Cmin,ss should be used consequently; AUC at steady state may be replaced with symbol AUC(0-τ),ss Proposed change: Cmax, Cmin and AUC at steady state => Cmax,ss, Cmin,ss and AUCτ,ss
483-491	25	Comment: both points may be combined Proposed change: bioequivalence between the immediate release and the modified release product is shown in terms of Cmax, Cmin and AUC at steady state. In case of significant differences in the shape of the plasma concentration-time profile, applicant have to justify lack of relevance for efficacy and safety based on the exposure – response and profile shape - response relationships.
492-496	20	Comment: The criterion is phrased in a way that it remains unclear if bioequivalence is requested or if Cmax and Cmin should lie within the well-defined therapeutic window
492-496	22	Comment: Because the concentration-time profiles following a modified release products are usually different from those following IR drug products, the therapeutic efficacy cannot be extrapolated from IR and therapeutic efficacy and safety cannot be waived. For example, concentration-time profiles following a once daily MR drug product will rarely reflect the concentration-time profile for the IR drug administered bid, tid or qid, although Cmax, Cmin and AUC over a daily dosing interval at steady state could be statistically bioequivalent. We don’t believe that the first bullet providing for bioequivalence solely based on pharmacokinetic parameters is appropriate. Inclusion of shape factors and well documented exposure-response information for both efficacy and safety should be available as part of the justification of waiving therapeutic studies.
492-496	24	Comment: The requirement “below the Cmax,ss” and “above the Cmin,ss” is not appropriate for non-inferiority/superiority assessment.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change: The terms "below the Cmax,ss" and "above the Cmin,ss" should be changed to "below or equal Cmax,ss" and "above or equal Cmin,ss" based on one-sided tests using a similar approach as for bioequivalence testing (i.e. upper limit of the 90% CI <125.00% for Cmax,ss and lower limit of the 90% CI >80,00% for Cmin,ss).
494-496	13	What does "strict bioequivalence" mean? This should be explained or just reduced to "bioequivalence" assuming the 90% confidence interval of the ratio test/reference to be in the 0.80 – 1.25 range. Furthermore for such waiver, it is requested that Cmax of the MR formulation should be below, Cmin,ss above that of the IR formulation. Would a requirement of ≤ and ≥, respectively, not be more appropriate?
494	25	Comment: Term "strict bioequivalence" should be clarified or replaced by "bioequivalence". Proposed change: strict bioequivalence
500-501	15	Comment: Studies should establish the clinical benefit of the new formulation relative to the authorised immediate release formulation… Proposed change: Please add: "... if such benefit is claimed."
500-501	22	Comment: The criterion is phrased in a way that it remains unclear if bioequivalence is requested or if Cmax and Cmin should lie within the well defined therapeutic window Proposed change: Please rephrase unambigously
5.2.2. How to design clinical studies Lines 504-505	22	Comment: The word "benefit" suggests that superiority is to be demonstrated. Clinical superiority is not always the target of a modified release product, and dosing compliance might be another argument particularly in the case of multiple IR drug product intakes per day. Proposed change: Please consider deleting the following Clinical superiority is not always the target of a MR product. Non-inferiority study designs may be appropriate in some situations and replacing "establish the clinical benefit" by "clinical value".
5.2.2. How to design clinical	22	Comment: For the assessment of the efficacy and safety of certain therapeutic classes it would be more appropriate to specify that the effects of the formulation should be measured throughout a dose interval at steady state of the modified

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
studies 509		release formulation, rather than a 24-hour period. If the intent of the new formulation is to provide the same safety/efficacy profile as the immediate release formulation over the dose interval of the modified release product then that profile needs to be investigated over the dose interval, not a pre-defined interval. For example, if the IR product is administered four times a day and the modified release product is administered twice a day, then the effects of the modified release product should be compared to the IR product over a 12 hour period. In some circumstances, such as in the assessment of diurnal variation in absorption, there is a rationale for 24-hours. Proposed change: 'In the assessment of the efficacy and safety of certain therapeutic classes it is necessary to measure the effects of the formulation throughout a 24-hour period and particularly at the end of dosage interval (e.g. assessment of breakthrough pain). In some cases (e.g. assessment of diurnal variations), a 24 h period might be more appropriate'
509-510	25	Comment: Both sentences may be merged. Proposed change: In exceptional cases only, an extrapolation can be made to indications other than those investigated in the trial, if it is appropriately justified by the applicant.
5.2.2. How to design clinical studies 535	22	Comment: If one considers that the mechanism of action is the same between indications then showing bioequivalence in exposure between formulations in one indication should lead to obtaining marketing rights to all indications in the approved label. Testing in all indications wastes money and time and leads to unnecessary testing/exposure in healthy volunteers and hinders the adoption of novel therapies to the other patients covered under other approved indications. Proposed change: 'In general an extrapolation cannot be made to indications other than those investigated in the trial. However, this may be possible if it is appropriately justified by the applicant, notably in cases where the mechanism of action is the same between indications.'
Lines 538-561	22	Comment: Clarification request: If a MR formulation is superior in efficacy to the reference listed product, can it truly be considered under this guidance, or do other guidance documents (e.g. for new products in concerned therapeutic area) apply? We would suggest adding a general sentence referring to relevant scientific guidance documents. Proposed change: 'When superiority is claimed it has to be proven with clinical trials. Applicants are recommended to refer to relevant scientific guidance documents for the concerned therapeutic area.'

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
Lines 540-547	22	Comment: This text related to abridged applications for modified dosage forms referring to a marketed modified release form does not seem to mention any comparison of the test and reference product in terms of their comparative alcohol interaction / in vitro performance. (This topic is covered later in Section 6.9 but should be consolidated here.) Proposed change: Recommend text on this topic is added. For example Line 556 could be changed to read "In general, a generic is meant to be bioequivalent with the innovator under fasted and fed conditions, and have similar robustness to e.g. alcohol intake."
542-544	1	Comment: Please specify which reference to choose for development of a generic MR formulation referring to an approved MR product which has not been developed by the originator company, is not part of the global marketing authorization, and has not been approved on the basis of a full dossier. Proposed change: We propose that the article 10.3 (or 8.3 - of Dir 2001/83/EC as last amended) approach be considered acceptable. Additionally, where no reference MR product (originator or alternate) is supported by a full dossier then a marketed reference should be justified and used.
542-543	24	Comment: Please clarify that the term "line extension of an IR originator formulation" includes a scenario where the first MR formulation on the market has not been developed by the originator but by another (generic) company.
548	1	Comment: The term 'same dosage form' should be specified. A capsule and tablet are considered as the same dosage form (defined in the immediate release BE guidance) Proposed change: Please amend as suggested above.
548-550 and 556-561	20	Comment: the two paragraphs are redundant Proposed change: combine paragraphs into one to avoid repetition of the same idea
551-555	25	Comment: The sentence is of a general nature and should be placed in the paragraph similar to par 2. General considerations in the former guideline issued in 1999.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change: Introduce novel paragraph "General considerations".
553	1	Proposed change: "Studies are in general recommended to be conducted in healthy volunteers. However, if it is not possible to conduct studies in healthy volunteers for safety reasons, studies can be conducted in patients, preferably after both single and multiple dose administration in line with recommendations below. If it is not feasible **or is considered unethical** to conduct single dose studies in patients, these can be replaced by multiple dose studies."
556-561	1	Comment: We do not agree with the requirements for a generic product described in this section. Although generic products usually should not differ significantly from the reference medicinal product with regards to efficacy and/or safety, non-inferiority instead of equivalence in terms of safety is generally accepted, e.g. in the current draft guideline for local irritation, phototoxicity, sensitization, and adhesiveness (lines 757-759). Administration of a modified release product under conditions not recommended by the SmPC is to be considered as misuse, therefore non-bioequivalence under such conditions should not be considered as an efficacy parameter (at least same efficacy can be assumed if the food effect of the test product is lower) but as a safety parameter. In consequence, a product which is **not bioequivalent under food conditions not recommended according to the SmPC of the reference products** but shows a lower food effect than the reference should still qualify as a generic product. Such an approach would also be more consistent with guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, according to which food conditions not recommended by the SmPC of the reference product do not even have to be tested for bioequivalence in case of immediate release formulations. While it is acknowledged that for modified release products susceptibility for food might be higher and therefore further studies are needed, a lower food effect for the test product still seems to make a product suitable for a generic submission if bioequivalence has been demonstrated under the conditions recommended by the SmPC. In addition, from our perspective, products that can be administered **under different food conditions according to the SmPC of the reference product** and are bioequivalent only under one condition but show less food effect than the reference product under different food conditions should still be considered efficacious and safe. However, as they are not bioequivalent under all conditions recommended by the SmPC, in this case it is acknowledged that the product might not be suitable as a generic, but is eligible for an Article 10(3) application.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change: Please amend the guideline so as to provide clarity for the above described situations.
556-561	21	Comment: For products where bioequivalence can be shown in the SPC recommended condition but not in the non-recommended state due to less food effect, the product does not fulfil the requirements of a generic product, but could be eligible for an Article 10(3) application. Should 'due to less food effect' not be read as 'due to different food effect'?
556-561	24	Comment: This point was discussed controversially. One position suggested during the conference in Bonn and supported by a number of contributors was that there is no reason to prevent from generic approval if under conditions not covered by the SmPC bioequivalence has not been demonstrated and exposure of the generic product is non-inferior under the non-recommended conditions.
573-576, 656-659	22	Comment: This section does not make any comment on the expectations to establish BE on the various strengths of the generic product (if not proportional) and does not make any comment on the expectations to establish dose proportionality of multiple strengths of generic product. This section also does not provide guidance for assessment of dose-dumping and the effects of alcohol for abbreviated applications. Proposed Change: Please add specifics on these topics to this section.
573 and 657	22	Comment: Please provide clarification whether the reference products have to be sourced from the EU in the BE studies.
574-575	1	Comment: Should high fat meal be used also in cases where light meal is mentioned in the SmPC? Should the fasting study be replaced by a "light meal" fed study? The multiple dose study can be removed if there is no accumulation as discussed above.
579-581	14	Comment: The guidance recommends using a four period crossover trial where both the test and the reference products should be assessed under fasting and fed conditions. Please clarify if the statistical analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison in question. According to the guideline on the investigational of bioequivalence London, 20 January 2010Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *, in studies with more than two treatment arms, the analysis for each comparison should be conducted excluding the data from the treatments that are not relevant for the comparison in question. Should

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		the same rationale be followed for the modified-released products?
Lines 579-581	24	Comment: The design and the evaluation strategy of the 4-way crossover trial require clarification. Proposed change: The study should be performed as a single study with two combined 2-period 2-way crossover parts (Test fed vs. Reference fed in periods 1 and 2 as well as Test fasted vs. Reference fasted in periods 3 and 4) with separate ANOVAs (however food effect analysis is then confounded).
582-587	1	Comment: There is no apparent reason for doing the three-period fed study with the test formulation administered under fasting conditions too. This option is unlikely to be followed, given the option that follows. Proposed change: Please provide explanation or relevance for the extra period of dosing the test formulation under fasting conditions and any difference in criteria in comparison to the option that follows. Alternatively, this option should be removed.
582-587	21	Comment: Single dose studies - Prolonged release formulations for oral administration - The draft guideline proposes the following option to perform the single dose evaluation in fasting and fed state: Two cross-over trials. The first trial should compare the test and reference products under fasting conditions. The study treatments should be administered during two periods and with two sequences of treatment conditions. The second trial should compare the test and reference formulations following the administration of a high-fat meal at a specified time before taking the study treatment, as well as the test formulation under fasting conditions. The trial should be conducted with three periods and three complementary sequences of drug administrations. What is the added value of this option? When would the 3-arm study be required?
582-587	22	Comment: "a single dose fasting study comparing test and reference product" is considered misleading regarding the number of evaluations that may be required for different strengths. Proposed change: "single dose fasting study comparing test and reference product at each strength."

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
582-587	24	Comment: Rationale for this option with one 2-way and one 3-way crossover study is not clear. Proposed change: This option should suggest only one 3-way changeover with Test fed, Test fasted and Reference fasted, provided that for the reference product it has been demonstrated that there is no food effect.
582-587	25	Comment: If two separate 2-periods cross-over trials in fasted and fed state are acceptable as described in lines 588-591, performing 2-period and 3-period study seems to be unethical Proposed change: delete lines 582-587
587	14	Comment: It is recommended that the trial should be conducted with three periods and three complementary sequences of drug administrations. However we should read with three periods and six complementary sequences, since there is a potential of six different sequences with a three-treatment, three-period study. Proposed change: "The trial should be conducted with three periods and six complementary sequences of drug administrations."
592-615	1	Comment: It is suggested to remove the requirement for multiple dose studies, in line with other legislations, e.g. US-FDA.
592-615 593	13	Comment: This paragraph should reflect the above comment that MD studies are required whenever the PK is time-dependent (auto-induction or auto-inhibition). Moreover, the criterion for percentage of AUC(0-τ) relative to AUC(0-∞) should be revised in light of the accumulation that is associated with a given %AUC(0-τ). It can be demonstrated that a value of 20% for %AUC(0-τ) after single administration results in an accumulation ratio of 1.25 (125%) for AUC(0-τ) (steady-state / first administration), which should be considered as acceptable and not relevant degree of accumulation based on definitions in various regulatory guidelines. The criterion of 10% would require the conduct of MD bioequivalence studies although only marginal accumulation is expected (see attached expert statement by Dr. C. Scheerans) Proposed change: A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean AUC(0-τ) after the first dose covers ~~more than 90%~~ at least 80% of mean AUC(0-∞).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
593-595 600-601	1	Comment: If the comment to line 592-615 is not taken into account, the criterion for waiving multiple dose studies should be that AUC(0-τ) after the first dose covers more than 80%, instead of 90%, of mean AUC(0-inf) for both test and reference products. The criterion of 80% is typically employed, as in the previous Health Canada BA/BE Guideline for MR products. Typically, differences of less than +/- 20% are considered clinically non-relevant. Proposed change: Please amend accordingly.
593-599 and 613-615	4	Comment: In order to waive the multiple dose study, AUC(0-tau) after first dose must cover more than 90% of mean AUC(o-inf) for both test and reference and bioequivalence of additional parameters representing the shape of the curve must be demonstrated. Partial AUCs of half of the dosage intervals are recommended, unless otherwise scientifically justified. On the other hand, scientific evidence supporting the use of Ctau equivalence is not considered sufficient. It would be appreciated if the PKWP could publish the scientific justification that supports the requirements from line 593-599. With this information it may be possible to generate the data and appropriate scientific justification for waiving multiple dose studies in specific cases that aligns with the view of the PKWP on what sufficient scientific evidence can be.
593-595	7	Comment: We support the proposal to conduct multiple dose studies unless a single dose study has demonstrated that the mean AUC (0-tau) after the first dose covers more than 90% of the mean AUCinf.
593-601	12	Comment: A multiple dose study should always be conducted, therefore the first paragraph should be deleted. Proposed change for line 600/601: A multiple dose study is required.
593	13	Link to Expert Statement supporting the proposed change (double click): 
593-595	14	Comment: The guidance mentions that "A low extent of accumulation should be demonstrated by an AUC0-t covering more than 90% of the AUC0-∞." We believe that the 90% is a too restrictive criteria to determine the need for a multiple-dose studies. Based on in-house bioequivalence data (on file at inVentiv Health) obtained with prolonged-release products, the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		AUC0-t / AUC0-∞ ratio would be below 90% for the majority of the prolonged-release products. So virtually all prolonged-release products would require a multiple-dose BE study if this criteria is being followed. Proposed change (if any): A low extent of accumulation should be demonstrated by an AUC0-t covering more than 80% of the AUC0-∞.
593-594:	17	Comment: What if the single dose study is not done with the highest dose due to tolerability reasons? Is a multiple dose study mandatory in such cases? Please clarify.
593–595	18	Comment: Less than 10% accumulation is considered overly strict. Note that according to Canada's HPFB/TGD the limit is 20% for more than two decades [sic]. US' FDA and Brazil's ANVISA generally don't require MD studies at all. SD studies are sufficient for Japan's NIHS, although MD studies "may be employed for drugs which are repeatedly administered to patients". Hence, these countries' experiences strongly indicate that no problems are evident. Proposed change: […] more than ~~90~~80% of mean AUC(0-∞) for both test and reference, and consequently a low extent of accumulation is expected.
593-595	19	Comment: A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean AUC after the first dose covers more than 90% of mean AUC for both test and reference, and consequently a low extent of accumulation is expected. Pharmascience comment: 80% should be used as the cut-off for the need of a multiple dose study. Since extent of accumulation is limited even at 80%, Ctau,ss is expected to be low and variable therefore unlikely to be clinically relevant.
593-595	19	Comment: This sentence recommends the need and/or waiver of a steady-state study. In the case of combination products for which one of the compound demonstrates no accumulation and the other compound demonstrates accumulation, is BE assessment at steady-state for only the compound demonstrating accumulation sufficient?
593-595	22	Comment: Under which conditions a 3-period design (item 2) is requested? Specify circumstances when food effect (fed/fasted) has to be performed?
593-600	22	Comment: "A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean AUC(0-τ) after the first dose covers more than 90% of mean AUC(0-∞) for both

