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Overview of comments received on ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022)

Please note that comments will be sent to the ICH M13A EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	0	0	General	In general, this guidance does not align well with the estimand thinking process otherwise promoted in ICH E9 (R1). Incorporating the estimand framework in this guidance would make the choices pertaining to study populations and the data used for making claims much more transparent. For instance, the concept of intercurrent events should be introduced to benefit the guidance around exactly what treatment effect is targeted.	
EFPIA	0	0	General	At the end of the day, we must follow what HA gudiance say therefore what is the overall suggestion if this guidance contradicts a HA guidance?	Recommend to comment on this in the document.
Adamed Pharma SA	0	0	general	In accordance with the EMA GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE: "The use of urinary excretion data as a surrogate for a plasma concentration may be acceptable in determining the extent of exposure where it is not possible to reliably measure the plasma concentration-time profile of parent compound." Will it still be possible to use urinary data to support conlusion about bioequivalence according to ICH M13A? If such a solution will be still possible, in our opinion, the document should specify the pharmacokinetic parameters on the basis of which bioequivalence will be demonstrated as well as clarify for which compounds will it apply. In addition in the current BE guideline there are useful recommendations on urine sampling and urinary PK parameters which were removed from the M13A.	

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European Industrial Pharmacists Group (EIPG)	0	0		compared to the previous guideline (Guideline On The Investigation Of Bioequivalence - CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **20 January 2010), which reported the possibility of conducting the study in two stages, in this ICH Guideline M13A this design is not proposed nor mentioned. In the previous version, the following text was present: It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analysed. If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis. If this approach is adopted appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be clearly defined before the study. The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%). For example, using 94.12% confidence intervals for both the analysis of stage 1 and the combined data from stage 1 and stage 2 would be acceptable, but there are many acceptable alternatives and the choice of how much alpha to spend at the interim analysis is at the company's discretion. The plan to use a two-stage approach must be pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses. When analysing the combined data from the two stages, a term for the stage should be included in the ANOVA model. As the possibility of conducting the study in two stages is not indicated, it is not possible to do a first run with several subjects and then make the evaluation of the result with a penalty (94.12% CI instead of 90%). If I have BE I do not continue if not recalculation of the sample and treatment of the additional subjects and then final statistics always with 94.12% CI.The possibility of applying a two-stage design would be a really interesting aspect because there are many situations in which this approach is used which, moreover, could facilitate the conduct of the study by reducing the time of its execution. Moreover, it is well specified by the statistical literature how it is possible to adequately control the error of the first type and not incur incorrect conclusions	To reinstate the 2 stage study process possibility
ORBIS project	0	0		The ORBIS project members are pleased to have been given the opportunity to comment on the draft ICH guideline under public consultation by the EMA. ORBIS project is supported by the European Union under Horizon 2020 (Marie Skłodowska-Curie grant agreement No 778051). ORBIS consortium - led by prof. Janina Lulek - consists of universities, pharmaceutical companies and R&D enterprises. The team involved in this public consultation includes representatives of the Poznan University of Medical Sciences (Poznań, Poland), Celon Pharma S.A. - Pharmaceutical Company (Warsaw, Poland), University of Ljubljana (Ljubljana, Slovenia) Note: The comments presented below are those of the authors and do not necessarily reflect the European Union's or the respective institution's position on the subject.	Legend: <u>underlined</u> - new text added; ~~crossed out~~ - text deleted
ORBIS project	0	0		We greatly appreciate harmonisation of bioequivalence recommendations by the ICH. It is an important step to increase supply of high-quality medicines for the global community of patients. It also has a positive ethical impact as reducing number of duplicated bioequivalence studies will reduce unnecessary exposure of healthy subjects to clinical studies of medicines. We express our gratitude to all persons involved in moving forward harmonisation of bioequivalence, including the team preparing the draft version of ICH M13A guideline. We hope our comments below will be helpful for optimisation of guideline content.	none
ORBIS project	0	0		Our general view is that current EMA Bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) is better structured and better facilitates planning BE study than draft ICH M13A. It is also more transparent regarding criteria for deciding which studies are necessary.	Better match titles and content of paragraphs. Avoid any ambiguities related to study design.
ORBIS project	0	0		The Pharmaceutical Strategy for Europe (European Commission, 2020) states: "Generic and biosimilar medicines provide a large number of patients with accessible and affordable treatments. They also allow health systems potential savings in costs through their positive effect on pricing competition". For immediate-release solid oral dosage forms with systemic action, we should promote that a single bioequivalence study is sufficient if biowaiver is not applicable. The ICH M13A adds additional costly barriers for generics to enter the market in some cases (not specified in detail): both fasting and fed studies and pH-dependence study, two doses studied in case of non-linear PK. This increases uncertainty of regulatory requirements and cost of generic immediate-release solid oral dosage forms development. In turn, it may influence company decisions on launching new generics. In consequence, it may decrease generic competition and patient access to medicines. Imposing new barriers is contrary to current geopolitical situation. The latter one suggests that support of the European pharmaceutical industry is critical, especially because of dependence on API supply from East Asia. Summing up, implementation of ICH M13A in its current form seems to be not in line with Pharmaceutical Strategy for Europe.	Avoid more than one BE study recommended for a single generic if it is orally administered immediate-release solid oral dosage form. Specify cases where additional BE studies are required by listing APIs, pharmaceutical forms and excipients in dedicated appendices.

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ORBIS project	0	0		We express our concerns that the draft ICH M13A guideline may not achieve its goal of harmonisation due to numerous paragraphs with unclear decision criteria. They may be interpreted by regional Regulatory Authorities in the different way for particular products. This issue is particularly important for the number and conditions of BE studies recommended (fasting, fed, pH-dependence) or pAUC (addition of this PK parameter may change required sample size). We acknowledge that general rules cannot cover all specific cases, but adding list of specific cases in appendices or ICH-harmonised product specific guidelines could be a solution here. Appendices or ICH harmonised product specific guidelines could be reviewed and supplemented periodically by ICH members or a working group. In case of difficulties in harmonising rules for "specific cases", please consider defining "immediate-release solid oral dosage forms" in such a way, that more complicated formulations will be out of scope of the guideline. It would be better to have applicable guideline harmonised only for typical cases than have uncertain rules (precluding true harmonisation) for all cases.	Adding appendices (or establishing ICH-harmonised product specific guidelines) with specific cases, e.g. when fed or pH-dependent study is recommended. Exclude "specific cases" from the scope of the guideline by appropriate definition of "immediate-release solid oral dosage forms".
ORBIS project	0	0		Addition of decision schemes would greatly facilitate the same interpretation of guideline by all stakeholders. This is especially important for number of studies recommended and their conditions. Numbered lists (e.g. lines 260-263) would increase readability of the guideline.	Adding decision schemes and numbered lists.
ORBIS project	0	0		We have observed discrepancies in terminology with 'Guideline on the investigation of Bioequivalence': 'comparator product' is used instead of well-established 'reference product'. We suggest consistent use of the term 'reference product', as a specific type of comparator product, instead of the term 'comparator product'. Listing 'placebo' in definition of comparator product in Line 651 is not applicable to BE studies. Please also consider that in case of introducing "comparator" instead of "reference", the well-established T/R ratio changes to T/C ratio. The latter term may be confusing by suggesting some relation between Concentration (C) and time (T), both important in BE studies with primary PK endpoints.	comparator product => reference product

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	3	6	Section 1.1	This guideline is intended to provide recommendations on conducting bioequivalence (BE) studies during both development and post approval phases for orally administered immediate-release (IR) solid oral dosage forms designed to deliver drugs to the systemic circulation, such as tablets, capsules, and granules/powders for oral suspension.	In a pre-approval scenario i.e., during development – is a BE needed or would an adequately powered rBA study suffice? Please clarify whether the statement above is specifically for generics or applies to NCEs?
SciencePharma, Poland	3	6	1	There is no information in the draft Guideline regarding the oral solutions or parenteral products.	Is is suggested to add information regarding the reuirements for parenteral formulations and oral solutions as in the current CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** guideline.
EFPIA	15	15	1.2.1	The reference to non-oral drugs with "immediate action" is equivocal. BE studies rely on systemic exposure comparison, independently of the mechanism of action, direct or indirect, immediate or delayed.	Delete "… with immediate action…" (TL/SH: immediate rlease)
EFPIA	17	21	1.2.1	It would be beneficial in the introduction section it is explained that bioequivalence is recognized surrogate for therapeutic equivalence if PK/PD correlation is established (among other purposes of BE), as this is not defined in any document. So, it would be nice if ICH guideline would finally address that gap	
EFPIA	18	20	Section 1.2.1	In addition, there may be situations in new (innovator) drug development when demonstration of BE may be critical for approval decisions.	Please provide examples when BE is critical for new (innovator) approval decisions
EFPIA	22	23	1.2.1	It is not bioavailability that should be the same, it should be exposure after absorption, as there could be situations where bioavailability between two formulations could differ and this would be overcome by using different dose levels to match exposure levels	

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EUFEPS Network on Bioavailability and Biopharmaceutics	22	22	1.2.2	The draft guideline does not explain the meaning of "same drug substance(s)". As it is assumed that this results from different definitions in different legislation, this underlying reason may be clarified in order to emphasize the need to take local requirements/regulations into account.	If no harmonization is intended here due to differences in legislation, reference to approaches in differrent regions could be made.
Jazz Pharmaceuticals	22	22	1.2.1	Does the definition of “drug substance(s)” include a prodrug where the drug substance may differ but the active moiety would be same between the two drug products? Please provide clarity as whether this definition of bioequivalence is for the same drug substance only, or whether it can apply to a prodrug.	
EFPIA	23	24	1.2.1	Please see previous comment - It is not necessarily always the case where molar doses are same (e.g. in case of formulation upgrades where bioavailability between formulations is different).	
Jazz Pharmaceuticals	24	24	1.2.1	Please provide greater clarity on the scope for variance in factors, such as different molar dose, where the same effect and safety profile is seen. For example, could sponsors consider two products where the resulting exposure meets BE criteria between the test product and the reference product but where the two products have different molar dose and the same active moiety?	