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		test and reference, and consequently a low extent of accumulation is expected." This seems overly stringent. While accumulation may be a concern, it should be predictable from single-dose evaluations for a molecule that demonstrates linear PK.
593-595	24	Comment: During the conference in Bonn it was suggested to consider 80 % instead of 90 % as criterion for the need of a multiple dose study with reference to the Canadian guideline.
594 and subsequent text	22	Comment: A multiple dose study should not be necessary if the dose interval is less than the terminal elimination half-life since half-life, not dosage form, generally controls accumulation. An exception would be if terminal elimination half-life does not control accumulation for a particular product. Proposed change to the text (in 'tracked changes' mode): 'A multiple dose study is needed unless […] scientifically justified. **Moreover in cases where the dose interval is less than the terminal elimination half-life a multiple study is not needed since t1/2 will control accumulation, not the dosage form.** In all other cases, where accumulation is likely ($AUC_{(0-\tau)}$ after the first dose covers less than 90% of the mean $AUC_{(0-\infty)}$) a multiple dose study is required.'
594 and subsequent text	20	Comment: AUC0-τ (AUC under the dosing interval?) is not defined unambiguously in the Definitions section Proposed change: Add to definitions section
596-599	11	Comment: In our opinion, in situations when a multiple dose study is not needed, the decision whether partialAUC is to be regarded as a parameter for demonstrating bioequivalence should be made on a case-by-case basis. partialAUC should not be required as primary endpoint for all products tested. Some modified release formulations are designed just to diminish adverse reactions and the shape of the concentration vs. time curve has no clinical significance. In such situations, similarity should be established based on AUC0-t, as the total extent of absorption is the most important issue. partialAUC should be treated as secondary endpoint.
596-599	24	Comment: It is not clear whether the terminal partialAUC should be determined up to τ, t or up to ∞? This point should be

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		clarified.
Lines 596-599	24	Comment: Bioequivalence with regard to partialAUC is required for a waiver of a MD study. If, consequently, partialAUCs are defined in the protocol as BE criteria and eventually fail (while Cmax, AUC(0-t) and AUC(0-∞) pass), does this mean that an MD study is required, or does it mean that the SD study failed? Proposed change: If BE assessment fails for partialAUCs this does not invalidate single-dose BE assessment based on Cmax, AUC(0-t) and AUC(0-∞). However, MD study cannot be waived.
597-599 800 804-805	1	Comment: Apart from requirements for special formulations like biphasic or pulsatile release where the shape of the drug concentration-time profile has been well documented to be related to the clinical effects, partial AUC should be completely removed from the criteria for which bioequivalence has to be demonstrated. Justification: Partial AUC depends mostly on tmax and, to a lesser extent, on other aspects related to the shape of the plasma drug concentration-time curve. However, according to previous regulatory opinion and according to the current draft guideline, tmax is considered less relevant and statistical evaluation is not required. This approach makes sense as extended release products are intended for continuous administration, therefore small differences in tmax are less relevant. However, differences in tmax will in most cases lead to differences in partial AUC as well; therefore it does not seem to be justified to request bioequivalence for this parameter. We consider the shape of the plasma curve to be adequately characterized by AUC, C(max,ss) and C_τ under multiple dose conditions plus AUC and C(max) after single dose administration for assuring bioequivalence. Even in those cases where steady state studies are waived due to insignificant accumulation, the plasma profile should still be adequately characterized by AUC and C(max) as they are very similar under single dose and multiple dose administration and C_τ is of little clinical relevance as the value will be very low anyway. Hence, there is no added justification for requiring bioequivalence for partial AUC in this situation. Proposed change: Please amend accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
597-599	3	Comment: Additional clarity needs to be provided for calculation of early partial AUC and terminal partial AUC.
597-599	7	Comment: As stated above, we encourage the adoption of a shape analysis. The cut-off time point needs to be defined in the protocol, and we suggest that the median tmax be considered (for both single- and multiple-dose studies) rather than half the dosing interval.
Lines 597–599	18	Comment: We are not aware of a single [sic] publication exploring the relevance of a truncation time point at τ/2. Therefore, we are somewhat astounded to read the word "usual" in this context. Please enlighten us. A PK-derived metric could be the inflection point of the profile, which occurs in a one-compartment model at two times the tmax. For an in-depth discussion of relevant metrics see • Endrényi et al., Pharm Res 1998; 15(3): 399–404 • Endrényi and Tóthfalusi, The APPS J 2012; 14(4): 321–5 Proposed change: An early partialAUC and a terminal partialAUC separated by a predefined time point, which should be ~~is usually the half of the dosage interval are recommended, unless otherwise~~ scientifically justified by the applicant. Note 1: Let's call the truncation time point T. For constancy with comments on lines 800 and 804 below, a distinction should be made between delayed release or pulsatile products on one hand, and prolonged release or multiphasic products on the other. For the former in a SD study the terminal partial AUC should be pAUC(T-t) and for the latter pAUC(T-∞). Note 2: For the (lack of) relevance of the terminal pAUC (except for multiphasic products) see comments on lines 804–805 below.
598-599 804-805	1	Comment: It is unclear what the purpose of requiring partial AUC is for the waiver of multiple dose study. The consequences are unclear in cases where partial AUCs are defined in the protocol and eventually fail (while Cmax and AUCt, AUCinf pass). Does it mean that a multiple dose study is required? In this case, a multiple dose study would not make sense as there is no accumulation. Or does it mean that the single dose study failed? It is suggested to allow a waiver of a multiple dose study in cases where there is no accumulation without the need to calculate partial metrics.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Proposed change: Please clarify or remove partial metrics as a prerequisite for waiving the multiple dose study.
598	13	For a drug with a τ of 24 h would the terminal partial AUC be AUC(12-24) or AUC(12-∞)?
598 (and line 800)	22	Comment: AUC0-τ (AUC under the dosing interval?) is not defined unambigously in the Definitions section Proposed change: Add to definitions section
600-601 721-724 741/742	1	Comment (Minor): It does not appear clearly whether multiple-dose or steady-state studies are always required. There are specific cases when steady state is reached only after several months of multiple dosing (e.g. long-acting release formulation with long elimination half-time like t1/2 of 30 days) and it may not be feasible to reach steady state for them. Even if such a study could be performed in a parallel design, high drop-out rates have to be expected. Proposed change (if any): As a parallel to situations when there is no significant accumulation, please introduce a possibility to waive steady state studies in the case of inordinately long accumulation phases. In such cases, a definition of the build-up period that would be considered sufficiently long for waiving a multiple-dose study should be introduced. Please specify the parameters to demonstrate bioequivalence for a long acting intramuscular/subcutaneous depot formulation / TDDS in a multiple dose study. Cmax, Cmin (at the end of dose interval) and AUC(0-τ) of the first dosage interval after the defined build-up period are proposed.
Line 600	13	Proposed change: In all other cases, where accumulation is likely (AUC(0-τ) after the first dose covers less than ~~90%~~80% of mean AUC(0-∞)) [….]
Lines 600–601, 612–615	18	Comment: We consider waiving the MD study based on BE of SD Cτ adequately justified – as long as the drug exhibits linear pharmacokinetics. See the price-winning [sic] paper by Paixão et al., (Eur J Pharmaceut Biopharmaceut 2012; 80(2): 410–7). Contrary to the assertion of García-Arieta et al. (Int J Pharm 2012; 423(2): 321–5) that Cτ is not predictive of MD, the few reported cases demonstrate exactly the opposite. Of the six reported cases failing to show BE in MD, five failed on Cτ in SD as well. We are not a friend of post hoc power, but obviously none of the studies was sufficiently powered (median: 11.8%, quartiles: 3.3–13.4%) to demonstrate BE of Cτ – not unexpected, since at the time of submission Cτ was

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		not a requirement. The remaining case showed an increase of CVw in MD, so the study is inconclusive. We think that this paper present some kind of negative "cherry-picking" since only failing studies were included. Actually, the authors have shown in real examples that C_T is indeed a reliable predictor of MD performance of prolonged release formulations. It might not have been the authors' intention, but in fact, these findings do not refute but rather support the work by Paixão et al. It would have been nice to know how many studies passed. Without this number the relevance of the authors' findings cannot be set into perspective (false positive rate?). We are aware that the simulations are limited to linear PK and about concerns expressed by Endrényi and Tóthfalusi (The AAPS J 2012; 14(4): 813–9 and Int J Clin Pharmacol Ther 2013; 51(6): 525–8). Therefore, waiving the MD BE study should be limited to drugs exhibiting linear PK. Proposed change: In all other cases, where accumulation is likely (AUC(0-τ) after the first dose covers less than ~~90~~80% of mean AUC(0-∞) for both test and reference) and the drug exhibits linear pharmacokinetics, waiving of the multiple dose study is justified if bioequivalence is demonstrated for C_T. If bioequivalence is not demonstrated for C_T a multiple dose study is required. Weak alternative: Mandate applicants to assess C_T in an exploratory manner for a limited time (i.e., market authorisation will not be blocked if the common PK metrics in SD and MD passed, but failed BE for C_T). Collect data and publish (!) the results. Based on the outcome the requirement (waiving or not) can be easily changed in the Q&A-document EMA/618604/2008. The FDA used a similar appoach twenty years ago, when all MR studies had to be of a replicate design – in order to assess the subject-by-formulation interaction. The requirement was lifted after two years. That would be a scientific approach, not reading tea-leaves.
601-603	1	Comment: For prolonged release products taken BID under fasting or fasting and food – steady state studies should be conducted under fasting conditions. In this case, what is the minimum fasting time required before each dose? Practically it would be impossible to fast for the second dose.
602-606	3	Comment: The calorific content of the meal given for the build up prior to the profiling day should be provided.
602	25	Comment: "originator" may be replaced with "reference"

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		Proposed change (if any): originator reference
603	14	Comment: When a multiple-dose study is required, the draft guidance recommends that "If the SmPC states that the product has to be taken in fed condition only the study should be performed in fed conditions…" This recommendation is very similar to the one found in the Guideline on investigation of bioequivalence applicable to immediate-release drug products (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 20 January 2010). This recommendation regarding "fed condition only" should be clarified since this might be interpreted in different ways. In some cases, the instructions with regards to food intake are not very clear in the SmPC, e.g.: the drug product should be taken with food; the drug product should preferably be taken with a meal; it is recommended to take the drug product with food. In such cases, under which food conditions should the study be conducted?
604	1	Comment: If the food effect after high fat-high calorie meal is assessed in the single dose fed study, information of the meal influence on formulation performance is already investigated, therefore additional high fat-high calorie meal assessment in multiple dose study is not relevant in this respect. High fat on the day of profiling only leads to different conditions, so C(0) and C(tau) might be different; in other words: steady state for high fat meal conditions might be different from steady state for light meal. Should high fat meal be used also in cases were light meal is mentioned in the SmPC? Proposed change: Please clarify that the recommendation to assess absorption after high fat-high calorie meal in multiple dose study apply in cases where single dose fed studies with a high fat-high calorie meal could not be performed due to ethical concerns. Otherwise normo-caloric meals should be sufficient throughout the study.
604	17	Comment: The statement "..although it only needs to be high fat high calorie content on the day of profiling" deviates from the application of clinical scenario of the meal composition in the target population and only covers the "worst-case scenario" on the profiling day. Therefore, additional clause on the profiling day can be excluded.
604-606	24	Comment: Extent of food effect is intended to be characterised after single dose, whereas the steady state study is not a food effect study. Thus, it does not make sense to switch to a high-fat meal on the day of profiling while "normal" breakfast is used throughout all other days (during steady state build-up phase.

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		Proposed change: If the SmPC states that the product has to be taken in fed condition only, the study should be performed in fed conditions (standard meal, not high-fat, high-calorie) including the day of profiling.
605-606	24	Comment: Fasting conditions should be specified. Proposed change: Fasting conditions in a multiple dose study need to be adapted to realistic situations, i.e. morning administration requires an 8 hours fasting interval whereas for all other administrations 4 hours fasting prior to administration is sufficient, fasting after each administration should be defined as 2 hours minimum.
608	22	Comment: We would appreciate more guidance for the "predefined time point" and whether both partial AUCs or only a single, most critical partial AUC is under consideration for bioequivalence assessment. The cut-off time point for the partial AUC should be either predefined based upon well established efficacy and safety information or based upon time points (e.g. observed Tmax) of the reference formulation. It should be noted that the cut-off time may differ in fasting and fed conditions of drug product intake. If justified, predefined cut-off time may be adapted based upon the observations with the reference drug product in the study. Bioequivalence of the partial AUCs of the early and late part should ensure that both products are therapeutically equivalent over the daily dosing interval.
609	12	Comment: In case of a flip flop the "terminal half-life" can be misleading. Proposed change: …(at least 5 times the pharmacokinetically relevant half-life).
610-611	1	Comment: What if the drug half-life is extremely long? What is meant by "taking the apparent half-life into account"? Subjects should not be excluded from the statistical analysis if steady state is not achieved and the validity of the multiple dose study should not be compromised if the percentage of individual subject not reaching steady state is less than 20% of the subjects. Proposed change: (if achievement of steady state is deemed to be necessary) "Whether the steady-state has been achieved is assessed by comparing **preferably** at least three pre-dose concentrations for each formulation **or two pre-dose values (plus value at the end of profile)**."
610–611	18	Comment: What is meant by "comparing at least three pre-dose concentrations"? Testing for a significant difference of the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		slope (C vs. t) from zero? Might show a significant result for low variability and otherwise for high variability. Can subjects not being in steady state excluded from the assessment of BE? Proposed change: Clarify / give example(s)
610	20	Comment: A visual inspection should suffice Proposed change: We suggest the following addition: "Whether the steady-state has been achieved is assessed by comparing visually at least three pre-dose concentrations for each formulation".
610-611	24	Comment: Steady state can be demonstrated with two pre- dose values and thus, it is not necessary to have 3 values prior to dosing. If appropriate, post-dose value, i.e. C(tau), can also be taken into consideration as well. Proposed change: Whether the steady state has been achieved is assessed by comparing at least two pre-dose values.
612-615, 723-724	22	Comment: The term "washout" is the correct term to be used here. "..., provided the build up washout period is sufficiently long..."
616	1	Comment: When there are safety concerns of dosing healthy volunteers, a clear guidance should be given for the cases where the higher strengths can only be investigated in patients under multiple dose regimen. In this case, can the bracketing approach be used for two extremes with single dose study being performed on healthy volunteers with the lowest strength and multiple dose study performed on patients with the highest strength? Presumably, the response to this scenario should not depend on the type of the modified release formulation, ie PR/DR single/multi unit. Proposed change: Provide clarification for the situation described above.
620-622, 631-632, 665-666 and 675-676	13	Is a dose proportionality study with all tablet strengths required or are BE studies required for each strength? The guideline is not unambiguous here.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
621-622	1	Comment: If the formulations of various strengths are scaled (proportional), a fasting study on the highest strength only should be adequate if the dissolution of various strengths, when compared to the bio-strength, meets the f2 criterion. Proposed change: Please attempt to harmonise EU requirements on this topic with those existing in other jurisdictions like US FDA and Health Canada, where the requirement of doing a fasting study for strengths other than the highest strength for proportionally formulated products should be taken out if the dissolution of various strengths, when compared to the bio-strength, meets the f2 criterion.
621-622	22	Comment: Request clarification on the use of multiple-dose parameters for single-dose studies. The parameter definitions for single- and multiple-dose PK are unclear.
623-629	22	Comment: According to section 6.6. 'Bracketing approach' this type of approach is clearly possible in a number of cases. So we would suggest replacing "is also possible if justified" with "may be used." Proposed change: 'Fasting state: a single dose study under fasting conditions is required for each strength. However a bracketing approach (see section 6.6) is also possible if justified may be used.'
624-629, 634-639, 668-673, 678-683	24	Comment: If different strengths are proportional in composition as requested in the IR guideline they cannot fulfil the requirement of same size and shape; thus the criterion of same size and shape can only be applied to a deviation from proportionality as defined in the "5% exception rule" (4.1.6. General biowaiver criteria c). However, this seems not to be meant here. There is a need for clarification.
626 and 636	1	Comment: The other strength(s) can be waived 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. Section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) point **d)** states: ''appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing (see section 4.2)'' and section **4.2.2**: ''dissolution should be investigated at different pH values''. Considering complexity of MR dosage forms our suggestion is to add the following sentence in lines 626 and 636: ''For dissolution testing at different pH values (normally pH 1.2, 4.5. and 6.8), preferably with paddle apparatus or basket apparatus, the selected conditions of the method (i.e. medium, volume of the medium, agitation speed) could differ from

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		compendial standards''. Proposed change: Please add the following sentence in lines 626 and 636: ''For dissolution testing at different pH values (normally pH 1.2, 4.5. and 6.8), preferably with paddle apparatus or basket apparatus, the selected conditions of the method (i.e. medium, volume of the medium, agitation speed) could differ from compendial standards''.
626-629, 670-673	21	Comment: Proportional strengths with different size/shape - The guideline is very unclear to which extent those differences towards size and shape must be assessed as being relevant/significant. Some examples in the guideline to be included by EMA/CHMP may be useful.
627-628 637-638 671-672 681-682	1	Comment: Alternatively to the comment to lines 621-622, the possibility of a biowaiver based on a study with a single strength is precluded "if proportional strengths have different size/shape…" This statement is unusual as different strengths of proportional formulations will usually be a different size and most likely a different shape. If applicable the intent behind this statement should be further clarified. Surface area would be deemed a more appropriate parameter upon which to base decisions for biowaiver depending on the mechanism of release. Proposed change: "~~**If proportional strengths have different size/shape two strengths representing the most extreme difference should be tested in vitro and in the fasted or fed state."**~~
630	1	Comment: In case the comment to line 621 is not taken into account, it is suggested to perform the single dose studies required for each strength under fasting conditions irrespective of the intake recommendation. The fasting study is more sensitive to detect formulation differences, while the food conditions reflect the gastrointestinal physiology. A food study with a high fat meal with the highest strength should be regarded as the worst case scenario. Proposed change: Remove line 620 and lines 630-639.
6.1. Prolonged release	22	Comment: It should be sufficient to conduct studies using only one strength if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturer) and

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
formulations for oral administration 6.1.1. Strength(s) to be evaluated 631-632		the dissolution profiles are similar. Moreover it is not possible for composition-proportional strengths NOT to have different sizes. We recommend deleting this requirement. Proposed change: 'Fed state: One single dose bioequivalence study at the highest strength conducted in fed state may be sufficient. The other strength(s) can be waived if the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. A study utilizing one strength should also be sufficient in cases where the strengths are proportional, the formulations contain identical beads or pellets (produced by the same manufacturer) and the dissolution profiles are similar. However, if the strengths of the test product do not fulfil these criteria or if proportional strengths have different size/shape two strengths representing the most extreme difference should be tested in fed state.'
641-642	1	Comment: There should be an option to do the multiple dose study at a lower strength because of safety concern (the highest safe strength) Proposed change: "A multiple dose study should be performed with the highest strength unless it is shown that there is no accumulation as detailed in section 6.1 **or unless there are safety concerns, in that case, a lower strength may be used**.
641	7	Comment: As stated above, we understand the rationale for investigation of the highest dose in multiple dose studies, but for some preparations (e.g. strong opioids) this places a significant burden on healthy volunteers, even when covered by co-administered naltrexone. We hope a clinical justification, avoiding the need for investigation of particularly high doses, would be acceptable.
641-644	24	Comment: Bracketing approach should also be considered here.
642	5	Comment: Or due to safety/tolerability reasons.
650-652	5	Proposed change: Pharmacokinetics
Lines 650-651	22	Comment: According to section 6.6. 'Bracketing approach' this type of approach is clearly possible in a number of cases. So we would suggest replacing "is also possible if justified" with "may be used." Proposed change: Fed state: a single dose study under fed conditions is required for each strength. However, a bracketing

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		approach (see section 6.6) is also possible if justified may be used.
651 and 692	12	Comment: Why are multiple unit MR formulations for substances with linear PK being treated differently than multiple unit delayed release formulations with regard to the recommended strength to be studied ("any strength" versus "highest strength")? It would be more consistent and also better from a bioanalytical point of view to study always the highest dose unless otherwise justified.
660 to 708	22	Comment: In case of multi-strength MR formulation, despite linear PK, differences in absorption or other PK processes may be expected at highest strength. Therefore, instead of demonstrating BE at any dose, BE against the originator formulation should normally be demonstrated at highest strength unless there are clinical reasons for restricting the dose in subjects in a PK study. Proposed change: If the pharmacokinetic of the originator modified release product are linear the studies can be conducted at "highest" strength.
665-666	1	Proposed change: Please attempt to harmonise with other jurisdictions like US FDA and Health Canada. The requirement of doing a fasting study for strengths other than the highest strength for proportionally formulated products should be taken out if the dissolution of various strengths, when compared to the bio-strength, meets the f2 criterion.
Line 656-659	13	Comment: Why is a multiple dose BE study required for prolonged release formulations but not for delayed release formulations? What is required when the test formulation is a DR form and the reference is a PR form?
667-673 677-683	1	Comment: Please clarify how to deal with gastric retentive tablets (like metformin) in which the lower strength usually have a filler to increase tablet size. Does this unique condition qualify for waiver? Proposed change: Please introduce the following requirement: The lower strength qualifies for a biowaiver as long as the dissolution is comparable (f2 at 3 pH's) and the formulations are effectively proportional other than the additional filler.
668 and 678	1	Comment: Please refer also to the general comment section on dissolution media.

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		For delayed release formulation, the usual dissolution buffers applicable to IR formulation are not suitable for obtaining a bio-waiver of additional strength. Rather the two stage dissolution should be used: 2 hours 0.1M Hydrochloric acid followed by 45 minutes Phosphate buffer pH 6.8. So some account should be taken of this regarding conditions specified in 4.1.6
670-673 680-683	1	Proposed change : "However, if the strengths of the test product do not fulfil these criteria ~~**of if proportional strengths have different size/shape**~~ two strengths representing…
Line 671	13	Comment: 'if proportional strengths have different size' is unclear since this seems to apply to every formulation with proportional strength.
674	1	Comment: In case the comment to line 665-666 is not taken into account, it is suggested to perform the single dose studies required for each strength under fasting conditions irrespective of the intake recommendation. The fasting study is more sensitive to detect formulation differences, while the food conditions reflect the gastrointestinal physiology. A food study with a high fat meal with the highest strength should be regarded as the worst case scenario. Proposed change: Remove line 664 and lines 674-683.
684-686	11	Proposed change: When evaluating proportionality in composition, the ~~proportionality~~ similarity of gastro-resistant coating with respect to the surface area (not to core weight) should be considered to have the same gastro-resistance (coating layer in mg/cm2 surface).
691-695	11	Proposed change: Taking into account that the provision is in the section relating to delayed release formulations, please change following sentence: "If the pharmacokinetic of the originator ~~modified~~ delayed release product are non-linear the studies must be conducted with the most sensitive strength as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98)."
697	1	Comment: The described behaviour is not limited to single unit dosage forms, but can also occur for gastro-resistant multiple unit formulations that can be trapped in the stomach by a high fat meal. Suggest change: "Gastric emptying of ~~**single unit**~~ **modified-release** dosage forms …"

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
697-704	13	Comment: How many subjects may be excluded from the analysis? A clear restriction with regard to the percentage is missing. What does "comparable frequency" mean?
699–703	18	Proposed change: Define what a "non-existing concentration profile" is, e.g., less than 5% of the geometric mean AUC of the reference of the study population excluding the presumed outlier(s).
700-701	24	Comment: Clear definition of criteria for a "non-existing profile" needs to be given considering a realistic sampling schedule (see comment referring to lines 705 – 708). Here reference is made to the comment of how long adequate sampling needs to be realised. Proposed change: Non-existing profile within the time of adequate sampling (e.g. up to 12 h postdose).
701-703	1	Proposed change: Define a "non-existent" profile as (e.g. <5% of the reference AUC) in line with the existing definition in the bioequivalence guideline for Immediate Release products.
701-704	3	Comment: If the phenomenon of lack of concentration is observed for a number of subjects, what would be the acceptable percentage of excluded subjects for a particular study. Also if this phenomenon is mainly seen for the reference product.
701-703	24	Comment: The incidence of "outliers" due to delayed gastric emptying is a phenomenon often not related to formulation characteristics but just to coincidence. Limitation of acceptability to the incidence of occurrence after administration of the reference product is not appropriate. Thus, comparable incidence after administration of test and reference should be acceptable.
702	13	Comment: This needs further specification, e.g. how many outliers of the total dataset are acceptable and what "comparable frequency" means.
705-708	24	Comment: The requirement of a proper sampling period should be specified by adequate limitation of such period. Proposed change: Therefore the sampling period should be designed in a way that measurable concentrations are obtained during adequate time period, i.e. for the first 12 hours postdose.
713	1	Comment: In case a biphasic product combines an immediate-release and an modified-release phase, the requirements for studies should be according to each of the phases (i.e. a fasting study for the immediate-release phase and a fasting and

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		fed study for the extended-release phase).
717	8	Comment: Intramuscular preparations are used frequently in psychiatric practice but for two main reasons: first, 'rapid tranquilisation' of acutely agitated patients, often with mania or experiencing acute schizophrenic episodes; and second, in the long-term treatment of patients with schizophrenia, in whom insight is often impaired and treatment adherence only limited. In both groups, most patients will be receiving other psychotropic drugs. Proposed change: Some guidance on the method for determining the pharmacokinetic properties of intramuscular preparations in patients already receiving commonly prescribed drugs might be helpful.
717-724	21	Comment: Intramuscular/Subcutaneous Depot Formulations - Multiple-dose study comparing test and reference products are generally required for depot formulations. In case the drug substance in the depot formulation has a very long half-life can then a steady state study be waived on ethical reasons? In such situation the subjects are exposed to the drug substance for a very long time?
717-724	23	Comment: Bioequivalence criteria Proposed change: Considering the nature of the product, as depot preparations are meant for long period usage (once in a month, once in three months preparations), peak plasma/ serum concentrations may not be of relevance. The extent of the release of the formulation is important and needs to be comparable. Considering this, agency can recommend about the accepting the bioequivalence studies with the comparison of AUC alone for the test and reference products.
719 741-742	1	Comment: In a situation where it is not possible to perform single dose studies with an intramuscular/subcutaneous depot formulation or a TDDS in healthy volunteers for safety reasons, it may also not be feasible to conduct classical single dose studies in patients for ethical reasons neither. To ensure zero pre-dose concentrations and an adequate sampling period for a classical single dose study, a stabilised patient would indeed have to remain untreated or be switched to other medication prior to and after the first dosage interval for study reasons only. This is however unacceptable from an ethical point of view, as it may worsen the underlying disease. It may not be feasible to recruit naive patients who only receive the test or reference product for the first time.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		In patients who are already under treatment with the originator drug, considerable pre-dose concentration of the drug may be present which will compromise the results of a single dose study. Proposed change: Please add the following elements to this section "**In situations where it is not possible to perform single dose studies with an intramuscular/subcutaneous depot formulation or a TDDS in healthy volunteers for safety or ethical reasons, only perform multiple dose studies in patients and allow non steady state end points as discussed above for long half-life drugs or in cases where the delivery rate exceeds the biological half-life of the drug."**
720	1	Comment: A multiple dose study for a depot formulation or implant with a long acting time is not feasible. A definition is needed for the maximum time of application for which a multiple dose study is requested. Alternatively depot formulations or implants should be discussed in a separate paragraph. Proposed change: Please clarify the required time to achieve steady state.
720	14	Comment: For Intramuscular/Subcutaneous Depot Formulations; The guidance requires performing a multiple dose study comparing test and reference products. We consider non-ethic giving multiple doses of these products to normal healthy volunteers and believe that exceptionally, only single dose studies should be performed for these depot formulations. Since the absorption half-life of such products is usually very long (e.g., as it is the case for methylprednisolone, medroxyprogesterone, acetate, octreotide IM, etc.), the subjects would be exposed for a very long period of time to the medication if multiple-dose studies are required, which could raise significant safety concerns. This should not be considered acceptable from an ethical standpoint. Proposed change: For safety concerns, multiple dose studies are not required for Intramuscular/Subcutaneous Depot Formulations.
Line 720	24	Comment: In certain cases, for example very long dosing intervals in case of im/sc depot formulations, it might be sufficient to perform a single dose study only or to investigate multiple dose settings without reaching (and demonstrating) steady state. However, this depends on the type of formulation and thus, should be adequately justified.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
721-722	11	Proposed change: We suggest a rewording of the sentence 721-722 into: "A multiple dose study is needed unless a single dose study has been performed with the highest possible strength (…)". The proposed rewording is caused by the fact that for some active substances single dose studies on the highest strength are impossible to perform due to safety reasons.
721-724	11	Comment: Would comparison of partialAUC (as described in lines 596-599) also be necessary to justify the absence of a steady state study for an intramuscular/ subcutaneous depot formulation?
721-724	11	Comment: Some intramuscular/subcutaneous depot formulations contain active substance with such a prolonged release pharmacokinetics that it is impossible to conduct multiple dose study, therefore, we suggest to enable the possibility of exemption of multiple dose studies for such substances.
721-724	24	Comment: Please clarify whether partial area needs to be determined for these types of products as described for oral prolonged release products in order to justify waiver of the steady state studies.
723	1	Comment: As discussed above in our comments to lines comment on lines 593-595 and 600-601. Proposed change: Change 90% to 80%
724	22	Comment: Apply comments from 6.1 to 6.2.: - We do not see the need for this study generally if the dose interval is less than the terminal elimination half-life since t1/2 will control accumulation, not the dosage form. - According to section 6.6. 'Bracketing approach' this type of approach is clearly possible in a number of cases. So we would suggest replacing "is also possible if justified" with "may be used." Proposed change: - (lines 667-672): 'Fed state: One single dose bioequivalence study at the highest strength conducted in fed state may be sufficient. The other strength(s) can be waived if the criteria described for waiver of strength described in section 4.1.6 of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. A study utilizing one strength should also be sufficient in cases where the strengths are proportional, the formulations contain identical beads or pellets (produced by the same manufacturer) and the dissolution profiles are similar. However, if the strengths of the test product

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		do not fulfil these criteria two strengths representing the most extreme difference should be tested in fed state.' - (line 675): 'Fed state: a single dose study under fed conditions is required for each strength. However a bracketing approach (see section 6.6) is also possible if justified may be used.'
726-727	1	Comment: Please refer also to the general comment section on dissolution media. Details of in vitro dissolution data are included in CMC. Define methodology for dissolution and pHs expected for i.m./s.c. depot formulations (usually liquid formulations). Cross check with quality guideline.
727 - 728	24	Comment: The rationale for the requirement to select the dose "based on pharmacokinetic linearity and safety" only in case of i.m./s.c. depot formulations is unclear as this is not suggested/required for other formulations, e.g. transdermal patches, single unit prolonged and delayed release forms, in other sections of the guideline. Also in these other cases pharmacokinetics is often significantly impacted by formulation properties (flip-flop-pharmacokinetics). Proposed change: The highest strength should be selected in these cases as well.
730-732	1	Comment: In a situation where it is not possible to perform studies with an intramuscular/subcutaneous depot formulation in healthy volunteers in therapeutic dosage for safety reasons: Proposed change: Please add the following to this section: "**In case therapeutic doses cannot be administered to healthy volunteers for safety reasons, non-therapeutic doses are acceptable for safety reasons for a bioequivalence trial if the originator product is marketed in only one concentration and the different doses are achieved by choosing the total volume to be injected and dose proportionality can be shown."**
731	12	Comment: As higher doses usually result in more robust PK profiles, the highest dose should be studied whenever possible.
732	5	Comment: The situation where no dose proportionality is present should be indicated here as well. Probably a bracketing approach can then be used?