SciencePharma, Poland	37	51	1	It is not clear whether those 3 guidelines (M13A, M13B and M13C) will superseed the current local guidelines (e.g. those issued by EMA or FDA).	It is suggested to add the information whether the current guidelines will be superseeded while ICH guidelines comes into effect or alternatively, the current guidelines will be still binding in terms of issues that are not covered by ICH guidelines.
EFPIA	47	58	1.3	The scope of the guideline should clearly set what is in the scope of the current guideline. It currently looks more like a position paper about future guideline developments, rather than the scope definition of M13A. It should state what is in scope (BE of IR solid oral dosage form and BE for other IR formulation where systemic exposure is suitable for establishing BE) and just state what is out of scope (biowaiver considerations, BE of modified/extended release formulations, special cases like highly variable drugs, etc). Future guideline developments are defined in ICH M13 concept paper and workplan.	Remove lines 47 to 58 (TL/SH not in scope should be in)
EUFEPS Network on Bioavailability and Biopharmaceutics	62	72	2.1.1	Standardisation and the possibility to extrapolate study results to other populations is a key concept of bioequivalence studies and this is described in the current draft. * There is no empiric evidence that extrapolation of results from studies in healthy subjects (in either sex...) to the patient population is problematic. * However, some countries still require studies in the local population, at least in certain cases, thus limiting the principle of extrapolation. M13A should address this topic. It is understood that a general guideline cannot overrule local regulations/laws, however, an emphasis, that extrapolation between populations is considered adequate in most instances, but local requirements may have to be considered, may underline this field of tension. * Considering the concept above, it is also not understandable, why the current draft recommends to include both male and female subjects - this limits the execution of BE studies significantly in some countries. * In a meta-study (185 mixed-sex studies passing BE) discordant qualitative interaction was observed only in 1.62% of datasets (https://bebac.at/lectures/Brussels2023.pdf). * In addition, inclusion of just a few subjects of one gender (since no proportions are given) has limited value. * This was also investigated in a larger review by FDA in the 1990's where in ~1000 trials no indication of a sex effect was observed. * It should be considered, that also well intended recommendations may (will) be interpreted also by regulatory agencies resulting in a request to include both sexes (regulatory creep). At least a clarification, that not fulfilling this recommendation is not a reason for non-acceptance of a trial as valid should be considered.	Conducting BE studies in healthy subjects is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the product is intended, even if there are differences in pharmacokinetics between the study and the target population. Due to this principle it is acceptable to run BE studies in any population, irrespective of ethnic origin, age, gender or other characteristics.
EUFEPS Network on Bioavailability and Biopharmaceutics	62	72	2.1.1	It is understood that clinical investigations in females and affiliated data is often lacking and should be endorsed. However, in the context of a straightforward comparison of formulations is is the intention of bioequivalence trials, the achieved improvement seems questionable.	

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EUFEPS Network on Bioavailability and Biopharmaceutics	62	72	2.1.1	*The recommendation to include both sexes is even less clear for crossover studies. In case the previous comment is not accepted, the recommendation to include both sexes should at least be removed for crossover studies	
Medicines for Europe	62	72	2.1.1	Standardisation and the possibility to extrapolate study results to other populations is a key concept of bioequivalence studies and this is described in the current draft. Of note, this principle applies even if the PK characteristics are different between the study and the target population. It is, for example, not uncommon to see such differences between healthy volunteers and patients or between different age groups. However, some countries still require studies in the local population, at least in certain cases, thus limiting the principle of extrapolation. M13A should address and resolve this topic. In addition, considering this concept it is also not understandable why it is recommended in the current draft to include both male and female subjects - this limits the execution of BE studies significantly in some countries. Furthermore, recent analyses do not support the scientific rationale on the inclusion of males/females (Schütz H. Statistical challenges and opportunities in ICH M13A. 2nd Bioequivalence Workshop, Medicines for Europe, 26 Apr 2023, Brussels, Belgium. Available online https://bebac.at/lectures/Brussels2023.pdf) This is considered as a major comment from our perspective.	The subject population for BE studies should be selected with the aim of permitting detection of differences in the *in vivo* release characteristics between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed in healthy subjects unless the drug carries safety concerns that make this approach unethical. Conducting BE studies in healthy subjects is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the product is intended, even if there are differences in pharmacokinetics between the study and the target population. Due to this principle it is acceptable to conduct BE studies in any population, irrespective of ethnic origin, age, gender or other characteristics. The subject inclusion and exclusion criteria should be clearly stated in the study protocol. Subjects should be at least 18 years of age and preferably have a Body Mass Index ≥ 18.5 ~~<= BMI <=~~ and ≤ 30.0. ~~If a drug product is intended for use in both sexes, it is recommended the study include male and female subjects.~~
ProPharma <Zhaosha Li>	64	66	2.1.1	In order to reduce variability not related to differences between products, the studies should normally be performed in healthy subjects unless the drug carries safety concerns that make this approach unethical.	Please clarify if there is possibility to apply for biowaiver due to unethical risk of conducting such BE study in either healthy volunteers or patients, for instance, for a generic product of a potent hormone treatment product, e.g. androgens and estrogens.
EFPIA	65	68	2.1.1	the inclusion of patient instead of healthy subjects is only considered for safety purpose. in some cases extrapolation from healthy to patients could not be relevant because of physiological differences as an example (DI pH, bypass ...)	add a sentence including patients population in case healthy volunteers are not representative of target population and could cause bias in the evaluation
ProPharma <Bertine Vorstenbosch - de Wijs>	67	68	2.1.1	Conducting BE studies in healthy subjects is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the product is intended.	Please consider to add: "...to detect formulation differences and/or manufacturing process changes and to allow extrapolation.....".
EFPIA	69	71	2.1.1	With increasing obesity prevalence, ICH guideline should allow for inclusion of people with higher BMI`s when justified (i.e. when it is proven that BMI is not covariate which affects PK characteristic of a drug). ICH guideline should be flexible enough to allow for inclusion criteria which will ensure homogeneous population taking specific drug substance into account and relevant confounding factors should be addressed within inclusion/exclusion criteria	
EFPIA	69	70	2.1.1	no upper limit for age inclusion criteria	consider proposing 55 years
EFPIA	70	70	2.1.1	There should be a reference to the ability to give informed consent.	After "…18 years of age" add "and "capable of giving informed consent,"
EFPIA	70	71	2.1.1	no inclusion criteria with regard to Bodyweight	Body weight within 50-100kg

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Jazz Pharmaceuticals	70	70	2.1.1	Please consider raising the upper limit of the BMI from 30 to 32 which would be more in line with current demographic data. This would provide flexibility, increase feasibility in enrollment, and more accurately reflect the BMI for the targeted patient populations.	
Adamed Pharma SA	71	72	2.1.1.	In the ICH M13A the phrase from GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE: "Subjects could belong to either sex" has been replaced by: "If a drug product is intended for use in both sexes, it is recommended the study include male and female subjects".It would be helpful to clarify if it is just a recommendation or the study which include only one sex will not be accepted by the agencies. If the Agencies believe that it is not acceptable to conduct a study with participants of one sex only, this phrase should be reworded.	
EFPIA	71	72	2.1.1	It is suggested to add a justification in the protocol for a target of subjects of female sex.	Please consider specifying a minimum number of female subjects to be targeted.
EFPIA	71	72	2.1.1	MINOR COMMENT: Drug toxicity may prevent administration to one or the other sex. Therefore, we propose that the text be updated as indicated.	We recommend the ICH to please complete this sentence with the following statement:"If a drug product is intended for use in both sexes, it is recommended the study include male and female subjects, if supported by safety data".
Krka, d.d., Novo mesto	71	72	Section 2.1.1	The concept of bioequivalence is extrapolation of results to general population (healthy subjects to patients, young subjects to elderly, even adults to children). To require inclusion of both sexes into bioequivalence study questions extrapolation concept and seems redundant. There is no scientific rationale to require bioequivalence studies in both genders, combined or separately. Moreover, publication from Schütz H. (1), as well as inhouse data, indicate no significant gender*treatment interaction incidence above the test level (10%). References: (1) Schütz H. Statistical challenges and opportunities in ICH M13A. April 26, 2023. https://bebac.at/lectures/Brussels2023.pdf	If a drug product is intended for use in both sexes, ~~it is recommended the study include male and female subjects~~ the subjects can belong to either sex.
Richter Gedeon Plc	71	72	2.1.1	To extrapolate study results to other populations is a key concept of bioequivalence studies and this is described in the current draft. Like: from healthy to patient, age differencies, different races (some Authorities still request local studies, which should be addressed, too)) More strong recommendation to include both sexes is not aligned with this thinking and van cause operative problems in certain countries.	Please remove: ~~If a drug product is intended for use in both sexes, it is recommended the study include male and female subjects.~~
Adamed Pharma SA	76	78	2.1.1.	A more comprehensive explanation how the follow-up information about the pregnancy should be provided is needed, e.g. the need to include an additional pregnancy test at the end of the study in the protocol.	
EFPIA	76	78	2.1.1	Investigators should not decide on pregnancy or lactation.	Suggestion to re-word such that investigators ensure that female subjects that are pregnant or lactating are not included
ORBIS project	77	77	2.1.1	If lactating female subjects do not breastfeed there is no risk for children. We agree that special care should be taken, but exclusion of lactating female subjects may be considered discriminatory. Especially in the case of drugs which do not exhibit potential effects on milk production (ethical issue) and are not known to be extensively excreted into the milk.	lactating => breastfeeding; open possibility for lactating female subjects to participate in BE studies
Arab Pharmaceutical industry Consulting	78	78	2.1.1	Why Subjects should preferably be non-nicotine users if there is no contraindication of the product with smoking.	

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EUFEPS Network on Bioavailability and Biopharmaceutics	78	79	2.1.1	Most drug-drug interactions caused by smoking tobacco are caused by the smoke itself and not by nicotine.	Subjects should preferably be non-smokers~~nicotine users~~ and without a history of alcohol or drug abuse.
Medicines for Europe	78	79	2.1.1	Most drug-drug interactions caused by smoking tobacco are caused by the smoke itself and not by nicotine. While any consumption of nicotine should be banned during the study and while subjects abusing nicotine are not eligible for bioequivalence studies, the recreational use of tobacco without smoking it, similar to the recreational use of alcohol may not have to be restricted, not even with a "preferably" limitation. For smokers, the requirement to preferably not include them in a study makes more sense.	Subjects should preferably be non-smokers~~nicotine users~~ and without a history of alcohol or drug abuse.
EFPIA	81	82	2.1.1	There could be other situations when enrollment of non-healthy subjects could be appropriate. ICH should be less strict and allow involvement of "non-healthy" subjects when scientifically justified	
EFPIA	85	93	2.1.1	MINOR COMMENT: It would be useful to call out here that some studies may require more than one dose with a reference to section 2.1.6. Therefore, we propose adding the indicated clarification	We highly encourage the ICH to add the following clarification:"Under some conditions, a study using more than one dose strength may be required". (TL/SH: less than proportional increase due to solubility)
EUFEPS Network on Bioavailability and Biopharmaceutics	85	85	2.1.2	It's not understandable why two-period, two-sequence crossover study designs are recommended. It is understood that more complex designs will be part of subsequent parts of M13, but this restriction seems not necessary as it may give the impresssion, that other designs (Partial or full replicate studies seem to be equally suitable or even recommended in certain circumstances) are acceptable, "if scientifically justified", which seems inappropriate for not that complex designs as replicate or higher-order designs (Two reference, one Test). It may be a simple solution to omit the "two period, two sequence" part of the sentence. This change also has consequences for text proposed in other parts of the ICH draft text.	A randomised, single-dose~~, two-period, two-sequence~~ crossover study design is recommended …
Medicines for Europe	85	85	2.1.2	It is not understandable why only two-period, two-sequence crossover study designs are recommended. Partial or full replicate studies seem to be equally suitable or even recommended in certain circumstances.	A randomised, single-dose~~, two-period, two-sequence~~ crossover study design is recommended …
EUFEPS Network on Bioavailability and Biopharmaceutics	88	89	2.1.2	The recommendations which strength to chose are inconsistent in the current draft and cause confusion, even in context with the wording "in general". The appropriate approach is described in chapter 2.1.6 (see further comments below). Due to different possible scenarios, chapter 2.1.2 should not address the topic, not even with the "in general" clause.	~~In general, the highest to be marketed strength should be used in a BE study.~~
Medicines for Europe	88	89	2.1.2	The recommendations on which strength to chose are inconsistent in the current draft and cause confusion, even in context with the wording "in general". The appropriate approach is described in chapter 2.1.6 (see further comments below). Due to different possible scenarios, chapter 2.1.2 should not address the topic, not even with the "in general" clause.	~~In general, the highest to be marketed strength should be used in a BE study.~~
ORBIS project	88	93	2.1.2	This paragraph is confusing and inconsistent with paragraph 2.1.6 (commented below). Please consider moving this paragraph 2.1.6.	Avoid confusion by discussing strength(s) to be investigated only in paragraph 2.1.6.
EFPIA	94	95	2.1.2	Another reason for conducting a multiple dose study could be PK properties of the drug. For some drugs such as drugs displaying covalent or very long-term target binding (e.g. LYS006: Poller et al. 2022) the required washout phase may be unreasonably long and the multiple dose design you describe in this paragraph more suitable. In this multiple design you compare the PK under condition of similar (likely complete) target occupancy. Suggest mentioning potential PK reasons to decide for a multiple dose design in healthy participants. B. Poller, D. Pearson, L. A. Leuthold, M. Fink, A. Jullion, P. Schweigler, et al. Human Pharmacokinetics of LYS006, an Oral Leukotriene A4 Hydrolase Inhibitor Displaying Target-Mediated Drug Disposition. Drug Metab Dispos 2022 Vol. 50 Issue 12 Pages 1472-1482	Modify text to mention that PK properties of the drug could support a multiple dose design. Poller et al. 2022 provides a literature example for such a case but does not explicitly discuss the study design implications of these properties.

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EFPIA	94	95	2.1.2	the option of repeated dose may also be considered in case of issues quantification limit or very low doses (low level of the compound to allow an appropriate PK profile after single dose)	add the possibility to perform a multiple dose in case of quantification limit issue
EFPIA	95	95	2.1.2	There are products which require multiple dose studies for other reasons, such as product PK characteristic (e.g. high variability). ICH guideline should be flexible for other reasons than only those currently listed	
ORBIS project	99	99	2.1.2	The term 'stable Ctau' is not clear.	Define criteria of 'stable Ctau'
EFPIA	102	102	2.1.2	Consider not limiting to elimination half-lives which may be unnecessarily long to reach steady state. Using the effective or accumulation half-life (Boxenbaum 1995) should be allowed as an alternative.	Modify text to also allow the effective or accumulation half-life and add the reference for clarity: H. Boxenbaum and M. Battle: Effective half-life in clinical pharmacology. J.Clin.Pharmacol. 1995 Vol. 35 Issue 8 Pages 763-766
EFPIA	103	103	2.1.2	Definition of long-half life (more than 24h) is given further down in the text. These should be clearly defined on the first occurence of this term, otherwise guideline appears unclear.	Consider replacing: 'For drug with long elimination half-lives, a parallel design may be employed...' with 'For drug with long elimination half-lives (i.e. more than 24h), a parallel design may be employed...'
EFPIA	103	103	2.1.2	Clarify the elimination half-life from which point a parallel design may be considered	Please clarify the elimination half-life under "For drugs with long elimination half-lives..,", eg. in alignment with section 2.1.8.2
Adamed Pharma SA	106	106	2.1.2.	In our opinion, the statement "alternative study designs" can be interpreted in different ways, so it is worth specifying what exactly this term includes.	
EFPIA	106		2.1.2	Alternative study designs are acceptable, if scientifically justified	Consider refering to ICH M13C (complex designs)
EFPIA	107	110	2.1.3	the sample size estimation is not detailled while key point of the study success	mention that the sample size is determined by: 1/ the errror variance (within subject variability) and how this parameter is estimated : historical/published data. 2/the expected difference between the reference and test formulation, 3/the required power 4/ the limits: NTI or not NTI
EFPIA	109		Section 2.1.3	...to achive a pre-specified power and pre-specified type 1 error.'	Suggest providing the pre-specified type 1 error (alternatively refer to Section 2.2.3.1 lines 392-395) as this is a regulatory requirement and not sponsor's choice (as opposed to power)
Medicines for Europe	109	109	2.1.3	Change of terminology with respect to sample size estimations.	The number of subjects to be included in the BE study should be based on an appropriate sample size ~~calculation~~ determination to achieve a pre-specified power and pre-specified type 1 error.
EFPIA	111	111	2.1.3	The reference to use of "spare" subjects is not clear. If specified in the protocol the use of replacement subjects to accommodate for dropouts and still meet the required number of completers despite potential over enrollment may still be acceptable.	Please clarify the use of the word "spare" and how this works with clinical trial enrollment numbers

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EFPIA	111	113		As long as the Sponsor remains blinded to the outcome, suggest allowing flexibility to adjust sample size following bioanalysis and blinded review of the bioanalytical data. This is important because PK variability may be uncertain prior to study initiation/protocol development.	We strongly encourage the ICH to please add the following text: In cases where PK variability is uncertain, and if prespecified in the study protocol, the sample size may be adjusted following bioanalysis and blinded review of the PK data. No assessment of bioequivalence can be done as part of this interim blinded review. (TL/SH: Innovator shpould know varaiability, topic of 13C?)
EFPIA	113	115	Section 2.1.3	Line 113 to 115: The number of evaluable subjects in a pivotal BE study should not be less than 12 for a crossover design or 12 per treatment group for a parallel design.	Please clarify, or remove 'pivotal'. What scenario would "pivotal" apply to, would this be for a drug that has several BE studies and 1 is selected as pivotal?
Gilead Sciences	114	115	2.1.4	Can per treatement group for a parallel design be more than 12 subjects? If yes would it be clearer to state " ...at least 12 subjects for a cross over or per treatement group for a parallel design?	
Jazz Pharmaceuticals	114	115	2.1.3	Regarding the minimum sample size of 12, is it reasonable for the sponsor to justify a sample size below 12 where products have low inter-individual variability? Please consider including clarification or additional advice for this case.	
ORBIS project	117	117	2.1.4	The sentence is very general. Does a generic drug product accepted by one regulatory agency meet the criteria for the comparator product?	The definition of the comparator product needs to be more specific.
EUFEPS Network on Bioavailability and Biopharmaceutics	119	123	2.1.4	An essential condition of the BE concept is that study results are not only relevant for the biobatches investigated in a study but representative for the medicinal products in general. Thus, it should be mandatory (not advisable) to test more than one batch of the comparator product (if available), similar to the test product.	
ORBIS project	119	121	2.1.4	The phrase 'assay content' and the criteria for reference batch selection are not clear. Please consider adding selection criteria for batch selection and define percentage of permitted deviation from the nominal content.	It is recommended that the mean content of the drug substance in 10 units drawn from the reference product’s batch falls within 95 – 105% relative to the mean content in 10 units drawn from the test product’s batch, and the maximal difference between any of the drawn units of the reference and test products' batches should be not greater than 10% relative to the test product.
ProPharma <Anna K. Klein>	119	121	2.1.4	The selection of the batch of the comparator product used in the BE study should be based on assay content. It is advisable to investigate more than one batch of the comparator product when selecting the batch of comparator product for use in the BE study.	I understood what you meant by saying 'based on assay content'; however, only when I read the explanation below with refr to +/- 5% difference. Maybe adding an additional sentence or words would make it more clear? Please clarify if 1 batch is the minimum required by the authorities?