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
734-737	7	Comment: We note that, for patch formulations, generics may be permitted to contain a higher drug content than the originator. We would suggest that every effort to reduce the active content of a patch preparation should be encouraged. Proposed change: We believe that a generic patch formulation should not contain more active drug than the originator product.
738-739	1	Comment: It is understood that comparable adhesion has to be shown, however, no confirmatory statistics should be required for adhesion. Proposed change: Replace "non-inferiority in terms of adhesion" with "comparable or better adhesion properties". Replace "adhesion equivalence" with "comparable or better adhesion properties".
738-739	7	Comment: We note the proposal to assess adhesion equivalence (reference also made to non-inferiority, so clarity is requested here). Further details on how these assessments would be made would be helpful, ie, how to conclude equivalence with respect to adhesion scores.
738-744	7	Comment: For BE studies following the adhesion assessment, please provide guidance on whether the taping of any patches that become partially unstuck would be acceptable practice?
738-739	13	Comment: Lines 738 and 739 of the guideline are somewhat contradictory in requesting "non-inferiority in terms of adhesion" on one hand, and "adhesion equivalence" on the other hand. While the first term allows better adhesion of the generic TDDS, the latter excludes this. It is assumed that this "adhesion equivalence/non-inferiority" is expected to be shown in vivo in humans. This might be added for clarification. The term "adhesion equivalence" (if this should be kept) should be defined in more detail to make the expected data package, in particular with respect to number of subjects, transparent. The same would of course apply if non-inferiority would be requested.
738	14	Comment: Regarding the endpoint to be used for the evaluation of non-inferiority in terms of adhesion; Should we use the same endpoint as presented in the Rivastigmine Actavis Guidance (EMA/CHMP/739928/2012)? Please clarify.
738	20	Comment: An in-vitro study to demonstrate adhesion equivalence between a new and a reference TDDS should be fine Proposed change: We then suggest the following change: "Equivalence testing of TDDS should comprise both non-

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		inferiority in terms of adhesion and bioequivalence where adhesion can e.g. be studied using an in-vitro model."
738	22	Comment: Demonstration of BE in a multiple dose study may be redundant for oral drug products 1) if the SD BE study has demonstrated bioequivalence between Test and Reference product in terms of Cmax, AUC and partial AUCs, and 2) if no time-dependent kinetics apply for the reference product and 3) if the drug substance and excipients are qualitatively and quantitatively similar for Test and Reference product. However, for transdermal and intramuscular depot formulations, given that the kinetics are the result of the interplay between drug, excipients and local environment of skin or muscle, respectively, (which may be influenced by excipient-driven inflammation reactions), the time-dependency may be different for a new Test product if the excipients are qualitatively and/or quantitatively different for Test and Reference product. In this case, a multiple dose study may be required in addition to a single dose study.
738-739 797-814	24	Comment: There is a discrepancy regarding equivalence and non-inferiority and affiliation is not clear. This is expected to be clarified in the quality part of the guideline. Furthermore, we would like to emphasize that a better patch adhesion than the originator should be acceptable for the generic product and thus the equivalence approach should not be chosen for patch adhesion. Proposed change: Testing of TDDS should comprise both bioequivalence assessment and comparative characterisation of patch adhesion.
739	20	Comment: The term "adhesion equivalence" is misleading as one is striving for non-inferiority.
739	22	Comment: The term "adhesion equivalence" is misleading as you are striving for non-inferiority.It is not clear if there is a specific meaning for non inferiority of adhesion. For example would a study need to be powered to show non-inferiority? Proposed change: rephrase
741-742	1	Comment: It is suggested to remove the requirement for multiple dose studies for TDDS, in line with other legislations, e.g. US-FDA. Proposed change: Please add the following notion to this section: "**Bioequivalence of TDDS should generally be only**

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		assessed after single dose if there is no significant drug accumulation as described above."
Line 741-742	13	Comment: The questioned rationale of the added value of MD studies, when bioequivalence was shown for SD, as outlined in the comments to line 576, applies also to TDDS. It is proposed to restrict for requirement for a MD bioequivalence study to substance with non-linear pharmacokinetics over time. Proposed change: Bioequivalence of TDDS should generally be assessed after single dose application over the intended wearing period of the TDDS, and in addition after multiple dose application in case of time-dependent pharmacokinetics.
741-742	24	Comment: the requirement of multiple dose studies was controversially discussed during the meeting and the general necessity of multiple dose studies was questioned. One possible approach was to apply similar criteria as for MR formulations for a waiver, however it has to be made sure that the single dose study is predictive for steady state situations.
742	15	Comment: Please consider to waive requirement for multiple dose studies if it can be shown that no accumulation takes place.
743-744	11	Comment: We suggest including a clear description, an explanation of what is meant by 'highly standardized' in the sentence: The application site should be highly standardized and be the same for both test and reference. In our opinion the guideline should provide some criteria for this standardization.
6.5. 743-744	22	Comment: Single dose testing is more sensitive than multiple dose testing. Proposed change: 'Bioequivalence of TDDS should generally be assessed after single dose as these are generally more sensitive than multiple dose studies.'as well as after multiple dose application. .'
746-747	1	Comment: It is puzzling as to why more parameters need to be evaluated for TDDS products than for MR products. Proposed change: "Bioequivalence should be assessed using the same main characteristics and statistical procedures as for prolonged release formulations ~~**including fluctuation**~~. In addition, evaluation of lag-times and profile shape ~~**is recommended**~~ **may be performed if it is clearly documented that they are related to clinical effects."**
749	7	Comment: Type error

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		Proposed change: ...authorisation of multiple strengths is required, a bioequivalence study can be performed...
754	22	Comment: Typically a different site will be used for the cross-over because patches are generally rotated between several sites. Typically sites are allowed a recovery period before reapplication of a patch. Proposed change: 'The study design including the site of application should be justified in terms of its sensitivity to detect formulation differences. The application site should be highly standardized and be the same for both test and reference. Due to rotation of patches between several sites a different site is typically used for the cross-over.'
757-765	25	Comment: Those lines are not connected with title of the paragraph Proposed change: Those lines should be transferred to the paragraph 6.5. (not 6.5.1.)
758-759	1	Comment: It should be further specified when the studies on tolerability, irritation and sensitisation, phototoxicity and adhesion properties are required for a generic patch development. In general, for generic products, it should be sufficient to investigate local tolerance and adhesion properties in the bioequivalence study/studies. In case of a similar qualitative composition to the reference product or in cases where all the used excipients are well-known, additional data should not be required for a generic product. Proposed change: "In order to ensure equivalence in terms of safety **in cases where there are major changes in the qualitative composition of the generic TDDS as compared to the originator TDDS and the added excipients are not well-known,** comparative state-of-the-art studies are required to investigate …"
761	1	Comment: The potential to produce phototoxic reactions should be known for the drug substance and so a justification can be based upon known drug substance data and excipients.
762	5	Comment: The effect of sauna and sun cream should be indicated here as well.
764-765	1	Comment: Both the guideline under review and the draft Guideline on Quality of Transdermal Patches imply the importance of studies to evaluate adhesive performance under normal human behaviours (e.g. in the Annex 2 of the draft Guideline on Quality of Transdermal Patches: moisture resistance to washing, showering, saunas, use of moisturisers, etc.). However, no further details of expectations on study design or criteria for evaluation have been included.

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		Proposed change: We would like both guidelines to clarify that this does not apply to generic patch developments. This should be further elaborated in the guideline under review.
767-774	1	Proposed change: "Where bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition **and/or if dissolution profiles are not similar**, […]"
767-774	13	Comment: For the bracketing approach, is only a single dose, fasting BE study required with the lower strength?
775-776	1	Proposed change: "However, for prolonged release formulations release-controlling excipient should be **qualitatively** the same and mechanism should be the same for all strengths **of the test product**."
6.7. 778 et seq	22	Comment: the text states "similar dissolution / release profiles" but does not clarify what constitutes similarity. Proposed change: Please add clarity on what constitutes similarity.
779	1	Proposed change: Please clarify that "existing dose range" refers to the approved dose range according to the SmPC of the reference product and not to the existing range of available strengths of the reference product (e.g. if the highest dose can only be achieved by administration of two tablets of the highest strength, this dose should still be considered as part of "the existing dose range").
783	1	Proposed change: "A new strength outside the existing **therapeutic** range requires a clinical development."
783	5	Comment: In principle this is agreed, but in case a new higher MR strength is to be used instead of two of a currently registered strength, BE may be sufficient.
783	15	Comment: A lower strength product intended for an indication with a comparable group of patients will most likely show a comparable safety profile. The ethics of repeating safety studies in such a context might be questionable. Proposed change: At the end of line 783, please add the following or comparable wording, "Certain parameters, e.g. skin safety profile for TDDS, may not need to be re-evaluated, if the new strength and the intended indication are not expected to alter the overall safety profile."
783	22	Comment: Regarding 6.7 'New strength for an already approved MR product' if a new strength is developed which is

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		bracketed by other strengths and meets the release-controlling and size/shape requirements and manufacturing requirements, then a new study should not be required because it falls in the category described in Section 6.6 'Bracketing approach'. Proposed change: 'For a new strength with proportional composition to approved strength(s) a bracketing approach may be applicable. For a new strength with non-proportional composition to approved strength(s), the new strength has to meet the requirements as described in relevant sections above (section 6.1-6.5). If a new strength is developed which is bracketed by other strengths and meets the release-controlling and size/shape requirements and manufacturing requirements, then a new study should not be required because it falls in the category described in Section 6.6.'Bracketing approach.'
783	22	Comment: Include the words "dose strength" for clarity. "A new strength outside the existing dose strength range requires a clinical development."
784	22	Comment: It is not clear if the trunctated partial AUC should be derived in the same way for MR and reference IR. Proposed change: specify
786, 787-788	10	Comment: Why should a truncated AUC (0-72h) not be acceptable for oral MR products? The average gastro-intestinal transit time is in the order of 24h, so even taking into account inter-individual variability, absorption cannot occur once the formulation has left the body. This restriction should be limited to TDDS or IM/SC depot administration, if deemed relevant.
786 ff	13	Comment: Although the value of partialAUC is well appreciated, there is no real guidance on how to use it.
787-788	11	Comment: Truncation after 72 hours might be too early for some modified release products, but nevertheless it should be possible to justify a time until when to continue the study, especially for products with very long elimination phase. We propose that for such products, a shortened sampling period covering the whole absorption phase could be considered as justified.
787-788	12	Comment: In case the waiver of a multiple dose study will depend on the proportion of AUCinf covered by AUCtau after a single dose, AUCtau should always be calculated in SD studies.

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787	13	The difficulties in calculating AUC(0-∞) for MR formulations should be acknowledged. It is oftentimes problematic to determine the terminal t1/2 for MR forms due to distal absorption.
787-788	22	Comment: Parameters and criteria to assess dose dumping are not clearly described. We would recommend that some principles are given in the guideline.
6.8.1, 787-88	22	Comment: We would recommend some clarification on whether half-life should be included in the PK parameters following single dose.
788	1	Comment: Unless for multiphasic modified-release products where it is clearly documented in the SmPC that the clinical effect of the drug is related to the shape of the PK profile, the requirement of partial AUC should be excluded. Proposed change: Please remove the requirements of partial AUC.
788	1	Comment: A truncated $AUC_{(0-72h)}$ is not acceptable for MR products however truncation at a later time (predefined timelines), if scientifically justified based on the reported information on the pharmacokinetics of the drug in the SmPC, is acceptable for products with long half-life. Proposed change: The guideline should refer to truncated AUC at 120 hours, 96 hours or 72 hours post Tmax for the different formulations.
788	13	Comment: The partialAUC should be defined more clearly in order to avoid arbitrary case by case definitions.
788	18	Comment: No truncation makes sense for prolonged release products (flip-flop PK). However, this concern is irrelevant for delayed release products. Proposed change: A truncated AUC(0-72h) is not acceptable for ~~MR~~prolonged release products.
788	22	Comment: It is not clear how AUC 0-infininity should be calculated, extrapolation of a terminal elimination phase can in some cases lead to severe overestimations for ER products and it is sometime difficult/impossible to determine a correct elimination half life from ER plasma. Proposed change: It is suggested in such cases the requirement for AUC to infinity is omitted since this aspect is covered by steady state date where AUC 0-t (where t= end of dosing interval) equals AUC0-inf in single dose (if elimination/first

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		pass metabolism is linear and no inhibition/induction).
788	22	Comment: Consider for formulations where the formulations is typically out of the body by 24 hours, AUC (0-72) should be sufficient as the formulation is no longer controlling release. Proposed change: "A truncated AUC (0-72) may be considered as an alternative for comparison of the extent of exposure for formulations that are passed from the body by 24 hours."
788	24	Comment: Use of truncated areas for BE assessment should also be applicable to oral modified release products. However, it is acknowledged that 72h might be too short in this case. Proposed change: Truncation period of 96 h should be adequate for characterisation of oral MR dosage forms.
788	25	Comment: determination of partial areas in all cases seems to be unnecessary and may lead to development of sophisticated MR products to limit competition between manufacturers; not accepting use of AUC(0-72h) in case of oral MR products is a step backwards from BE guideline and leads to unethical duration of PK sampling as well as unnecessary costs for pharmaceutical industry. The concept of AUC(0-72h) is based on gastrointestinal transit time. From the physiological point of view it is not possible for absorption to extend beyond 48-72 hours for oral dosage forms. The assumption is met for MR products also in case absorption limiting factor is gastrointestinal transit time, but not pharmaceutical formulation. Extension of sampling period does not provide additional information in quality of MR product, but leads to increased drop-out and fewer samples taken in more relevant time near tmax. Proposed change: partialAUC and tmax should be determined. A truncated AUC(0-72h) is not acceptable only for non adhesive oral MR products.
789–790	18	Comment: "For multiphasic modified release products additional parameters to be determined include partialAUC, Cmax and tmax in all phases." Consistent with the Q&A document EMA/618604/2008, Section 11. However, since these PK metrics are derived from individual profiles the terminology is somewhat fuzzy. In some individuals the highest concentration is observed at the truncation time point (no distinct trough, but a "shoulder" at its best). Remove these PK metrics – also in order to harmonise with FDA's product-specific guidances for methylphenidate and zol-