EFPIA	120	121	2.1.4	Clarify which methods would aply to assess the reference (comparator)	Please clarify acceptable methods for comparator batch product
EFPIA	122	123	2.1.4	For BE studies to be conducted with intended Commercial Formulation (iCF), is it acceptable to use iCF batch from development and not from launch site? Is the iCF from development considred a representative of the product to be marketed?	A clarification about bridging formulations may be added to the guideline
EFPIA	124	132	2.1.4	Compared to the FDA guidance, these are very strict for test product in pivotal Bioequivalence on batch size	Please consider better consistency with FDA guidance: Guidane for Industry Bioavailability and Bioequivalence Studies Submitted in NDAs or INDS - General Considerations

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	124	132		While the scope is oral frorms it is indicated that the principles of this guideline can apply to other forms as well. It is proposed that this passage is clearly limited to oral forms. Also, we propose that the 5% criteria is not to be mandatorily applied to dosage froms where pharmacopoeia allows for wider assay specification that 95-105%	
ProPharma <Bertine Vorstenbosch - de Wijs>	127	129	2.1.4	The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified. In case of a production batch smaller than 100,000 units, a full production batch is required.	Please consider to clarify that these are the targeted nominal/theoretical batch sizes. Due to sampling & testing (e.g. IPC), inspection (e.g. capping), etc. the actual IR solid oral dosage form batch sizes might in practice be lower than initially aimed for.
EFPIA	130	130	2.1.4	"assayed content"- Content may be misleading as it can refer to as the API as well as excipients. It is assumued that it is assay content of API, please clarify?	
EUFEPS Network on Bioavailability and Biopharmaceutics	131	132	2.1.4	The assay content of a reference product is typically measured using the analytical method developed for test product. However, in certain cases, excipient(s) present in the reference product may interfere with the analytical method developed for test and therefore, the method must be modified appropriately.	Delete the sentence on line 131, after comma: '~~, as determined wtih the test procedure proposed for routine quality testing of the test product.~~'
Krka, d.d., Novo mesto	131	132	Section 2.1.4	Although the assay content of a reference product is typically measured using the analytical method developed for test product, this may not always be the case. It may be necessary to develop separate method, especially when different excipients are used in the test and comparator products.	Delete the sentence on line 131, after comma: '~~as determined wtih the test procedure proposed for routine quality testing of the test product~~.'
Medicines for Europe	131	132	2.1.4	The assay content of a reference product is typically measured using the analytical method developed for test product. However, in certain cases, excipient(s) present in the reference product may interfer with the analytical method developed for test and therefore, the method must be modified appropriately.	Delete the sentence on line 131, after comma: '~~, as determined wtih the test procedure proposed for routine quality testing of the test product.~~'
ProPharma <Bertine Vorstenbosch - de Wijs>	131	131	2.1.4	Unless otherwise justified, the assayed content of the batch used as test product should not differ by more than 5% from that of the batch used as comparator product, as determined with the test procedure proposed for routine quality testing of the test product.	Please consider to add "+/-": "... +/- 5% from that of the batch used as comparator product".
EFPIA	134	135	2.1.5	MINOR COMMENT: Administering some drugs with food minimizes variability, so in the case of those drugs, administration with food might better isolate potential differences between the drug products. Therefore, we propose that the text be updated as indicated	We strongly encourage the ICH to please update the concerned statement as follows: "BE studies should be conducted under standardised conditions that minimise variability to better detect potential PK differences between drug products, which may be achieved under fasted or fed conditions, depending on the drug product. For IR solid oral dosage forms, single-dose BE studies conducted under fasting conditions typically provide greater discrimination between the PK profiles of two products. Therefore, for the majority of these drug products, BE may be demonstrated in a single study conducted under fasting conditions".
EFPIA	139	142	2.1.5	As fasted and fed studies are further discussed below for high-risk and non-high products, this paragraph on high - risk products seems redundant.	Please delete this paragraph and replace with one sentence referring to "High-risk products" section below for BE studies under fed conditions.
Richter Gedeon Plc	141	142	2.1.5	Even for "high-risk products" both BE study (fasted and fed) should not be needed for a product that should be taken only in the fasted state or only in the fed state, in alignment with the label.	If the drug intake restricted to fasted by the label, bioequivalence should be conducted only under fasting conditions. If the drug intake is allowed with food intake only by the label, bioequivalence should be conducted only under fasting conditions.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ORBIS project	142	142	2.1.5	The sentence 'In such cases, BE under fed conditions also needs to be demonstrated.' needs to be clarified. It is unclear whether the fed conditions study should be conducted as a new two-period study in an independent group of subjects, or as four-period study at fasted & fed conditions. Are both approaches acceptable? Are in vitro or modelling approaches instead of clinical study acceptable?	Add information about acceptable fed study designs. We recommend guiding that it is acceptable to conduct either two separate two-period cross-over studies or a four-period cross-over study.
EUFEPS Network on Bioavailability and Biopharmaceutics	143	149	2.1.5	Apart from a validated PBPK modelling approach or a semi-mechanistic absorption model, the rationale for selecting meal administration conditions can be described mechanistically with either clear administration instructions (based on PK reasons) or relatively well known absorption mechanisms, hence a purely mechanistic justification is suggested to be added here.	New text: Add in line 149 ", but other supportive argumentations are not excluded."
Medicines for Europe	143	149		Appart from a validated PBPK modelling approach or a semi-mechanistic absorption model, the rationale for selecting meal administration conditions can be described mechanistically (using an in vitro approach) with either clear administration instructions (based on PK reasons) or relatively well known absorption mechanisms, hence a purely mechanistic justification is suggested to be added here.	Proposed Change: The rationale can be supported by in vitro mechanistical approaches or by modelling,e.g. ….
ORBIS project	148	148	2.1.5	The term "appropriately" is not clear. Please consider defining criteria for validation or adding reference to appropriate guideline/appendix. Please indicate whether validation should be a part of regulatory application or should be supplied upon request.	Define criteria for validation or add reference
EFPIA	154	154	2.1.5	Clarify non-high-risk products when the term is used for the first time	Please consider defining "non-high-risk products" for consistency and clarity.
ORBIS project	154	164	2.1.5	The terms 'high-' or 'non-high-risk' products are misleading. Using the term 'high-risk product' may be confusing for general public. Patients may react negatively when a "high-risk product" is prescribed and patient compliance may be decreased. Please consider an alternative term referring directly to possible challenges regarding bioequivalence study and not associated with the safety, e.g., BE-challenging-product.	Replace terms 'high-' or 'non-high-risk' products with terms not suggesting any risk or safety concerns to the patients.
ORBIS project	155	163	2.1.5	Please specify if labelling is related to test or comparator product or both.	Please specify if labelling is related to test or comparator product or both.
ORBIS project	161	163	2.1.5	The rationale to conduct BE study in less favourable conditions regarding safety is lacking.	For a product that is labelled to be taken only with food due to tolerability reasons, e.g., stomach irritation, a single BE study conducted under ~~either fasting or~~ fed conditions is ~~acceptable~~ recommended.
EFPIA	162	163	2.1.5	If a product has to be taken with food due to safety reason, like stomach tolerability, it is not ethical to run the study in fasting condition.	Line 162 and 163 should be changed to read "stomach irritation, a single BE study conducted under fed conditions is recommended to demonstrate bioequivalence."
EFPIA	164	164	2.1.5	could propose to perform Fassgf/Fassif and FessGF/Fessif biorelavnt comparitive dissolution profile to anticipate if both drug products are high risk	could propose to perform Fassgf/Fassif and FessGF/Fessif biorelevant comparative dissolution profile to anticipate if both drug products are high risk
EFPIA	164	189	2.1.5	The definition of "high risk products" as described in lines 165 to 189, is not clear and open the way to misunderstandings. Initially it is stated that these products are those where PK may be influenced by a complex formulation and/or manufacturing method, then several examples are provided, like nanothechnologies, lipid based formulations, low soluble drugs, etc. In many cases these formulations have an impact on PK that results in delayed or slowly prolonged release or differential release based on gastrointestinal pH. However, this guideline is related to immediate release products. Therefore, it would be helpful to clearly specify which high risk products would fall within scope of this guideline and which not. If all products would fall under this guideline, then the title should be revised.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
GENEPHARM S. A	165	179	2.1.5	It is understandable and clear that for high risk products that were to be taken with or without food, a fed study also may be needed for controlling any food effect specific to the formulation technology (e.g solid dispersion). It is not clear by the wording in the text what is needed in case that a high risk poduct that in clinical practice should be taken only with food, which means that a fed study will be done in any case, if a fasting study is needed although in reality it will never be taken in fasting conditions. This comment also applies to the case that a high risk product should be taken only in fasting condition, which means that there is no reason to test the food effect in a formulation that will never be taken with food.	
Krka, d.d., Novo mesto	165	175	Section 2.1.5	In order to avoid confusion and misinterpretation of high-risk products, it is recommended to further clarify the meaning ''High-risk products'' by additional text/definition.	High-risk products are those where the drug substance solubility in combination with the complexity of the formulation design or manufacturing process leads to an increased likelihood that in vivo performance will be impacted differently by varying gastrointestinal (GI) conditions between the fasted and fed states. For these products, performance differences related to differences in formulation and/or manufacturing process may not be detected with a single BE study, i.e., results from a fasting BE study may not be extrapolated to predict fed BE study outcome or vice versa, thus both fasting and fed BE studies should be conducted. High risk For example, some drug products containing low solubility drug substances (as defined by the BCS low solubility criterion described in ICH M9) and have complex formulation and/or manufacturing methods (such as solid dispersions, microemulsions, lipid-based formulations, nanotechnologies, or other specialised technologies) to ensure sufficient solubility of the drug substance and dissolution of the drug products or to manage the impact of food.
Medicines for Europe	165	167	2.1.5	Revised wording suggested in accordance with the text further below.	High-risk products are those where the drug substance characteristics in combination with the complexity of the formulation design or manufacturing process leads to an increased likelihood that in vivo performance will be impacted differently by varying gastrointestinal (GI) conditions between the fasted and fed states.
ORBIS project	166	166	2.1.5	The term "performance" is unclear. It is suggested to replace the term "performance" with the term "release" as more specific. Justifying, the term "performance" may include many processes, e.g. drug transit from the stomach to the small intestine, which is undoubtedly different at fasted and food states irrespective of the formulation.	performance' => 'release'
EFPIA	167	186	2.1.5	The first and second paragraphs appear not to be fully aligned - the first paragraph states that "BE studies should be conducted under fasted and fed conditions" for high riak products unless there are ethical concerns, but the second paragraph states that BE under both conditions may be warranted if there are substantial differences in manufacturing process or excipients. Please clarify the expectation from the regulatory autorities in the text - should BE always be conducted under fed and fasted conditions for these products, or only in cases where substantial changes have been made between the test and reference products?	Please consider clarifying the text as described.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	167	179	2.1.5	If the drug is approved to be administered with food, it shouldn't be necessary to establish BE is under fasted conditions regardless of the manufacturing complexity. There could be value in understanding the relative BA for fasted versus fed, but it should not be expected to meet BE under fasted conditions if the clinical recommendation is to take with food. The same logic applies for the alternative situation for a drug that is labeled to be taken fasted, and therefore only a fasted BE study would be clinically relevant. Our experience is that it is already very challenging to demonstrate bioequivalence for these high-risk drugs even when only trying to match the label condition (eg. with food). Having to also match the fasted condition, which is not clinically relevant, becomes an almost impossible task. Furthermore we note that for some molecules the new formulation has a less pronounced food effect and the original, which is favorable for patients, and reduces variability. Requiring this improved formulation to match both fed and fasted BE prevents it from entering the marketplace.Therefore, we propose that the text be updated as indicated. which is not clinically relevant, becomes an almost impossible task. Furthermore we note that for some molecules the new formulation has a less pronounced food effect and the original, which is favorable for patients, and reduces variability. Requiring this improved formulation to match both fed and fasted BE prevents it from entering the marketplace. Therefore, we propose that the text be updated as indicated.	We strongly encourage the ICH to please update the concerned text as follows: "High-risk products are those where the complexity of the formulation design or manufacturing process leads to an increased likelihood that in vivo performance will be impacted differently by varying gastrointestinal (GI) conditions between the fasted and fed states. For example, some drug products containing low solubility drug substances (as defined by the BCS low solubility criterion described in ICH M9) have complex formulation and/or manufacturing methods (such as solid dispersions, microemulsions, lipid-based formulations, nanotechnologies, or other specialised technologies) to ensure sufficient solubility We strongly encourage the ICH to please update the concerned text as follows: "High-risk products are those where the complexity of the formulation design or manufacturing process leads to an increased likelihood that in vivo performance will be impacted differently by varying gastrointestinal (GI) conditions between the fasted and fed states.
EFPIA	167	179	2.1.5	If the drug is approved to be administered with food, it shouldn't be necessary to establish BE is under fasted conditions regardless of the manufacturing complexity. There could be value in understanding the relative BA for fasted versus fed, but it should not be expected to meet BE under fasted conditions if the clinical recommendation is to take with food. The same logic applies for the alternative situation for a drug that is labeled to be taken fasted, and therefore only a fasted BE study would be clinically relevant. Our experience is that it is already very challenging to demonstrate bioequivalence for these high-risk drugs even when only trying to match the label condition (eg. with food). Having to also match the fasted condition, which is not clinically relevant, becomes an almost impossible task. Furthermore we note that for some molecules the new formulation has a less pronounced food effect and the original, which is favorable for patients, and reduces variability. Requiring this improved formulation to match both fed and fasted BE prevents it from entering the marketplace.Therefore, we propose that the text be updated as indicated. which is not clinically relevant, becomes an almost impossible task. Furthermore we note that for some molecules the new formulation has a less pronounced food effect and the original, which is favorable for patients, and reduces variability. Requiring this improved formulation to match both fed and fasted BE prevents it from entering the marketplace. Therefore, we propose that the text be updated as indicated.	For example, some drug products containing low solubility drug substances (as defined by the BCS low solubility criterion described in ICH M9) have complex formulation and/or manufacturing methods (such as solid dispersions, microemulsions, lipid-based formulations, nanotechnologies, or other specialised technologies) to ensure sufficient solubility of the drug substance and dissolution of the drug products or to manage the impact of food. For these products, performance differences related to differences in formulation and/or manufacturing process may not be detected with a single BE study, i.e., results from a fasting BE study may not be extrapolated to predict fed BE study outcome or vice versa. Therefore, for drugs labeled to be taken without respect to food, a fasting BE study should be performed. For drugs labeled to be either taken fasted or with food, the BE study should be performed fasted or fed respectively, in accordance with the label. In both cases, a fed versus fasted relative bioavailability assessment should also be performed. When safety concerns make it unethical to administer a single dose of the drug product under either fed or fasted conditions, then the BE study should be conducted under the condition with less safety concerns".
EFPIA	171	175	2.1.5	to the list of technologies in line 173-4 suggest adding "co-processed API" as a technology to address low solubliity criteria	(such as solid dispersions, microemulsions, co-processed API, lipid-based formulations, nano technologies, or other specialised technologies)
EUFEPS Network on Bioavailability and Biopharmaceutics	171	175	2.1.5	Beyond solubility, also solubility kinetics may need to be considered, e.g., with nanoformulations the solubility kinetics not the solubility itself is increased.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	171	175	2.1.5	The definition of high-risk products requiring studies both under fasting or fed conditions should be as concise as ~~and~~ possible. In this sentence the deletion of "For example," would help significantly and reduce uncertainty. It would then also be clear then that only low-solubility drug substances could fall into the category of high-risk products.	~~For example, s~~Some drug products containing low solubility drug substances (as defined by the BCS low solubility criterion described in ICH M9) have complex formulation and/or manufacturing methods (such as solid dispersions, microemulsions, lipid-based formulations, nanotechnologies, or other specialised technologies) to ensure sufficient solubility of the drug substance and dissolution of the drug products or to manage the impact of food.
Richter Gedeon Plc	171	175	2.1.5	A more direct, practical definition should be given in the guideline for helping to decide developer which product should be regarded as "high risk product", and to minimise the need for frequent consultations with authority	E.g. High risk product definition should apply for test products that: -belongs to BCSII or BCSIV classes AND -differing qualitatively or quantitatively with regards to excipients with known relevant effect on bioavailability OR -have complex formulation which differs from reference product
EFPIA	171	172	2.1.5	BCS high solubility criteria are set very tightly, and it is not the case that a drug which is low solubility according to BCS will automatically require a solubility/dissolution enhancing formulation approach. In fact, many BCS Class 2 and 4 drugs are successfully developed as simple immediate release tablets. As this section seems to be focussed on drug products which use solubility/dissolution enhancing approaches, suggest to remove the reference to BCS low solubility criteria, as this could create confusion for applicants.	Suggest to remove the reference to BCS solubility criteria.
EFPIA	175	175	2.1.5	drug substance and dissolution, should precise that it refers to dissolution rate	add rate after dissolution
EFPIA	175	179	2.1.5	For drug products with complex formulation and/or manufacturing methods, the requirement from conducting BE studies under fed and fasted conditions should be updated to be in line with the product labeling. This is the current recommendation per the CHMP Guideline on the Investigation of Bioequivalence, which states "However, for products with specific formulation characteristics (e.g. microemulsions, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required unless the product must be taken only in the fasted state or only in the fed state" (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf)	For these products, BE studies should be conducted under both fasting and fed condition unless the product must be taken only in the fasted state or only in the fed state.
EFPIA	175	178	2.1.5	For these high risk products, BE studies should be conducted under both fasting and fed conditions, irrespective of the product labelling with regard to food intake, except when safety concerns make it unethical to administer a single dose of the drug product under either fed or fasted conditions.	The rationale for food BE study for enabling formulations of low solubility is difficult to understand since for such drugs the fasting state is the most discriminating conditions and in fed state, similar exposure is obtained irrespective of formulation. There are very few examples, if any, where BE has been obtained in fasting conditions but not in fed state. This concern is particularily valid in case of post-approval changes implying that the same formulation principle is used.
EUFEPS Network on Bioavailability and Biopharmaceutics	175	177	2.1.5	* In case of high-risk products, a waiver to run a study under one food condition is granted, when safety concerns make it unethical to administer a single dose of the drug product under either fed or fasting conditions. I is not clear, however, if this provision refers to drug administration in healthy volunteers or in patients. * If it refers to healthy volunteers, it could be considered as too relaxed as long as the product labelling includes the alternative food condition for a patient study. *If it refers to patients, the unethical condition can hardly be part of the product labelling, so the wording should more clearly require only one study which is in line with the product label. *If it refers to patients, the wording should be changed and refer to drug administration under multiple dose instead of single dose conditions.	
ORBIS project	175	175	2.1.5	The phrase 'dissolution of the drug product' used as simplification is confusing.	dissolution of the drug product' => 'dissolution of the drug substance from the drug product'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ProPharma <Bertine Vorstenbosch - de Wijs>	175	179	2.1.5	For these high risk products, BE studies should be conducted under both fasting and fed conditions, irrespective of the product labelling with regard to food intake, except when safety concerns make it unethical to administer a single dose of the drug product under either fed or fasted conditions. Then the BE study should be conducted under the condition with less safety concerns.	Please consider to add a Decision Tree to clarify the steps to be taken.
EFPIA	176	177	2.1.5	In general, for a new formulation, a BE study and a food effect study is required. If the original formulation has no food effect, and the new formulation also has no food effect, is a food effect BE study still required, especially if the product label allows dosing without regards to food? For an immediate release formulation, it is recommended to conduct a fed BE study if data from food effect study demonstrate a difference from the original formulation, for example, no food effect for reference formulation, but a food effect is observed for the new formulation.	"For these products, BE study under fed conditions might be needed, if a food effect is observed with the new formulation, where there is no food effect with the reference formulation."
Medicines for Europe	176	179	2.1.5	Even for "high-risk products" a BE study under fasted and fed condition should not be required for a product that is labelled to be taken only in the fasted state or only in the fed state.	In cases in which the SmPC restricts the drug intake to either fasted or fed conditions a full study program (BE study under fasted and fed conditions) should not be required.
ORBIS project	176	179	2.1.5	In case SmPC of comparator product limits administration to only fasting or only fed conditions, BE study should be recommended at conditions specified by SmPC.	Add sentence: In case SmPC of comparator product limits administration to only fasting or only fed conditions, BE study should be recommended at conditions specified by SmPC.
Krka, d.d., Novo mesto	178	179	Section 2.1.5	It should be clear that no multiple dose studies in patients are required in case a single dose study (under condition unethical for healthy volunteers) cannot be performed. One single-dose study on healthy volunteers under the condition with less safety concerns should be sufficient.	~~Then~~ In such cases one single dose BE study should be conducted under the condition with less safety concerns.