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		pidem, where only both pAUCs and the (global) Cmax are required. Proposed change: For multiphasic modified release products additionally ~~parameters to be determined~~ include partialAUC~~, Cmax and tmax~~ in all phases. Note: If the metrics will be kept, it is appreciated that they should not be assessed for BE (i.e., not mentioned in lines 800–814) and only reported. EMA/618604/2008 should be updated accordingly.
789-792	1	Comment: In case the comment to lines 790-800 is not taken into account, it is suggested to limit the requirement for partial metrics to products and conditions (e.g. fasting and fed) where the reference product clearly exhibits a multiphasic profile and where there is clear evidence in the SmPC that the multiphasic profile is required for the efficacy and/or safety of the product. This implies that partial AUC will only be requested for food conditions recommended according to the SmPC. Proposed change: "For multiphasic modified release products **where the reference product clearly exhibits a multiphasic profile and where there is clear evidence in the SmPC that the multiphasic profile is required for the efficacy and/or safety of the product** additional parameters to be determined **for the food conditions recommended according to the SmPC and for under which a multiphasic profile is observed** include…"
789-792	20	Comment: It is not clear if the truncated partial AUC should be derived in the same way for MR and reference IR.
789	22	Comment: Partial AUC should be more clearly defined (e.g. partial from zero to tmax of reference formulation?). Proposed change: Please add clarity on how partial AUCs should be defined and when evaluation of partial areas are expected to be provided (e.g. for rapid onset claims for e.g. dual profile / pulse profile products?)
790-800	1	Comment: Please refer also to the comments above (lines 597-599). Partial AUC has little clinical relevance for MR products (apart from multiphasic products or products with pulsatile release) where differences in Tmax are less important. As partial AUC is not requested for IR products it is hardly understandable why it should be requested for MR products. Proposed change: partial AUC should be removed from the parameters to be assessed.
Lines 791–792	18	Comment: Even for products with two distinct release phases (i.e., a trough is evident in profiles) the time point of the

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		trough varies between studies dependent on the sampling schedule. Such differences might even exist if within the same study profiles are assessed based on the medians, arithmetic, or geometric means. For products like zolpidem extended release tablets determining a truncation time point based on the PK is simply futile. Hence, the truncation time point should be based on PD rather than on the PK. This would also harmonise the GL with FDA's requirements. Proposed change: The time point for truncating the partialAUC should be based on the ~~PK profile for the IR and MR parts respectively~~ pharmacodynamics of the drug/product (early onset and sustainment of effect) and should be justified and pre-specified in the study protocol.
794-796	7	Comment: We feel that clarity is needed on the requirements for assessing Cminss and Ctauss under different circumstances. It is not currently clear from the text that Ctauss is intended as a tool to assess shape at steady state, and may leave the reader unclear why Cminss is required in some cases and Ctauss in others. If Ctauss is required to assess shape for generic applications, does that replace the need to also quantify Cminss in those circumstances or would both be required? Proposed change: Clarify that Ctauss is a shape parameter providing information on the behaviour of the latter phase of the profile. Clarify whether Cminss would also be needed when Ctauss is calculated.
795	3	Comment: The method of calculation of Cmin ss should be clearly defined, as this is very much debatable by different statisticians.
796,801	1	Comment: By stating that C_{TSS} is sufficient for abridged applications, can it be understood that Cmin, where pre-specified in the protocol, would also be accepted as more accurate parameter? Are both options anticipated or only C_{TSS} will be considered as the relevant parameter in generic medicines applications? Proposed change: Multiple dose: AUC_{0-T}, Cmax, C_{TSS} or Cmin
797-805	12	Comment: We consider it important that test formulations exhibit comparable release characteristics to the reference formulations. Therefore, we support the inclusion of the proposed partial AUCs as an additional acceptance criterion in single dose studies.
797-814	13	Comment: For TDDS, "adhesion equivalence" or "non-inferiority in terms of adhesion" (see also comment to lines 738-739)

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		is requested in this draft guideline. It would be beneficial to include the respective acceptance criteria in section 6.8.2 for consistency and transparency.
800	1	Comment: Four co-primary variables need to meet the acceptance criteria for demonstration of bioequivalence (!). Apart from comments on necessity of partial AUC (please refer to comments above, eg, 597-599), the requirement to prove bioequivalence both for AUC(0-t) and AUC(0-inf) puts unjustified additional burden to the applicant which might become very relevant for sample size e.g. for Narrow Therapeutic Index drugs where the 90-111% acceptance range has to be met for AUC). From our perspective, AUC(0-t), which refers to observed concentrations is still the most reliable parameter for demonstrating bioequivalence in AUC also for modified release products. However, if AUC(0-inf) is considered more important for some reasons, then bioequivalence assessment for AUC(0-t) should be removed instead.
800 and 804	1	Comment: For single dose studies, AUCinf is included among the parameters that must meet the BE criteria. However, the AUCinf parameter is not required to meet the BE criteria for IR products and a similar approach should be used for the MR products. Moreover, DR formulations are similar to IR products, with the exception of the enteric coating, and thus should have to meet BE on the same parameters. Proposed change: Remove AUCinf from the list of parameters that need to meet the BE criteria.
800	4	Comment: Please clarify that the partial AUC requirement is only in cases of waiving steady state studies. Since it is already in the corresponding section it does not need to be included here. Proposed change: partial AUC
800	11	Comment: In our opinion, partialAUC should not be included as a mandatory primary parameter for single dose studies of all modified release formulations. Or was it the intention of the guideline that it applied only in those cases where no accumulation is predicted (AUC_T >90% of AUC_∞) and for multiphasic modified release products? In general, we think that the use of partialAUC as primary or secondary endpoint should be judged on a case-by-case basis. The applicant should have a possibility to waive demonstration of bioequivalence for partialAUC if he can justify that potential differences in this parameter would not be clinically relevant.

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800	14	Comment: In single-dose studies on prolonged-release products with risk of accumulation, the guidance recommends to demonstrate bioequivalence by showing equivalence after statistical evaluation of the following parameters: AUC(0-t), AUC0-∞, Cmax, and partialAUC. Should partialAUC be defined as the AUC from time zero to the time of the maximum concentration of the reference product (AUCreftmax), or AUC during a dosing interval, or any other partial AUCs? To avoid any misinterpretation the notion of partial AUC should be clarified in the Guideline document.
800, 804	18	Comment: AUC(0-t) and AUC(0-∞) are highly correlated. Since commonly the variance of the former is higher than the one of the latter, if a study passes AUC(0-∞) likely it will pass AUC(0-t) as well (hint: Intersection-Union Tests). If BE is demonstrated for AUC(0-∞) BE of AUC(0-t) is of no additional value. For prolonged release formulations (flip-flop PK) AUC(0-∞) is the more relevant PK metric. Furthermore, in a linear pharmacokinetic system SD AUC(0-∞) equals MD AUC(0-τ). EMA should not follow FDA's bad practice of requiring both – also in consistency with the IR GL. Proposed change: For delayed release / pulsatile products bioequivalence should be demonstrated after a single dose for AUC(0-t) and for prolonged release / multiphasic products for AUC(0-∞).
800, 804	20	Comment: AUC0-t and AUC0-inf should provide the same information regarding bioequivalence, so statistical analysis of AUC0-t (as more robust parameter) should suffice. Proposed change: Omit AUC0-inf from primary endpoints listed
800	21	Comment: Partial AUC - Section 6.8 of the drafted guideline is too general towards the bioequivalence parameters that are required for the different types of Modified Release formulations. As mentioned in lines 787-788, the bioequivalence parameters AUC(0-t), AUC(0-∞), Cmax, partialAUC are applicable for all types of MR formulations. However, as apparent from the literature, partial AUC would only be applicable for multiphasic formulations and not for prolonged or delayed release drug products. Authorities are asked to indicate more clearly the bioequivalence parameters that are required per Modified Release formulations.
800,	21	Comment: Partial AUC - As it is understood by the applicant, partial AUC shouldn't be a requirement for demonstration of

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
593-606		bioequivalence. On the other hand, partial AUC can be a parameter for justification of waiving a steady-state (multiple-dose) study for prolonged drug products. Considering the partial AUC: - Would it be acceptable to submit a drug product with no risk of accumulation but for which the partial AUC of the Single Dose has failed (and therefore a Steady-State study couldn't be waived) but for which the subsequent Steady-State study has passed? - When truncation is applied to determine partial AUC, there are in fact 2 partial AUC per curve. Would partial AUC as referred to in the draft guideline be defined as for instance AUC0-12h or as AUC12h-∞? - How do the regulators see the requirement of partial AUC bioequivalence testing when the study is performed in fed state and partial AUC is mainly dependent on gastric emptying, which is more dependent on physiological than on formulation factors?
800	22	Comment: Request clarification for multiphase release formulations. What happens if partial AUCs are not BE, but the total AUC is BE? Can the formulations still be deemed BE?
800, 804	22	Comment: Request defining duration for partial AUC. Is equivalence expected for all 4 PK parameters?
800	24	Comment: partialAUC does not make sense as binding criterion for bioequivalence assessment as partialAUC depends mostly on tmax and, to a lesser extent, on other aspects related to the shape of the plasma concentration curve. However, tmax is considered less relevant and its statistical evaluation is not required. Proposed change: Delete this parameter as binding criterion for BE assessment.
800	24	Comment: AUC0-∞ should not be used as parameter for confirmatory analyses for bioequivalence studies because this parameter is always influenced by individual assessment of terminal elimination rate constant. Proposed change: Delete this parameter as binding criterion for BE assessment.
800	25	Comment: If comment to the line 788 is accepted there should be change in required parameters Proposed change: AUC(0-t), AUC(0-∞) or AUC(0-72h) if applicable, Cmax, partialAUC

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
801	1	Comment: The parameter $C_{\tau,SS}$ is usually much more variable than AUC and C_{max} due to its low level. Proposed change: A different criterion should be applied to this parameter. For example, only the point estimate needs to be within 80-125% or only the lower bound of the 90% confidence interval needs to be greater than 80%.
801	22	Comment: AUC0-t and AUC0-inf should provide the same information regarding bioequivalence, so statistical analysis of AUC0-t (as more robust parameter) should suffice. Proposed change: Omit AUC0-inf from primary endpoints listed
Lines 804–805	18	Comment: Depending on the properties of the formulation partial AUCs might not be optimal PK metrics. Example: "Flat" profiles with bad-defined tmax. One alternatives is the plateau time t75% (time interval where C ≥75% of Cmax; aka Peak-Occupancy-Time POT-25). BTW, this metric is mandatory in Russia. Another alternative is the HVD (Half-Value Duration, time interval where C ≥50% of Cmax; aka Peak-Occupancy-Time POT-50). The latter is less variable than the former. Both were already suggested decades ago (e.g., Steinijans et al., Shape Analysis in Single- and Multiple-Dose Studies of Modified Release Products in: Blume HH and KK Midha (eds) Bio-International 2, medpharm Scientific Publishers 1995, Stuttgart, pp 193–206), and an abundance of literature is available – contrary to the terminal pAUC, where we are not aware of anything published so far (except for multiphasic formulations). Instead of single handed introducing a novel PK metric the selection and justification of a suitable shape metric should be left to the applicant. Proposed change: ~~AUC(0-t),~~ AUC(0-∞), Cmax and a representative ~~parameter~~metric of the shape of the curve, e.g., ~~(~~early and terminal partialAUCs~~)~~
804-805	24	Comment: BE assessment for partialAUC is required for a waiver of a MD study. Thus, if partialAUCs are defined in the protocol as BE criteria and fails in a study (while the parameters Cmax, AUC(0-t) and AUC(0-∞) pass), this should not invalidate the positive result of the single dose study. However, MD study will be required. There is a need for clarification.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
805	1	Comment: The requirements of early partial AUC and terminal partial AUC are overly stringent that even the brand product may have trouble passing against itself due to day-to-day variation. Proposed change: Unless for multiphasic modified-release products where it is clearly documented in the SmPC that the clinical effect of the drug is related to the shape of the PK profile, the requirements of these two additional PK parameters should be excluded.
806	1	Comment: The acceptance limit listed is 80% – 125% however reference is made to CPMP/EWP/QWP/1401/98 where the acceptance limit is stated as 80.00% – 125.00%. Proposed change: Please clarify which limit is correct.
Section 6.8.2 806	22	Comment: Partial AUCs are required following single dose studies, but not following multiple dosing. If any multiple dose bioequivalence study would be finally required, it is unclear why no partial AUCs analysis would be required as the shape of the concentration-time profiles may change and lead to compromised safety or efficacy.
806-809	24	Comment: A clear definition of how to perform replicate design studies in steady state is missing. Proposed change: Replicate characterisation of exposure at steady state can be done on two consecutive days.
806-809	24	Comment: The guideline allows application of a widening of acceptance criteria for $C_{\tau,ss}$. In case that widening shall be applied to $C_{\tau,ss}$ only, is it acceptable not to characterise the whole profile twice? There is a need for clarification.
810	1	Comment: The possibility for widening the acceptance range for the specified parameters is appreciated. However, it is not clear how replicate design studies under multiple dose conditions should be performed: Is it sufficient to justify widening by calculation of the intra-subject variability based on two consecutive administrations of the same product in steady state - even if the criterion to wait for 5 x t1/2 (as requested between different treatments according to lines 608/609) is not fulfilled. This aspect is very relevant for products with treatment periods of several weeks and/or long half-life where the treatment period for a replicate design study could be unacceptably long. If consecutive treatments in steady state can be used for widening, please clarify if it is possible as well, assuming that only the acceptance range for C_{TSS} needs to be widened, to use two consecutive C_{TSS} measurements once steady state is

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		reached in a study with non-replicative design.
810	1	Comment: How can acceptance criteria for partial AUC be applied if a definition for partial AUC (definition of cut-off) is missing? Proposed change: In case partial AUC metrics are needed, this should be specified in product specific guidelines together with the proposed cut off to be used. Scaling should also be allowed for partial AUC.
810	18	Comment: The option for scaling pAUCs is highly appreciated.
811-814	13	Comment: The guideline is rather vague with regard to the magnitude of the difference in median tmax. How should the expression "there should be no apparent difference in median tmax and its range between test and reference product" be interpreted?
811	22	Comment: The 80-125% acceptance criteria for bioequivalence may not be appropriate for SC/IM depots (pg 22) which in general do not limit release to just 24 hours like their oral counterparts. While the criteria for AUC is reasonable, it would appear that a broader Cmax range might be appropriate for systems designed to release drug for one week or more. Products designed for long-term release will have variability in Tmax and Cmax. In part this will be due limited time points around the actual Tmax. Having an acceptable AUC while having a Cmax at 130% (or 75%) will not necessarily be an issue for many products. The current criteria will lead to lots being rejected that should be considered acceptable.
811-814	24	Comment: The guideline is rather vague with regard to the acceptable magnitude of the difference in median tmax. Proposed change: However, there should be no clinically relevant difference in median tmax and its range between test and reference product.
812–814	18	Comment: Regrettably nonparametric statistics as the only serious method of assessing tmax was removed from the IR GL, leaving "no apparent difference in median tmax and its variability between test and reference product". What was the rationale to deviate from the IR GL's "variability" to "range" in the MR draft? The range has a breakdown point of zero, i.e., a single value [sic] may change the outcome. In order to be consistent with the IR GL use the same wording. Otherwise