EFPIA	180	186	2.1.5	We propose that for low solubility drug substances which have been formulated to reduce the food effect, that a fed versus fasted relative bioavailability study be performed for the test material, and compared with that obtained previously for the comparator. However we do not believe it is necessary to perform a BE study under both fed and fasted conditions but rather that the conditions for the BE study be matched to the label, or if labeled to be taken without regard to food, then BE performed in the fasted state. Therefore, we propose that the text be updated as indicated.	We highly recommend the ICH to rephrase as follows: "Especially for low solubility drug substances, the comparator product may be the result of an extensive formulation and/or manufacturing process development program, obtaining for instance a specific formulation without a food effect. If the test product uses a substantially different manufacturing technology or particle size control method from the comparator, or if substantially different excipients are used in the test and comparator that are likely to impact dissolution, solubility, or permeability, this warrants the need for assessment of the relative bioavailability of fed versus fasted conditions, in addition to the BE assessment as described above".
EUFEPS Network on Bioavailability and Biopharmaceutics	180	186	2.1.5	Industry needs clear guidance when studies under both conditions are required. In lines 182-186, there is currently a stand-alone sentence with a very broad range of scenarios where both fed and fasting studies are require: "If substantially different manufacturing technology or particle size control method from the comparator, or if substantially different excipients are used in the test and comparator that are likely to impact dissolution, solubility, or permeability. Since such situations are not unusual, the requirements need to be narrowed, e.h. if applicable only to the cases described in the previous sentence of lines 180 to 182. It should be clarified, that these two sentences are to be read together and are connected by an "and" and not by an "or".	Especially for low solubility drug substances, the comparator product may be the result of an extensive formulation and/or manufacturing process development program, obtaining for instance a specific formulation without a food effect. In these cases, and if the test product uses a substantially different manufacturing technology or particle size control method from the comparator, or if substantially different excipients are used in the test and comparator that are likely to impact dissolution, solubility, or permeability, this may warrant the need for BE studies under fasting and fed conditions.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	180	186	2.1.5	It is not clear if the second sentence in this paragraph refers only to the cases described in the first sentence, it seems so, but the wording needs to be modified. The second sentence is very broad, and may result in fasting and fed studies for almost every low soluble drug. It should be clarified that this is indeed relevant only for complex formulation and/or manufacturing methods. If the second sentence does not refer to the cases described in the first sentence (see proposal in column G), please specify in which cases it's applicable and/or narrow the scope. In addition to this, information on particle size control, for example, is considered confidential information and is not known to generic companies.	Especially for low solubility drug substances, the comparator product may be the result of an extensive formulation and/or manufacturing process development program, obtaining for instance a specific formulation without a food effect. In these cases, and if the test product uses a substantially different manufacturing technology ~~or particle size control method from the comparator~~, or if substantially different excipients are used in the test and comparator that are likely to impact dissolution, solubility, or permeability, this may warrant the need for BE studies under fasting and fed conditions.
EFPIA	182	185	2.1.5	Same comment as for Line 176-177, a fed BE study should only be required if there is an effect of food on the new formulation.	"If the test product uses a substantially different manufacturing technology or particle size control method from the comparator, or if substantially different excipients are used in the test and comparator that are likely to impact solubility or permeability, a BE study under fed conditions might be needed, if a food effect is observed with the new formulation, where there is no food effect with the reference formulation."
EUFEPS Network on Bioavailability and Biopharmaceutics	182	186	2.1.5	Information on particle size control method is considered confidential information and is not known to generic companies. It is also not clear why there is an emphasis on the particle size control method and not the particle size itself.	If the test product uses a substantially different manufacturing technology-or particle size ~~control method~~ from the comparator, or if substantially different excipients are used in the test and comparator that are likely to impact dissolution, solubility, or permeability, this may warrant the need for BE studies under fasting and fed conditions.
Krka, d.d., Novo mesto	182	182	Section 2.1.5	Clear definition of "without food effect" should be included to avoid misconception with "without clinically relevant food effect". Definition of food effect by FDA (1) " food effect is established if the 90% confidence intervals for the ratio of population geometric means, based on logtransformed data, for either AUC0-∞ or Cmax fall outside the 80–125% bioequivalence limits..." can be applied. References: (1) Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations, FDA, CDER, June 2022	Especially for low solubility drug substances, the comparator product may be the result of an extensive formulation and/or manufacturing process development program, obtaining for instance a specific formulation without a food effect established by means of bioequivalence.
Krka, d.d., Novo mesto	182	186	Section 2.1.5	It is not clear if the second sentence in the paragraph refers only to the cases described in the first sentence. As the second sentence is very broad, and may result in fasting and fed studies for almost every low soluble drug it should be clarified that this is indeed relevant only for cases of specific formulations without food effect (established through bioequivalence). In addition to this, information on particle size control is considered confidential information and is not known to generic companies.	In these cases, and if the test product uses a substantially different manufacturing technology or particle size control method from the comparator, or if substantially different excipients are used in the test and comparator that are likely to impact dissolution, solubility, or permeability, this may warrant the need for BE studies under fasting and fed conditions.
ORBIS project	182	186	2.1.5	The term "substantially different" is not clear, and needs to be specified. It is suggested to add a list of excipients, manufacturing technologies, particle size control methods considered as "substantially different". Please review whether all information needed for the decision is available for applicants in advance to patent expiry (e.g. particle size control may be considered confidential).	Clarification needed
SciencePharma, Poland	182	183	2	In terms of comparability of test product and comparator it is more substantiated to compare the particle size itself instead of particle size control method. Moreover, it is not clear, what are the criteria to assess the manufacturing technology or excipients as "substantially different".	It is suggested to modify the text as follows: *"If the test product uses a substantially different manufacturing technology (e.g. high-risk comparator versus non-high-risk test product) or particle size ~~control method~~ from the comparator (…)"*

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUFEPS Network on Bioavailability and Biopharmaceutics	186	186	2.1.5	A paragraph should be added, which says that in case both fasting and fed studies are required it's equally acceptable to conduct two separate studies or one four-way crossover study investigating both conditions in the same study (similar to the current EU guidance). The latter design can help to assess the food effect of the products in the study.	Add: In cases where information is required in both the fed and fasted states, it is acceptable to conduct either two separate two-way cross-over studies or a four-way cross-over study.
Medicines for Europe	186	186	2.1.5	Please add a paragraph which explains that in case both fasting and fed studies are required it's equally acceptable to conduct two separate studies or one four-way crossover study investigating both conditions sequentially in the same study (similar to the current EU guidance). The latter design can help to assess the food effect of the products in the study, even if there is no randomizion for this evaluation.	Add: In cases where information is required in both the fed and fasted states, it is acceptable to conduct either two separate two-way cross-over studies or a four-way cross-over study.
EFPIA	187	189	2.1.5	This is already covered in the scope of the guideline, there is no need to repeat it for this specific section (it is not repeated in other sections of the guideline, so this is inconsistent).	Suggest to remove this sentence.
EFPIA	187	189	2.1.5	The above principles with regard to fasting and fed study conditions also apply when BE studies are deemed necessary to bridge formulation and/or manufacturing process changes during pre- or post-marketing phases.	What is implied by 'also' here, i.e. what is the base case referred to, e.g. generics? Please clarify.
EUFEPS Network on Bioavailability and Biopharmaceutics	187	189	2.1.5	For the post-marketing phase, a comment should be added that minor changes for high-risk product can still be covered by a justification for omission of bioequivalence studies (in-vitro profiles), even if the product in original marketing authorisation was tested only at one condition (fasting or fed).	
Krka, d.d., Novo mesto	187	189	Section 2.1.5	We understand that this requirement applies only when BE study is requested (but not in case of minor variations which can be substantiated with in vitro profiles). It should be clear that acceptabiliy of waiver for conduct of fasting and fed should be included, if properly justified.	The above principles with regard to fasting and fed study conditions also apply When BE studies are deemed necessary to bridge formulation and/or manufacturing process changes during pre- or post-marketing phases, BE study under most sensitive conditions (either fasting or fed) is sufficient, if properly justified.
Medicines for Europe	187	189	2.1.5	It is not clear why this paragraph is needed here. It's mentioned already in the introduction (lines 17-21) that the guideline applies in different scenarios and this statement applies to all requirements, not just the fed/fasting section.	
Richter Gedeon Plc	189	189	2.1.5	The following recommendation should be explicitly noted in high risk product's section: Rational for claiming 'Lack of relevant food effect differences between test and reference product' justified by modelling (e.g., appropriately validated/qualified physiologically based pharmacokinetic modelling or semi-mechanistic absorption models) should be accepted in certain cases to waive in vivo study. When such justification can be built, in vivo study should be conducted only in the most discriminative food condition even in case of high risk products. This approach should even be encouraged in case when the reference product's labeling advises intake in a specific condition with regards to food.	When there is a well defined difference between the high risk test and reference product a rationale can be given to justify the lack of relevant food effect differences by modelling. If the justification based on appropriately validated/qualified PBPK modelling results it is acceptable to conduct in vivo study only with the more discriminative condition (either fasting or fed state) and the in vivo study for the othe condition could be waived. This approach is encouraged especially in case of products that should be administered in a specific condition with regards to food intake based on product labeling.
EFPIA	190	219	2.1.5	in some cases : pediatric formulation classical food content may not be appropriate: ie apple sauce	propose an alternative to classical meal for pediatric formulations
Gilead Sciences	190	219	2.1.5	Consider to also cover in this section, other concommitant medications, e.g. vitamins, herbal meds, contraceptives.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUFEPS Network on Bioavailability and Biopharmaceutics	191	196	2.1.5	*Further restrictions are sometimes needed beyond the ones described currently in the draft, e.g. water standardisation is required for safety reason to hydrate subjects in regular manner or standardised water intake, or posture restrictions, are ways to reduce intrasubject variability. * Posture of the patient during and after peroral medication intake might be considered and standardized, preferably to an upright posture. There is data indicating that lying on the back or on the left side may influence gastric emptying kinetics opposed to sitting upright/standing. We would propose to add at least a sentence, that dependend on the investigated drug and population, more restrictions may be required and the design should consider those restrictions relevant for an appropriate comparison of treatments. Also: * Requirements related to food administration are not practical in steady-states studies. Please clarify that the "4 hours post-dose on each day of of drug administration" is considered for the profile days and was not intended for the steady-state build-up phase in a multiple-dose-study.	For studies conducted under fasting conditions, subjects should be fasted for at least 10 hours before drug administration. Subjects may be allowed water as desired, except for 1 hour before and at least 1 hour after drug administration. The dose should be administered with a standardised volume of water, in the range of 150 to 250 millilitres (ml). No food should be allowed for at least 4 hours post-dose on each day of drug administration (days of profiling only) and meals taken should be standardised with respect to composition and timing. Further restrictions, e.g. regarding posture of the subjects during and after administration, may be beneficial.