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		publish data or simulations demonstrating that such an approach is more relevant. Proposed change: However, there should be no apparent difference in median tmax and its ~~range~~variability between test and reference product.
813	4	Comment: There should be "no apparent difference" in median tmax and its range between test and reference products can be a very subjective issue. It would prevent many discussions if the PKWP could clarify what they consider "no apparent difference".
815	8	Comment: The Co-morbidity of alcohol use disorders with other forms of mental disorder is very common in psychiatric practice. The pharmacokinetic properties of a substance when co-adminstered with alcohol to a healthy young volunteer may be quite different to the properties when the same drug is given to a patient with alcohol dependence (and the common physical illnesses consequent upon alcohol dependence). Proposed change: It may be unrealistic to request that studies are performed in individuals with prolonged excessive alcohol consumption, but some thought about this, and potentially the inclusion of a qualifying statement might be helpful here.
815–821	18	Comment: The GL should rather concentrate on "intended use" instead of "misuse". Intake together with alcohol might range from "possible" to "almost never". Quite often terminal cancer patients take opiates together with hard liquor. On the other hand chances that this might happen with a pediatric product are negligible. We suggest that this requirement should be case-by-case (i.e., rather dealt in EMA/618604/2008 than in the GL). Contrary to the food effect (as pointed out in lines 558–561 where "better" is not considered "similar" and 2001/83/EC Article 10(3) instead of 10(1) is suggested) we don't think the same should be applicable here. If a generic shows less alcohol-induced dose dumping than the reference, it should still be possible to go with 10(3), or – alternatively – waive the requirement of clinical studies.
816-819	24	Comment: The in-vitro conditions of testing for potential influence of alcohol on drug release should be defined. Furthermore, acceptance criteria need to be defined. Proposed change: Conditions specified in the Q&A document should be included, e.g. 5%, 10% and 20%.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		The duration of testing does not need exceed the normal duration of gastric residence, i.e. 2 hours. Acceptance criteria for an insignificant effect of alcohol should be defined referring to the specifications for batch release.
816-819	24	Comment: So far the guideline suggests that in case that alcohol effect is observed for the generic formulation, reformulation is requested even if the originator exhibits comparable effect. This contradicts the normal requirements of generics and thus, should be modified.
819	22	Comment: It is unclear why delayed or multiphase release formulations would be developed for products where a fast onset of action is important. Suggest deleting the word "delayed." Proposed change: "For delayed and multiphasic release formulations..."
820-821	1	Comment: In general generic medicinal products are developed to mimic as closely as possible the reference product. If there is an alcohol effect which is also present in the reference product, it is to be assumed first that the originator was not able to avoid it by reformulation and second that the lack of clinical relevance had been indeed justified/demonstrated by the originator before. In this case, the relevant question to be addressed by the generic medicine applicant would be the extent of the effect in comparison to the reference, the alcohol effect of the generic not exceeding that of the reference. Proposed change: The applicant should discuss the possible clinical relevance in comparison to the reference product.
820-821	11	Comment: No justification should be provided for generic product if an alcohol effect is observed for the reference product. Furthermore it is not clear what is considered as "alcohol effect" and what would be a comparable effect in the reference product.
820-821	24	Comment: In case that the generic formulation shows a comparable or less pronounced alcohol effect when compared with the originator it should not be the task of the applicant to provide a justification for a lack of clinical relevance. Proposed change: Requirement should be deleted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
838-856	25	Comment: to facilitate reading colons should be deleted and parameters should be listed in alphabetic order Proposed change: colons should be deleted and parameters should be listed in alphabetic order
842	5	Comment: Please define partial AUC more clearly.
Definitions 842	22	Comment: it is noted that the text does not refer to the potential circumstance where the generic product behaves in vitro (in the presence of alcohol) similarly to the innovator product. Such similarity should not necessarily be taken as a guarantor that the two products will behave similarly in vivo (as the release mechanism of the two may differ) and it might be pertinent to recommend in vivo evaluation of the two products in the presence of alcohol. Proposed change: Consider adding text related to additional in vivo comparison.
842	25	Comment: partialAUC may be replaced by pAUC or pAUC Proposed change: partialAUC
846	25	Comment: 1/2 as subscript Proposed change (if any): t1/2
Definitions 847	22	Comment: The definition that "partialAUC" is "partial AUC" is not helpful. As this guideline is a reference document the definition should be more complete. Partial AUC is usually defined as the area under the plasma concentration profile calculated between two specified time points. Proposed change: 'partialAUC: The area under the plasma concentration profile calculated between two specified time points.'
848	25	Comment: subscript "ss" should be added Proposed change: AUC(0-τ),ss
865-867	13	Comment: The term "unless otherwise justified by e.g. very similar quantitative and qualitative composition" is very vague. While it might be justified to consider such waiver in case of the same qualitative and similar quantitative composition of a TDDS, qualitative changes like addition of new ingredients (even in small amounts) might change the sensitisation and

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		irritation properties of such system.
Definitions 856	22	Comment: The correct terminology should be used for 'terminal rate constant'. Proposed change: Terminal elimination rate constant.
857	25	Comment: τ may be added as an additional symbol indicating dosing interval Proposed change: τ dosing interval
858	1	Comment: According to the cross-references from the text of the guideline to this appendix, it appears that the proposed study is required for TDDS developments both of NCEs and of generic products. However, according to line 871, the proposed study design is for generic TDDS. Proposed change: The scope of the appendix and the proposed study design should be further explained and differences, if any, in the study design for NCE TDDS and generic TDDS developments should be addressed.
Line 868	15	Comment: Please add an additional bullet point "safety issues derived from the individual API under investigation"
869	1	Comment: In the section concerning the choice of strength for the evaluation of sensitisation and irritation, the bullet point 'previous human experience' should be elaborated further as the point as it stands is vague.
871	1	Comment: The guideline should allow flexibility with regard to the study design, in order to be suitable for each possible scenario. Proposed change: "**Example of an** Overall Study Design for a generic application"
Lines 871 ff	24	Comment: The confirmatory approach for the irritation study is difficult, the statistical model seems not adapted to the data structure and the clinical relevance of the acceptance limits is not clear. We recommend also against the background of international harmonisation a descriptive approach with a pre-defined number of single independent observations, e.g. a minimum of 30, for which comprehensive experience has been gained. These data could be generated during the bioequivalence trials also, so that further studies for characterisation of skin irritation may not be necessary. Such trials should be realised with the patch of largest size and under circumstances in

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		accordance with the application conditions in the SmPC.
872-873	1	Comment: A simultaneous application of test and reference containing verum patches for several weeks during the induction phase of a study to test sensitisation and irritation may be critical from a safety perspective as the approved labelled amount of API may be exceeded, depending on the strength that has to be investigated. According to lines 749-750, when the marketing authorisation of several strengths is required, bioequivalence studies can be performed with the highest strength, provided that the necessary requirements are fulfilled. In case of safety/tolerability limitations at the highest strength, the use of a lower strength is acceptable for size proportional formulations. If the highest strength has to be investigated in a study to test sensitisation and irritation, simultaneous application of test and reference is impossible as doubled amount of API would be given under off-label use and might have life-threatening side effects (e.g. respiratory depression in opioid containing patches). Please consider if it could be sufficient to perform sensitisation and irritation tests for transdermal products with vehicle patches only. Further information on local dermal tolerability of the verum containing TDDS may be received from the single and multiple dose bioequivalence studies. Proposed change: Please revise the requirement for simultaneous assessment of verum containing test and reference patches. It should be sufficient to perform sensitisation and irritation tests for transdermal products with vehicle patches only.
872, 923-930	1	Comment: What is the purpose of having a placebo arm in the study since the determination of equivalence/non-inferiority does not involve the placebo data? Furthermore, for a generic medicinal product, the comparison with the reference product should be sufficient. It is noteworthy that FDA does not require a placebo arm in a similar study. Proposed change: Exclude the placebo arm.
872-873	24	Comment: There are potential issues associated with testing for sensitisation and irritation using TDDS containing active drug. Simultaneous application of test and reference patches may result in drug exposures significantly higher than

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		intended.
872-873	24	Comment: Sensitisation and irritation tests for transdermal products performed with vehicle patches only should be sufficient and might be considered acceptable.
874-877	13	Comment: These lines describe detailed rules for screening investigations. The extent of screening investigations should, however, be defined in accordance to the safety profile of the individual product. (In contrast, recommendations with respect to specific in-/exclusion criteria are not given.)
874-877	24	Comment: Detailed rules for screening examinations should not be defined in this guideline, but need to be defined in the medical context. Thus, this paragraph should be deleted.
878-879	1	Comment: The statement that data of group 1 and group 2 are evaluated for both cumulative dermal irritation and contact sensitization is contradictory to the tables following lines 906 and 922 according to which group 2 is not evaluated for irritation. From our perspective, all treatment groups should be evaluated for their irritation scores. Proposed change: Please amend text accordingly.
878-879	1	Comment: It is not clear how to define sample size for group 2. If only group 1 is evaluated for irritation, its sample size can be estimated based on the statistical test for equivalence / non-inferiority for irritation scores. However, for group 2 it should be defined which sample size would be expected.
878-892	1	Comment: The proposed administration schemes for group 1 and group 2 need further justification. Why is actual treatment period of the reference product not considered in any of the schemes? Should patches in group 1 always be administered to the same sites as well? Should patches, as explained for group 2 currently, actually be administered to the same site as the previous patch even if the SmPC of the reference suggest different handling? Proposed change: Please amend text accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
878	22	Comment: A more complete definition of lag time would be helpful. Lag time is usually defined as the time taken for a drug to appear in systemic circulation following extravascular administration. Proposed change: lag time; the finite time taken for a drug to appear in systemic circulation following extravascular administration.
879-880	1	Comment: There should be options of applying the patches to other parts of the body (e.g. upper outer arm or upper chest) if permitted by the SmPC. The back of the subjects may not be ideal due to the effect of sleeping position. Proposed change: Test, reference and placebo transdermal patches should be applied to randomly assigned test areas on the backs or other parts, if permitted by the SmPC, of subjects in the two groups.
879-880	15	Comment: The requirement of test areas on the back is possibly contradictory to the requirement given in line 443, where safety testing on the site of application is required.
886	15	Comment: Please allow enough time for assessment after patch removal and application of new patch (cf. line 909) without shifting the time frame of reapplication of patches away from the same hour of day during each visit. Proposed change: Please add for clarification, that the patches will have to be attached for 24 +/-1 h, 48 +/- 1 h, or 72 +/-1 h, respectively.
886	22	Comment: Are these 2 assessments of sensitization really needed? Only one could be kept, the most relevant (either Group 1 or Group 2).
887-892	13	Comment: The proposed concept of the two groups with different frequency of patch change over the 21-day Induction/ Cumulative Irritation Phase might not be applicable to a variety of TDDS. While a 21-day wearing period of the same patch (Group 1) might not be feasible as the patch might detach before the end of this period, the frequent change in Group 2 might result in too stringent conditions because the upper skin layers are injured with each patch removal (stripping effect). The duration of patch wearing should be chosen and justified in accordance to the treatment regimen of the individual product. It might be longer than recommended in SPC, but 21 days might not be feasible or necessary in all cases. The frequency of patch change on a dedicated application site (three times a week over a total of 21 days) might provoke strong effects solely due to mechanical peeling effects during repetitive patch removal. Although it is well

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		understood to also investigate worse case conditions, this is considered a too extreme condition leading to strong mechanically caused irritation rather than really formulation and drug-related conditions. Should the replacement frequency during this 21-day period not depend on the intended wearing period of the product? Why should a 7-day TDDS be replaced after 48 or 72 h in Group 2 or worn over 21 days in Group 1? This might result in unrealistic conditions in both cases. It is proposed to apply the TDDS according to the intended use over 21 days. A differentiation into 2 groups would then not be necessary.
887	22	Comment: It is not clear what kind of information can be gathered from a daily removal of the patch system from an irritation perspective? Irritation can be provoked by repeated removal and hence confound any irritation provoked by the adhesive and/or adhesive and active drug substance. For opioids, for example, would there be a need to study the active drug substance? In general, these studies are difficult to perform with housing of subjects for a very long period of time.
889-892	1	Comment: There is no apparent reason for the need of Group 2 for testing contact sensitization. Since subjects in Group 1 will receive a new patch daily, there should be a greater chance of seeing sensitization of the products than when a new patch is applied only 3 times a week. Hence, if there is any significant difference in induction of contact sensitization in Group 1, it is unlikely to see a difference in Group 2. Proposed change: Exclude Group 2.
889	22	Comment: We would suggest to include a positive control like SLS and to specify that placebo is the adhesive without active drug substance.
902	5	Comment: Since three treatments (of which two active) are given simultaneously, it may be indicated that probably a low strength of the patch should be used in order to avoid potential overdosing.
906 (table)	1	Proposed change: Timelines in terms of test duration in days (i.e. Day 0 to Day 41) should be included for clarity. Likewise, time interval information for skin assessment should be included in order to align the tabulated information with the narrative of the guideline.
907-910	1	Comment: If the next patch is to be applied 1 hour after removal of the previous patch, please specify if the administration

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		period of the new patch can then be reduced by one hour. If not, it can lead to a significant shift in administration times after several administrations.
909	15	Comment: These studies are typically conducted in an ambulatory setting; minimization of waiting time for subjects might be relevant to avoid drop-outs (e.g. when subjects visit the clinic just before work and only have little time.) Proposed change: Please change to "... are applied within 1 hour".
914	1	Comment: Letter scores in Table 2 are mentioned, however, Table 2 uses numerical scores. Proposed change: Please correct as appropriate.
916	1	Comment: The meaning of "Dermal response scores require that at least 25% or more of the patch area demonstrate an observable response" is unclear. Would this mean that a score of 0 (no evidence of irritation) should be recorded when an irritation can only be seen on less than 25% of the area? Please clarify. Proposed change: Please explain.
919	22	Comment: The rationale why in the irritation study the application frequency is different than the frequency indicated by the label is unclear, could this be clarified?
920	1	Comment: Typo in the heading of column 2 in Table 2. Proposed change (if any): ~~**Dermal Response**~~ **Other Effects** Score
922	1	Proposed change: "combined with ~~**another**~~ **other** effects rating of 4 **or greater**."
922	1	Comment: Various typos in the 4th column. Proposed change: Add the "=" sign where appropriate. Also define "mean combined dermal response score".
922 (Table) Second row, last column	1	Comment: It is not clear why both Mean Irritation Score and Total Cumulative Irritation Score have to be assessed as they seem to represent the same data, so the outcome should be similar or identical. The same is true for Dermal Response Score. Please indicate as well how dropouts should be treated (Last Observation Carried Forward?)