Medicines for Europe	191	196	2.1.5	Sometimes further restrictions are needed beyond the ones described currently in the draft. Besides, suggested restrictions cannot be followed in MD studies with more than once-daily drug administration.	For studies conducted under fasting conditions, subjects should be fasted for at least 10 hours before drug administration. Subjects should be allowed water as desired, except for 1 hour before and at least 1 hour after drug administration. The dose should be administered with a standardised volume of water, in the range of 150 to 250 millilitres (ml). In single dose studies and on PK day in MD studies no food should be allowed for at least 4 hours post-dose on each day of drug administration and meals taken should be standardised with respect to composition and timing. Further restrictions, e.g. regarding posture, may be necessary.
Krka, d.d., Novo mesto	192	196	Section 2.1.5	Sometimes further restrictions or study standardisations are needed beside the ones described. Further, suggested restrictions cannot be followed in multiple-dose studies with more than once-daily drug administration.	For studies conducted under fasting conditions, subjects should be fasted for at least 10 hours before drug administration. Subjects should be allowed water as desired, except for 1 hour before and at least 1 hour after drug administration. The dose should be administered with a standardised volume of water, in the range of 150 to 250 millilitres (ml). In single dose studies and on PK day in multiple-dose studies no food should be allowed for at least 4 hours post-dose on each day of drug administration and meals taken should be standardised with respect to composition and timing.
EFPIA	193	194	2.1.5	Recommendations regarding water intake should be softened and flexible enough, to accomodate for situation where drug properties would require alternative conditions, if scientifically justified	
EFPIA	193	194	2.1.5	Restrictions regarding food intake should be softened and flexible enough, to accomodate for situation where drug properties would require alternative conditions, if scientifically justified	
Gilead Sciences	194	196		" No food should be allowed for at least 4 hours post-dose on each day of drug administration and meals taken should be standardised with respect to composition and timing." The first part of the sentence states no food, but the second part of the sentence states food administration. Consider separating the two, and clarify the second part of the sentence is referred to meals taken after dosing. Please also clarify what does 'timing' being referred to in the second part of the sentence.	
EFPIA	197	198	2.1.5	In the case of studies conducted under fed conditions, the same controls should be employed with the exception that a pre-dose meal should be provided.	Please specifiy what is meant by "same controls", does this mean fasted for 10 hours prior to meal?
EFPIA	198	200	2.1.5	No window is provided for when the drug needs to be given after the meal	e.g. add that dosing should occur 30 +-5 minutes after the start of the meal

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	198	200	2.1.5	No minimum % consumed of meal is indicated	e.g. add that subject must consume at least 75% of the meal
EFPIA	199	200	2.1.5	Do they have to consume all of the meal? If not, should this be documented?	Line 199- subjects start the meal 30 minutes before administration of the drug product and consume all of the meal
EFPIA	201	201	2.1.5	No need to specify "high risk". Cases under which fast and fed conditions are needed were alread defined, focusing here on high risk may generate confusion in the reader.	Delete "i.e., for high-risk products,"
EFPIA	201	208		Here again the assumption is that we will need to do a BE study for both fed and fasted conditions for high-risk compounds. As noted above this is a very high bar and unlikely to be achieved in many cases. Therefore, we propose that the text be updated as indicated	We encourage the ICH to update the text as follows:"For high-risk products, the BE study conducted under fed conditions should be conducted using a meal that is considered relevant to the label recommendation. With an additional assessment of fed versus fasted relative bioavailability. It is recognised that there may be situations where it is appropriate to administer a pre-dose meal with a different caloric/fat content from these recommendations, e.g., for studies performed in patient populations who cannot tolerate the recommended meal composition".
Medicines for Europe	201	208		A different type of meal might be selected for reasons beyond safety such as SmPC recommendations.	Proposed Change: It is recognised that there may be situations where it is appropriate to administer a pre-dose meal with a different caloric/fat content from these recommendations, e.g., for studies performed in patient populations who cannot tolerate the recommended meal composition or special SmPC administration recommendation.
SciencePharma, Poland	201	203	2	The sentence "If BE studies are conducted under both fasting and fed conditions, i.e., for high-risk products, the BE study conducted under fed conditions should be conducted using a meal that has the potential to cause the greatest effect on GI physiology." is too geneal, as it is not specified what aspect(s) of GI physiology sholud be taken into consideration.	It is suggested to specify, which aspects of GI physiology should be taken into consideration while choosing the meal with the greatest effect: "If BE studies are conducted under both fasting and fed conditions, i.e., for high-risk products, the BE study conducted under fed conditions should be conducted using a meal that has the potential to cause the greatest effect on GI physiology (e.g. GI transit time)."
EFPIA	203	206	2.1.5	BE study conducted under fed conditions should be conducted using a meal that has potential to cause the greatest effect on GI physiology. It may not always be the case that a high fat meal would be the most discriminatory as it may result in release of a higher amount of bile salts.	Please consider adding to line 203, "…GI physiology, in most instances this would be a high-fat meal…."
Medicines for Europe	203	206	2.1.5.	High-calorie meal should contain totally 800-1000 kcal, and at the same time, following caloric content is required: 150, 250, and 500-600 kcal, from protein, carbohydrate, and fat, respectively. Since 50% of total caloric contect must account for fat, the lower limit for calories from fat must be modified to 400 kcal.	The meal should be a high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal, which should derive approximately 150, 250, and 400-600 kcal from protein, carbohydrate, and fat, respectively.
ORBIS project	203	205	2.1.5	Numbers do not match. For 800 kcal meal, 400 kcal or less is sufficient to meet recommendation of approximately 50% fat content, while 500-600 kcal is recommended in line 205.	Numbers for calories from fat should match.
Adamed Pharma SA	209	211	2.1.5.	In our opinion, this section should specify on what basis the type of meal served to study participants needs to be selected for non-high-risk product i.e.: when a high-fat, high-calorie meal is recommended and when a low-fat, low-calorie meal will be acceptable for BE study.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	214	216	2.1.5	The composition of the meal to be administered should be described with specified with regard to fat content only as this is the component that is most likely to impact the absorption of a drug.	The composition of the meal to be administered should be described with regard to fat content (specified in grams, kcal, and relative caloric content (%)) in the study protocol.
ORBIS project	214	216	2.1.5	The sentence referring to the meal to be administered needs clarification. A more detailed description of the meal is suggested, not only its composition but also its texture, the possibility of taking the meal in liquid or semi-liquid form.	Clarification needed. We recommend stating that solid food should prevail in the meal as the most common case in real life. The "standard meal" contents can also be proposed.
EFPIA	217	219	2.1.5	herbal tea such as roiboos may have an impact on absorption behavior	exclude herbal tea such as roiboos from authorized beverage
Krka, d.d., Novo mesto	217	219	Section 2.1.5	It is not possible to know such effects for all food and drinks.	In all situations, It is recommended that subjects should abstain from well-known foods and drinks that may interact with circulatory, GI transporter, GI enzymatic, hepatic, or renal function, e.g., alcoholic or caffeinated drinks, or certain fruit juices such as grapefruit juice, during a suitable period before and during the study.
Medicines for Europe	217	217		"In all situations, subjects should abstain from foods and drinks that may interact with circulatory,..." Comment: It is not possible to know such effects for all food and drinks.	Proposed change: "It is recommended that subjects abstain from well-known foods and drinks that may interact with circulatory,..."
ORBIS project	219	219	2.1.5	The term 'suitable period' is not clear. The recommendation would be greatly appreciated as Regulatory Agencies have much more data on the issue than the applicants.	Clarification needed
Adamed Pharma SA	220	226	2.1.6.	The EMA GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE fully describe what is meant by the term of linearity of pharmacokinetics. In the ICH Guideline M13A, the authors refer to the term dose proportionality, but the exact criteria for this term are not defined. In our opinion, the need to include information on what criteria must be met in order to consider that pharmacokinetic parameters (Cmax, AUC) are dose-proportional is greatly recognised.	
Adamed Pharma SA	220	241	2.1.6.	There were precise criteria for the possibility of using the biowaver for other strenght of IMP in EMA GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE, section 4.1.6, which have been removed from the M13A. We are aware, that the M13B document, which will provide accurate information, is planned for the ICH M13 series. However, we wonder whether all documents from the M13 series will be introduced simultaneously? If not, this section of the guideline does not make a clear distinction how the use of the biowaver will be regulated during the transition period.	
EUFEPS Network on Bioavailability and Biopharmaceutics	221	241	2.1.6	*Due to its higher variability and/or inaccuracies in published studies (e.g. due to sparse sampling and small number of subjects) it's difficult to reliably estimate proportionality for Cmax. An assessment based on AUC only may therefore be sufficient. *A definition for proportionality should be provided., e.g. +/-25% may be used including a clarification that either arithmetic or geometric means can be considered.	Restrict proportionality to AUC only, give definition for proportionality (as in current EMA guideline +/- 25%)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	221	226	2.1.6	The recommendation to use the highest to-be-marketed strength in general should depend on PK proportionality. The selection in case of non-proportionality is described.in lines 230-241. So the general recommendation here should refer to cases with PK proportionality only. The solubility of the analyte does not necessarily relate to the solubility (and thus dissolution) of the active substance since these may be different (e.g. in cases where a metabolite is measured).	In case of an application with multiple strengths, the strength to be used in the BE study depends on the dose proportionality in PK and solubility of the active substance ~~analyte~~. Generally, the highest to-be-marketed strength can be administered as a single unit in cases of dose proportional PK, i.e., area under the concentration vs time curve (AUC) ~~*and Cmax*~~ , has been documented over the range of strengths. Selection of a lower strength may also be accepted if the highest strength cannot be administered to healthy subjects for safety and/or tolerability reasons ~~and dose proportional PK, i.e., area under the concentration vs time curve (AUC) and Cmax, has been documented over the range of strengths~~.