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
922 (Table) Last row, last column	1	Comment (Minor): Please explain the meaning of "2:2"
Lines 922 ff	24	Comment: It is not clear why both Mean Irritation Score and Total Cumulative Irritation Score need to be assessed as they seem to represent the same data. Thus, the outcome should be the similar or identical. The same is relevant for Dermal Response Score. Moreover, it should be indicated how dropouts should be treated (Last Observation Carried Forward?).
923-930	1	Comment: The acceptance range (0.8-1.25) would mean that equivalence testing needs to be performed. This is contradictory to lines 757-759, according to which a similar or less degree of local irritation is acceptable. Therefore non-inferiority should be sufficient for comparison of irritation between test and reference product.
924-925	22	Comment: Table 1 Dermal Response Score: Draize score could be more relevant and is not a mix as this one. Title of Table 2 should be "Other effects"
925 ff.	13	Comment: The proposed analysis in Appendix I (ANOVA, with treatment and subject as fixed effects) can be viewed as a t-test on the intra-subject differences. Can the desired results (ratio of least-square means, with associated CIs) be adequately derived from this ANOVA in the case of the summation of average of scores with a very limited range? The analysis method should be critically assessed.
929	1	Comment: How should be the 90% confidence interval calculated for a ratio of untransformed data? Proposed change: Clearly explain the method of calculation or provide a reference for the calculation.
930	15	Comment: Please align with wording in lines 757 and 865. If "sameness" or "equivalence" or "being comparable" is meant, please reconsider the requirement for a statistical evaluation.
934	1	Comment: We do recommend against IVIVC studies as systematic requirements in the case of generic medicines applications.
Line 934 ff.	13	Comment: While an IVIVC is requested for TDDS in line 253 of this guideline, no specific guidance about its technical implementation is provided in Appendix II. When an IVIVC for TDDS should be considered an appropriate requirement (see

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		also comment to line 253), technical details similar as those provided for oral MR formulations should be given in this section. The same applies to implants.
934	22	Comment: We would recommend clarifying the analysis to be performed is for the mean irritation score or for the cumulative irritation score.
941	2	Comment: "clinical relevance" of dissolution could hardly be established, only pharmacokinetics (or in vivo) relevance could. The only case in which a clinical relevance could be established is the existing known and described PK-PD relationship in addition to IVIVC. Proposed change (if any): b) to establish the in vivo relevance of in vitro dissolution tests and associated dissolution specifications
949	2	Comment: "… biowaiver, a validated Level A is a prerequisite" Level C or multiple level C could be used in rare cases even if in case of multiple level C a level A could be attainable (as mentioned in quality section draft 2012). In addition in the 492713/2012 is it mentioned line 495 "multiple level C correlations could be supportive" Proposed change: "… biowaiver, a validated Level A is strongly recommended
936-952	2	Comment: specify in the introduction that the formulation (or in vivo dissolution of the drug even if in this case it is more complex to rightly assess and play on the parameters except particle size) must be the limiting factor and not any physiological processes Proposed change: IVIVC could only be established when the factor controlling the appearance of the drug in the blood flow is linked with the formulation (for example: prolonger release (PR)) or the characteristics of the API (for example slow dissolution of API) and not with any physiological limiting factor (for example rate limited permeation).
943	21	Comment: In vitro in vivo correlation - An IVIVC can be used to support biowaiver claims in later phases of clinical development or post-authorisation if there are changes in formulation. Since extrapolation is not possible beyond the range of formulations tested, does this mean that only formulation changes are allowed that were used to make the formulation faster and slower and as such were taken along in the IVIVC study. If other formulation changes are allowed, which changes are allowed? How far may the new formulation deviate from the formulations used in the IVIVC?

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
946 - 952	16	Comment: FDA guidance notes that multiple level C correlations can be used for setting specifications. Needing to have a validated level A correlation as a prerequisite seems very restrictive. MSD proposes that EMA guidance aligns with FDA guidance and rephrases the wording in line 948 to be less stringent. Proposed change: Where an IVIVC is used to support regulatory decisions such as dissolution specification or biowaiver, a validated level A correlation is a prerequisitepreferable.
954 and 960	2	Comment: 954 "Generally, two or more formulations with sufficiently different dissolution profiles" • too broad wording as release mechanism must be the same between formulations and the different dissolution profiles must not result of a different technologies • in part one (492713) recommend to have at least 10% of difference in dissolution • 960: "the range of formulation" similar concern: must have the same release mechanism between all the formulations. Proposed change: in line 954 Generally, two or more formulations exhibiting the same release mechanism with sufficiently different dissolution profiles…
954 and 960	2	Comment: In certain cases when various strengths are use with non-strictly homothetic formulation (mainly single unit) a huge variation of geometry could exist between formulations even if designed to exhibit the same release. Must that be tested? Proposed change: clarify
954	21	Comment: In vitro in vivo correlation (study design considerations) - The draft guideline indicates: "...two or more formulations with sufficiently different dissolution profiles…" What is minimally considered as sufficiently?
955	2	Comment: Reference formulation: • does that mean that Wagner-Nelson (WN), Lou-Riegelman (LR) or Incremental method (Gerardin et al, J Pharmacokinet Biopham 1983, 11, 401-424) cannot be used as a reference (IR or IV) formulation is a mandatory arm leading to use only deconvolution on convolution based approach as stressed in lines 1024?

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		• For LR the IV is almost mandatory so I agree that between LR and deconvolution the latest is better. • What is the main difference between a one stage approach using differential equations and a model based deconvolution? • Line 1124 and 1125 WN and LR are not excluded when justified. In this case what is the interest of reference? Proposed change: clarify
955 and rest of the document	2	Comment: Reference formulation: Reference is used in the previous part of the guideline as the marketed product (such as in BE study for generic: the originator) as in line 294, 541, 565 and so on. In the present context it could be disturbing to use two different meaning for the same word. In guideline 492713/2012 a definition is given in deconvolution, try to use similar terms ("instantaneous absorption" see below) For injectable obviously IV or IM/SC solution will be the reference Proposed change: replace reference by "instantaneous absorption formulation (UIR): IV bolus oral solution, suspension or rapidly releasing IR" (as per 492713/2012), alternatively, formulation for deconvolution could be used
955	2	Comment: Reference formulation • If an additional arm is mandatory (IR or IV) the generic companies will rarely try to perform IVIVC and to submit them: too expensive in a competitive market • In some rare cases per os IR or solution could be instable in GIT (for example in gastric pH) • In many cases IV is not develop or available on the market
955	22	Comment: We would suggest developing a separate IVIVC guideline because IVIVC is discussed in this guideline and in "Guideline on the quality of oral modified release products".
956	5	Comment: Do we accept modified release products (to determine elimination constant)+literature data on an IR product for the purpose of deconvolution? and literature data only?(e.g. when no IR tablet /solution is available on the market).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Consider dose recommendations for the reference product.
956 and 1003	22	Proposed change: Please consider replacing "for the purpose of deconvolution" with "for the purpose of the estimation of individual drug disposition parameters".
958	2	Comment: "…even if product is recommended to be taken with food" – explain why Proposed change: "… even if product is recommended to be taken with food as the factor to be studied is the formulation effect alone and not the food effect combined with the formulation effect".
958	22	Comment: The statistical analysis used in BE studies takes the advantage of the cross-over design and as a result the power of the study is much greater than that of a parallel design study. However, the analysis used in IVIVC modelling does not take advantage of the cross-over design for the modified release formulations and as a result there is no specific reason to use a cross-over design for an IVIVC study unless the study is both a BE and an IVIVC study. Proposed change: Please consider replacing "Generally, two or more formulations with sufficiently different dissolution profiles and an appropriate reference formulation (for the purpose of deconvolution) with fast drug release (e.g. oral solution or immediate release formulation) are administered in a cross-over study in healthy volunteers." by "Generally, two or more formulations with sufficiently different dissolution profiles are administered in a cross-over or parallel design study in healthy volunteers. In addition, each subject receives an appropriate reference formulation (for the purpose of the estimation of individual drug disposition parameters) with fast drug release (e.g. oral solution or immediate release formulation)."
Line 958:	22	Comment: We would recommend clarification why fasted state is recommended.
963	2	Comment: it is specified here that it is discussed in oral guideline (quality); however, what is proposed is available for all type of formulations – that could be disturbing. Proposed change: This could be applied for IVIVC of injectable slow release, oral prolonged release … and is further discussed in the Guideline on quality of oral modified release product annex I and II and applicable to all type of formulations

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
963, 987	2	Comment: (EMA/CHMP/QWP/467527/2012) is not the right reference or it cannot be found on EMA website Proposed change: (EMA/CHMP/QWP/492713/2012)
964-967	2	Comment: how can selection of formulation/plasma samples to perform the initial IVIVC be based on an hypothetic IVIVC: line 966 "simulated using an assumed IVIVC relationship". I think it could be (i) disturbing why making IVIVC if I can use an hypothetic one, (ii) force to use a direct convolution approach as unique method to (a) select formulation (b) perform afterwards IVIVC (c) force in this case to make a lot of assumptions which are in the field of hypothesis. Proposed change: As the sensitivity of the plasma concentration-time profile for a given drug will depend on its particular disposition properties, it is advisable to base formulation selection on expected plasma concentration-time profiles (simulated using an assumed IVIVC relationship or range of possible relationships and the known disposition characteristics of the drug)
Appendix II, 964-967, 990-999	10	Comment: As written in line 1020, a linear relationship between the in vitro and in vivo release although desirable is unlikely. The example regarding a priori relationship of the IVIVC concerns IM/SC depot formulation. For oral formulations, it is difficult to imagine what the authors have in mind to perform a simulation a priori. Do they imply that a pilot study should be conducted? If this is the case, it should be written explicitly. If not, could the authors be more explicit in how they think this assumed IVIVC can be built up. Proposed change: be more explicit on how to perform the recommended simulation a priori
968	5	Proposed change: Please delete: "or for external validation" because at this moment in the guideline external validation has not been mentioned and it is confusing to mention it here.
970	2	Comment: I do not understand the meaning of the sentence "For this reason, judgement of whether the dissolution profiles for different formulations are "different" is normally based on % of labelled (or actual) content" % of content means content assay and not dissolution profiles for me. Proposed change: For this reason, judgement of whether the dissolution profiles for different formulations are "different" is normally based on f2 test or any other statistical approach. Refers to CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** appendix 1

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		Dissolution testing and Similarity of Dissolution Profiles
972-984	2	Comment: for PR formulations deconvolution vs oral solution results in release + dissolution of the API and the slower of the two phenomena is observed. It is assumed (to perform IVIVC) that the slower is release linked with formulation properties. That is clearly stated in introduction of guideline "Pharmaceutical dosage forms may be developed in which the rate and/or place of release of active substance(s) has in some way been modified compared with conventional release formulations" Proposed change: Clarify
972-984	2	Comment: this part reinforces the use of deconvolution as the only tool vs WN or LR.
972-984	2	Comment: phrase as it is, could only be apply for per os formulations. The guideline is for all formulations including for example injectable; in this last case IV or injectable solution are better than per os solution Proposed change: Clarify
973	1	Comment: What criteria in your opinion should be used for deciding which reference formulation (i.v. solution vs. oral immediate release formulation – solution, tablet,..) to use for deconvolution (as unit impulse function). Namely, in our experience, deconvolution with oral immediate release formulation data (solution or. solid formulations) does not always give meaningful results.
973	22	Comment: The guidance specifically asks for parent drug levels to be measured for IVIVC development. In case of a pro-drug with no pharmacological activity or very short half-life, it is more important to measure the active moiety than the inactive prodrug to assure pharmacological equivalence from future formulations. Proposed change: Parent and/or active drug levels are quantified as a function of time in blood or plasma.
976 + 982	22	Proposed change: Please consider replacing "calculation" with "estimation".
982	5	Comment: "(i.e. for drugs with high permeability)" it may be helpful to specify high permeability a little further or make a cross-reference to literature.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
983-984	2	Comment: does that mean that (i) either the convolution function is going to be change for each new study assuming that scaling and IVIVC remains constant (a priori yes, as mentioned in lines 1095-1103). (ii) or that a correction of bioavailability and functions is allowed for external validations (a priori no in absolute, relative to reference yes). In all cases that means that the IVIVC is study dependent and cannot be seen as a predictive tool, (i) it is dependent of subjects (and their co factors) leading to only use one stage approach assuming that IVIVC and scaling is still correct and that cofactors used were rightly selected (ii) that correcting factor between both references must be applied to all other tests formulations (iii) in case of use of IVIVC as surrogate which of the two convolution set is going to be used the initial (internal pred) or the other (external pred) or a third hypothetic one? Proposed change: review a large part of the "reference" section
983	5	Comment: "A reference formulation…." Should this be the reference formulation?
983 - 984	22	Proposed change: We would recommend adding appropriate guidance to cover the case of solubility and/or permeability limitations.
984	20	Comment: It is not evident why an IR reference treatment is needed for external validation of an IVIVC. Proposed change: Omit "...or external..."
984	22	Comment: We would recommend that the value of physiological based PK modelling approaches to IVIVC be considered, especially for products with solubility and/or permeability limitations.
986-988	2	Comment: 1- In vitro sampling must never be the limiting factor. In addition the interpolations or fitting is better when a maximum of sample is available. 2- What is the meaning of integrated approach is that referring to one stage or to method to select different in vitro techniques? If time scaling is anticipated that correspond to line 964-967 concept. Proposed change: see before *[refer to first comment on this page]*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
992-991-993	2	Comment: same comment as in 964-967 *[refer to second comment on page 95]*
992	2	Comment: • critical dissolution factor is something that must be studied to pre-validate dissolution for its discriminatory power • dpm for apparatus type reciprocal cylinders or flow rate for apparatus type flow through cells should also be mentioned, otherwise it looks like here only paddle or basket are mentioned. • The knowhow of the release mechanisms could help to anticipate such problem: a pH based release will be dependent of pH, an erosion based mechanism on mechanical and hydrodynamic stress (rpm), and so on. That implies that study of release mechanisms and their invariance among formulations is a prerequisite Proposed change: either specify a for example or cite the main usual in vitro apparatuses
997	2	Comment: 1- "time scaling" must be introduced with definition or a reference 2- What is a range of factors do you means a factor named range or a lot of factors used as covariates in one stage approach Proposed change: clarify range of factors
1000-1003	2	Comment: pilot studies to perform IVIVC must anyway be based on intra-subject variability to calculate a number of subject otherwise, • according to line 1065-1067 the dispersion of results will be an handicap for one stage approach • Difference between formulations must be detected if possible, in case of large variability it will not be possible It should be kept in mind that this study is nothing more than a comparative bioavailability study. Proposed change: Although no firm guidance can be given, a pragmatic approach would be to use, with a justification of the number of subject used, no fewer than 12 in a crossover IVIVC study.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
1002	22	Comment: With some modelling approaches it may be possible to establish and validate the IVIVC without including a reference formulation in the study. Proposed change: Please consider replacing "should" with "may".
1012	2	Comment: Agree an unique IVIVC and scaling (time) for all formulations used to establish IVIVC is a must, that underline a similar behaviour (even not at the same rate) between all formulations leading to a similar release mechanism.
1014 - 1016	9	Comment: Physiologically-based pharmacokinetic models provide an approach to predict directly the plasma-concentration time course using in vitro dissolution as an input. The models permit the inclusion of physicochemical, physiological and pharmacokinetic parameters derived from experimental data and as such provide a rational, mechanistic approach to prediction which can be tailored to the known properties of individual molecules to achieve IVIVC. Suggested changes: Two general categories of mathematical approaches to IVIVC modelling are one- and two-stage methods. The two-stage method is deconvolution-based. One stage approaches include convolution based methods, differential equation-based methods and use of mechanistic physiologically-based pharmacokinetic (PBPK) models.
1014	22	Comment: We would recommend that both the between subject and within subject variability (in absorption and disposition) need to be considered in deciding on the number of subjects.
1017	1	Comment: Could you propose one or two non-compartmental methods for deconvolution?
1020-1026	2	Comment: Would be preferable to split this part in various subparts to clarify the working process. 1- Always try first a linear relationship 2- If not working, analyse why: for example faster in vitro dissolution than in vivo absorption => time scaling 3- Try a time scaling; if linear, that means that in vitro and in vivo release mechanism are similar but not have the same rate; if nonlinear, that means that release mechanism are not equal in vitro and in vivo then find the explanation. For example for erodible formulations link with place in the GIT 4- If not a linear time scaling investigate the possibility to set up a new dissolution method more in phase with in vivo

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		results. 5- If nonlinear IVIVC the IVIV relationship must not be over-parameterized and this must be underlined. Nonlinear relationship including a time scaling must not be used as an a priori and initial equation, analyse in this case the consequence for example at time 0 (for example a quadratic could have an intercept which is highly negative). In this case investigate "lag time" scaling etc… Proposed change: propose steps to clarify and limitations
1020-1026	2	Comment: Not clear if work on mg, %D or % FD in vivo. In vitro usually the results are from 0 to 100% which denote the rate of dissolution. In vivo the corresponding would be the %fD (f relative BE to "reference formulation" use for deconvolution). That implies to correct, during the validation and prediction, by this observed f the results. Using % fD assess the rate in vivo and avoid "incomplete" absorption (see also reporting part) Proposed change: propose to work in % fD in vivo and % D in vitro
1021	22	Comment: It is not evident why an IR reference treatment is needed for external validation of an IVIVC. Proposed change: Omit "...or external..."
1025-1026	2	Comment: "Non-linear absorption" is used as a term. In case of non-linear pharmacokinetics IVIVC could not be used as the limiting factor is not only the formulation but physiology in addition. Proposed change: specify that it is link with the formulation example multiphasic release and not with non-linear PK
1025-1026	2	Comment: "absorption cut off" is used as a term. For per os administration in case of windows of absorption =>non linear pharmacokinetics IVIVC could not be used. Do you mean that in vivo per os absorption could not continue more than 18-24h (limit to be fixed)? In this case the f is going to be linked with GI transit time => AUC is wrongly estimated (impact on Cmax usually low). In case of implants or injectable => meaningless Proposed change: specify that it is link with the possible formulation incomplete absorption per os due to GI transit time. You could propose to limit the per os release for simulation (18-24h?) in order to have something that could anticipate

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		incomplete absorption. Vice versa you could propose to test GITT of 18-24-36h to analyse extreme cases.
1026-1027	2	Comment: I do not understand the sentence "Different time scales for each formulation points to the absence of a single relationship for the IVIVC formulations." That is obviously the cases in which IVIVC could not be used/validated as either the release mechanism are not similar or PK is not linear Proposed change: specify
1028-1033	2	Comment: agree totally, that highlights the usefulness to start always with a two-step approach to understand the processes, correct factors to be included and to analyse the various relationships. That means that the fact to use a two stage approach before any one stage approach is somehow mandatory. That must be highlighted. Only when the two stage is validated and robust, a one stage could be used for example to fix dissolution limits but that is an option and not mandatory. Proposed change: propose steps to develop validate and when to use the various approaches. Highlight from the beginning that the two stages (or steps) is the starting point.
1034	1	Comment: Why is the differential equation-based method (compartmental approach) classified as a single stage method only? Cannot it also be used for deconvolution-based approach, if non-compartmental methods or classical compartmental methods (Wagner-Nelson, Loo-Riegelman) do not show as adequate (e.g. instability of obtained results)?
1034-1067	2	Comment: One problem of the convolution based approach is that need an a priori knowhow of (i) the type of absorption (often modelling of absorption is mandatory), (ii) the type of relation (linear, non-linear), (iii) the possible time scaling (linear, non-linear), (iv) and depending of the software used the possibility to implement subject specifics cofactors (sex, etc…) or formulations, drug (API) cofactors. It is a less self-understanding and simple method. It could lead to numerous errors if wrongly handled (example absorption and dissolution modelling should be entered initially in the system) and less simple to see where the errors could be. Somehow with a wrongly tuned One stage, an IVIVC could always be found. In addition one stage required, in addition to PK, formulation and dissolution knowhow a good statistical background not to

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		lead to bad tuning of the software and/or function used. Proposed change: mention clearly that it might not be the best first approach. It is a useful tool when the problems were identified and the knowhow of in vitro and in vivo behaviour of the drug known. For example, it could be a god tool to set dissolution limits at the end. Anyway a two-steps approach can be used if validated even as in vivo surrogate tool.
1042	22	Comment: We would appreciate clarification as to why a linear relationship is desirable.
1049-1051	9	Comment: The differential equation-based approach utilises a traditional compartmental model framework for drug disposition and incorporates an input function. Alternatively, a physiologically-based pharmacokinetic (PBPK) model may be used. The PBPK model should be mechanistic and have sufficient experimental data to adequately describe the absorption, metabolism, distribution, and elimination phases of the drug being tested. As with the differential equation based convolution method, a PBPK approach uses the in vitro release profile as input into the model and a plasma profile will be generated that predicts the in vivo performance of the formulation. Crison, John, R., Timmins, Peter, Keung, Anther, Upreti, Vijay, V., Boulton, David, W., Scheer, Barry, J. 2012. Biowaiver Approach for Biopharmaceutics Classification System Class 3 Compound Metformin Hydrochloride using In Silico Modeling. J. Pharm Sci 101(50):1773-1782. 2. Brown J.R., Chien C., Timmins P., Dennis A, Doll W., Sandefer E., Page R., Nettles R., Grasela D. Compartmental Absorption Modelling and Site of Absorption Studies to Determine Feasibility of an Extended-Release Formulation of an HIV-1 Attachment Inhibitor Phosphate Ester Prodrug. J. Pharm Sci 102 (6): 1742-1751
1061	22	Proposed change: Please note that "differential based" should be "differential equation-based" in this sentence.
1062-1063	2	Comment: "This approach does not address adequately random variation in vitro……." Using average in vitro profiles is either logic or normal. 1- Dissolution variability is low in a majority of cases and should be lower than in vivo especially for PR formulations. 2- Individual dissolution cannot be paired to specific subject (i.e. is subject x having be dosed with a low or high dissolution tablet).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		3- If dissolution is very variable that means either a formulation, production or dissolution problem. 4- Other test (i.e. f2) is based on average dissolution with CV (RSD) values <20% first points and < 10% other points. 5- Other guidelines fix dissolution limits at max 6- In practice the leaflet never mentions that content could be 95-105% at max and depending tablet the efficacy and safety is modified and that patient must pay attention to it! 7- In practice it is assumed that all tablets give, as a mean, similar in vivo behaviour Proposed change: use of average dissolution is considered as usual.
1062-1067	2	Comment: the way it is presented seems to say that the only method to integrate variability is a one stage with non-linear mixed model => does that mean that EMA discourage other methods or strongly recommended only the one stage? If yes that is dangerous as the two stages (as mentioned earlier in the guideline) is the best way to analyse the initial data to understand the processes and is often more robust. Two stages could fail but hardly gives a wrong IVIVC (or it is obvious in this case when analysing the results). Proposed change: modify the sentence
1062-1070	5	Comment: "Most IVIVC analyses…. Concentration-time profiles." This seems more a IVIVC model qualification. Proposed change: It is proposed to move this paragraph to section 3.3 between lines 1080 and 1081.
1063-1064	22	Comment: Please consider either deleting this model equation or giving a more complete explanation of each of the terms and the way in which they are combined.
1064	2	Comment: "This approach does not address adequately random variation …… in vivo." The in vivo variation could be address in two-steps as the inter and intra individual variability is known from the BA study performed to initiate IVIVC. Inter-individual variability is linked with parameters intrinsic to the subject (metabolizer status, sex for example) and not,

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		or hardly, with formulation. Intra-individual variability is linked with various parameters and for example API, PK behaviour (and not formulation). Only this intra subject variability is of importance for BA/BE comparison as it is used to construct 90% CI for example. Knowing those two sources of variability either the difference between subjects could be anticipated but also the 90% CI be reconstructed around the estimated parameter vs. the target formulation ratio. Variability could be considered with the new formulation to be close to the tested one (for intra subject). So way to handle this problem exists. Proposed change: Clarify
1064-1067	2	Comment: "individualizing" the individual variability with a mixed effect analysis will improve predictability but means that cofactors could be included (subject or formulation dependent) or that somehow one IVIVC is made by subject …? IVIVC must be an universal tool to predict all cases and is not adapted to HVD.
1068-1070	2	Comment: Averaging before or after deconvolution would lead to almost similar results. The first thing to know before averaging is whether all subjects behave in a similar way in the absorption part of the curve (for example analysis of Tmax range, median and mean). If averaging is nonsense, in this case a one-step approach with incorporation of individual variability is a good way to solve the problem assuming that the right cofactors are known and included ... but how could a new formulation be predicted if results are so subject dependent?
1072-1074	2	Comment: this is a prerequisite which must be highlighted before
1074-1080	2	Comment: as before highlighting the use of one stage approach. Something more open should be given.
1078	2	Comment: graphic observed and predicted … what the criterion to assess goodness of prediction is? Proposed change: for example two graphics: predicted vs observed and slope analysis vs 1, second graphic observed and predicted vs time with 90 or 95% CI of mean on observed for each points and predicted values in this envelop
Appendix II,	10	Comment: Compared to previous guidelines on IVIVC, an additional parameter partial AUC is mentioned here. Given that

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
1079-1080		the PE for C max and AUC (0-t) need to be within the range for the 3 formulations + for the external validation, is this additional parameter really necessary? Proposed change (if any): remove partial AUC
1080	2	Comment: 1- partialAUC 2- In 6.8.1 partial AUC is not defined, in addition 6.8.1 refers to "generic" and not to NCE, partial AUC is mainly used for bi/multiphasic releases. Proposed change (if any): 1- Either partial AUC or AUCpartial Defined when partial can be used
1081-1082	2	Comment: "visual comparison", could that be considered as a scientific way to assess goodness of prediction? 2- Proposed change (if any): see comments on line 1078
1082	5	Comment: "within acceptable limits." Could the limits be specified, what is considered acceptable?
1088-1090	5	Proposed change: Please modify: The absolute value of the prediction error for all summary parameters should be less than 15% for each formulation and on the average for all formulations …..
1088 to 1090	22	Comment: Clarification: In a two stage approach, for the prediction of profiles: is it acceptable to use mean in vitro dissolution data and IVIVC to predict mean absorption and then use individual UIR to predict individual profiles. Proposed change: Please provide additional clarification.
1090	2	Comment: the average of % PE must be made on absolute values of each %PE Proposed change: average absolute percent prediction error (%PE) <10% for Cmax and AUC, plus %PE for each

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		formulation <15%
1091	2	Comment: must have a reason to discard a formulation as that could be a sign of non-robustness of IVIVC. One reason could be a different release mechanism (made or not on purpose!). In addition at least 2 formulations must remain. See line 954 and on-going Proposed change: Where an individual formulation is found to be inadequately predicted by the IVIVC, it is acceptable to redevelop the IVIVC excluding the outlier formulation, resulting in a narrower range of dissolution data included in the IVIVC. However at least two formulations must remain and the reason of exclusion justified based on either technological difference (release technology or production process) or outside of formulation range (too extreme variations). Refers to "2 Study Design Considerations".
1095	1	Comment: In which cases should external predictability (which means additional study, again with administration of reference formulation) be used in addition to internal predictability?
1095-1103	2	Comment: 1- That means that external validation is mandatory to use IVIVC as in vivo surrogate? 2- Why absolute value of prediction as no mean is made (stated each formulation)? 3- Explanation of the "reference" as an arm is found only here but introduced in 955 4- Suppose that IVIVC, scaling etc. are not linked with subjects groups (hopefully not) Proposed change: %PE <10% for Cmax and AUC or each formulation Explain use of the reference formulation
1095-1103	5	Comment: It may be added that if only two formulations have been used to establish an IVIVC, external validation should be conducted.
1098	5	Comment: What validation steps of the IVIVC are required? Internal predictability, external predictability, variability of the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		dissolution data/variability of the PK data etc.? It is difficult to use this Annex 2 for assessment of an IVIVC as the applicant can decide on the content of the IVIVC report.
1099-1100	1	Comment: The administration of the reference IR product with the external validation batch should be optional since the data for the external validation batch may be obtained as a part of a larger bioavailability study. Proposed change: The requirement for the prediction to be based on the reference IR product pharmacokinetics observed in the study used for external validation purposes should be taken out.
1103	5	Comment: "… than 10% for…" Should this be 15%? For internal predictability the prediction error for an individual formulation should be 15%, therefore, it seems that for an external predictability the margin is also 15%.
1103	22	Comment: The values of 15% and 10% appear to be arbitrary. We would appreciate some clarification and references about these values.
1111-1118	2	Comment: As mentioned before, in vitro dissolution are often express in % D or in mg up to labelled dose, amount absorbed is in mg corrected by relative BA (f) vs. "reference" after deconvolution, rate will be in mg/h. To have comparable graphics and overlay graphics it may be more interesting to compare in vivo %fD and in vitro %D as in this case the superimposition is simpler to assess. In addition a linear relationship between the two parameters would lead to a 1:1 relationship if both rates are equivalent. Proposed change: propose % fD in vivo vs %D in vitro
Line 1111-1118	13	If Appendix II should be intended also for TDDS or implants, an IVIVC might be based on ex vivo residual content data. The proposed graphical displays might show a high data variability for time points, when only a fraction of the entire content of the product has been released during its wearing period. The respective expectations might be considered to be described in more detail (together with other information relevant for an IVIVC of TDDS or implants).
1111	22	Comment: It seems counterintuitive that the acceptance criterion for external validation (10%) is more stringent than that for internal validation. We would appreciate some clarification for this more stringent criterion.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
1117	2	Comment: 1- What is an obvious time difference? 2- Levy plot could denote a real time scaling but also a difference in release mechanism between vitro and vivo Proposed change: try to quantify obvious using the %PE with and without time scaling or f2 between %fD vivo and %D vitro vs time?
1150	22	Proposed change: Please consider inserting "cumulative" before "dissolution".
1150-1182	25	Comment: introducing of tables was an excellent idea Proposed change: 3 tables will fit in one page
1153 – MD study 1163– MD study	1	Comment: Fasting multiple dose study should be mentioned Proposed change: Please amend accordingly.
1156 – MD study 1165– MD study	1	Comment: Fed multiple dose study should be mentioned. Proposed change: Please amend accordingly.
1162-1168	25	Comment: both tables are identical and should be merged while title should be changed; the tables are not in accordance with line 651-654 indicating other options or requirements Proposed change: Prolonged release multiple unit formulation (SmPC recommends intake under fasting or fasting and fed conditions)
1178-1182	25	Comment: both tables are identical and should be merged while title should be changed Proposed change: Prolonged release multiple unit formulation (SmPC recommends intake under fasting or fasting and fed conditions)
General	7	Comment: We would welcome a brief statement relating to fixed-dose combinations. Where a modified release preparation contains two or more active ingredients, a generic formulation should demonstrate bioequivalence to the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes
		originator product in relation to all active components.
General	7	Comment: There is currently a lack of clarity on the requirement for partial AUC shape assessments in single dose studies. Proposed change: Provide guidance on the requirement (or lack of requirement) for shape assessment other than for when biphasic products or the effect of food are being assessed. Specifically, for the development of a generic product, is the assessment of the shape of the fasted profile recommended in relation to the reference product?
General	8	Comment: Many patients with long-term conditions (including those with severe mental illnesses) are only irregularly compliant with prescribed medication, often missing a few days of treatment, then taking more than recommended, to 'catch up' with prescriptions. It may be uncertain whether the pharmacokinetic properties of a drug in only irregularly compliant patients are similar to those seen in closely observed healthy volunteers in pharmacokinetic studies. Proposed change: It seems sensible to consider whether investigations should take account of the potential for intermittent or erratic treatment adherence, when developing new drug formulations.