Medicines for Europe	221	241	2.1.6	Dose proportionality relates to both AUC and Cmax (current EMA guideline AUC only). In dose proportionality studies there is usually a small number of subjects enrolled, which is additional argument, why only AUC should be considered. Due to its higher variability and/or inaccuracies in published studies (e.g. due to sparse sampling) it's difficult to reliably estimate proportionality for Cmax. An assessment based on AUC only may therefore be sufficient.	Restrict proprtionality to AUC only, give definition for proportionality (as in current EMA guideline +/- 25%)
Richter Gedeon Plc	221	241	2.1.6	Dose proportionality should be showed on both AUC and Cmax (valid EMA guideline: only AUC). In dose proportionality studies the volunteer number is low, so it would not be suitable to evaluate proportionailty for Cmax.	Keep current EMA guideline for this part.
SciencePharma, Poland	221	229	2	The issue of PK proportionality is discussed in this section. However, the criteria for proportionality were not provided.	It is suggsted to add a sentence regarding the criteria for PK propotionality, similarly as in the curent CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** guideline: "PK is considered to be proportional if the difference in dose-adjusted mean AUCs and Cmax is no more than 25% when comparing the corresponding strengths."
EUFEPS Network on Bioavailability and Biopharmaceutics	222	222	2.1.6	The solubility of the analyte does not necessarily relate to the solubility (and thus dissolution) of the active substance since these may be different (e.g. in cases where a metabolite is measured).	"…on the dose proportionality in PK and solubility of the active pharmaceutical ingredient"
Krka, d.d., Novo mesto	222	223	Section 2.1.6	Definition of what can be considered as dose-proroportional pharmacokinetics is missing. In line with current EMA guideline, a difference of no more than 25% for dose-adjusted mean of AUC between strenghts should be acceptable to claim dose-proportional pharmacokinetics.	To be added in the line 222: In the context of this guideline, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength (or strength in the planned bioequivalence study) and the strength(s) for which a waiver is considered.
Krka, d.d., Novo mesto	222	238	Section 2.1.6	There is considerable variety in how dose-proportionality studies are conducted. Regardless, we can unequivocally state that dose-proportionality studies are most frequently performed on small number of subjects with independent cohorts (parallel design) (1) making the assessment of linearity on basis of Cmax parameter unreliable. As the Cmax parameter is generally much more variable than the AUC parameter, only AUC parameter should be considered for the assessment of linearity. References: (1)Jürgen Hummel, Sue McKendrick, Charlie Brindley, Raymond French. Exploratory assessment of dose proportionality: Review of current approaches and proposal for a practical criterion. Pharmaceutical Statistics 2008; 8(1):38-49	Assessment of linearity should be restricted to AUC parameter only, without C_{max} parameter; meaning C_{max} parameter should be deleted from lines 226, 230, 234, 236 and 238.
ORBIS project	222	222	2.1.6	It is confusing solubility of the analyte (possibly metabolite) is cited. Please consider changing to an active pharmaceutical ingredient.	analyte => active pharmaceutical ingredient (API)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUFEPS Network on Bioavailability and Biopharmaceutics	223	226	2.1.6	*The draft guideline allows the the use of a lower dose for safety reasons only in case of proportional PK. Since the only alternative is a patient study (usually under less sensitive multiple dose conditions) and since the guideline allows deviation from certain principles for safety reasons in other sections (fed/fasting administration), selection of a lower dose should also be acceptable in case of non-proportional PK.	
EUFEPS Network on Bioavailability and Biopharmaceutics	226	228	2.1.6	In case administration of multiple units is required, the rationale for "provided the total single-dose remains within the labelled dose range" is unclear . Higher doses should be acceptable as long as the total dose is safe for administration to the subjects. Otherwise, there are issues e.g. in BE studies for some respiratory products (which principles of this guideline apply to acc. to lines 14-16). Another example would be trials for levothyroxine, that generally depend on administration of supra-therapeutic doses.	Delete "the total single-dose remains within the labelled dose range and"
Medicines for Europe	226	228	2.1.6	Rationale for "provided the total single-dose remains within the labelled dose range" is unclear as long as the total dose is safe for administration to the subjects. This would make BE studies for some respiratory products impossible (which principles of this guideline apply to acc. to lines 14-16).	Delete "the total single-dose remains within the labelled dose range and"
ORBIS project	226	229	2.1.6	The recommendation that a single dose should remain within the labelled dose range is an unnecessary requirement and may be hard to meet for inhalation products. It may limit generic competition. The highest doses than labelled are studied during original drug development and dose safety margin may be significant. The sufficient recommendation to ensure patient safety is "total dose is safe for administration in study subjects".	If warranted to achieve sufficient bioanalytical sensitivity, multiple units of the highest strength can be administered, provided the total single-dose remains within the labelled dose range and the total dose is safe for administration to the study subjects.
EFPIA	228	228	2.1.6	In case of endogenous compounds, supratherapeutic doses may be needed to ensure a proper PK over baseline is measured. This could be done in case the PK proportionality is ensured up to the proposed dose.	Delete "single-dose remains within the labelled dose range and the total"
EFPIA	230	233	2.1.6	This paragraph describe how the dose proportionality shoud be assessed and is out of the scope of this guideline. The conditions under which doses are to be selected are described in the other paragraphs and the knowledge of proportionality or non proportionality is a prerequisite.	Delete lines 230 to 233.
ORBIS project	230	241	2.1.6	Please consider limiting dose proportionality verification to AUC only and indicate criteria, e.g. like in EMA BE guideline +/- 25% for AUC. Cmax related to a single measurement and is a subject of higher variation than AUC. In dose-proportionality studies, the number of subjects is limited. Thus, a single outlier strongly influences results which may falsely indicate a lack of dose-proportional PK observed in the study while PK is in fact dose-proportional. The same situation is far less probable for AUC.	Limit dose proportionality assessment to AUC and recommend the criterion (e.g., +/- 25% deviation from AUC.
ProPharma <Bertine Vorstenbosch - de Wijs>	230	241	2.1.6	For non-proportional increases in AUC and/or Cmax with increased dose there may be a difference between different strengths in the sensitivity to detect potential differences between formulations. To assess dose proportionality, the applicant should consider all available data regarding dose proportionality. Assessment of dose proportionality should consider single-dose studies only. For drugs with a more than proportional increase in AUC and/or Cmax with increasing dose over the therapeutic dose range, the BE study should in general be conducted at the highest strength. For drugs with a less than proportional increase in AUC and/or Cmax with increasing dose over the therapeutic dose range, BE should be established at the lowest strength if this situation is due to saturation of absorption.	Please consider to add a Decision Tree to clarify the steps to be taken.
EFPIA	232	233	2.1.6	The definiton of proportionality should be extended to at least include a comparative dissolution profile for different strengths. An FDA guidance specifies: Information on the types of recommended in vitro dissolution and in vivo bioequivalence studies for immediate-release and modifed-release drug productes approved as NDAs for specified pos-approval changes is provided in the following FDA guidances: SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Control; In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation	Assessment of linearity will consider whether differences in dose-adjusted AUC meet a criterion of ± 25%. Please consider clarify and aligning with FDA guidance.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUFEPS Network on Bioavailability and Biopharmaceutics	232	233	2.1.6	While there may be a higher risk to observe non-proportionality in multiple dose studies, such data may still be relevant for proportionality assessment (e.g. if proportional under m.d. conditions as well), especially if no or if only limited data from single dose studies are available. The wording could be adjusted accordingly.	
Medicines for Europe	232	233	2.1.6	While there is a higher risk to observe non-proportionality in multiple dose studies, such data may still be relevant for proportionality assessment (e.g. if proportional under m.d. conditions as well), especially if no or if only limited data from single dose studies are available. The wording could be adjusted accordingly. In addition, a definition what can be considered proportional is required, such as the one which is currently present in the EMA guideline.	To assess dose proportionality, the applicant should consider all available data regarding dose proportionality. Assessment of dose proportionality could be done using single-dose studies or multiple dose studies~~.~~ In the context of this guideline, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength (or strength in the planned bioequivalence study) and the strength(s) for which a waiver is considered.
EFPIA	233	233	2.1.6	Consider adding: Assessment of dose proportionality should consider single-dose studies only for support of a single dose BE study.	Consider adding: Assessment of dose proportionality should consider single-dose studies only for support of a single dose BE study.
Krka, d.d., Novo mesto	233	233	Section 2.1.6	There are cases where single dose dose-proportionality studies are not available. Namely, for certain active substances, not all strengths of a product can be administered to healthy subjects for safety and/or tolerability reasons, whereas single-dose studies cannot be conducted in patients. In such cases, linearity in pharmacokinetics is assessed based on data from multiple-dose studies in patients. Additionally, multiple-dose studies may be more discriminatory in assessing dose-proportionality. Accordingly, data from multiple-dose dose-proportionality studies should also be considered acceptable for the assessment of linearity in cases where data from single-dose studies are not available or are unreliable/underpowered.	Assessment of dose proportionality should consider single-dose studies or multiple-dose studies in case there is no reliable data from single-dose studies.
EFPIA	234	241	2.1.6	MINOR COMMENT	We encourage the ICH to provide further clarification on the following statement:"For drugs with a more than proportional increase in AUC and/or Cmax with increasing dose over the therapeutic dose range, the BE study should in general be conducted at the highest strength".
EFPIA	236	238	2.1.6	If we cannot show "saturable absorption" as the reason for an observed less than dose proportional increase, then we have to study 2 dose levels. Therefore, some clarity on how to determine saturable absorption will be helpful	We recommend the ICH to include examples of acceptable evidence to demonstrate "saturable absorption".
EFPIA	236	241	Section 2.1.6	For drugs with a less than proportional increase in AUC and/or Cmax with increasing dose over the therapeutic dose range, BE should be established at the lowest strength if this situation is due to saturation of absorption. If the less than proportional increase in AUC and/or Cmax with increasing dose is due to limited drug solubility, BE studiesshould be conducted at both the lowest and highest strengths. If the reason for non-dose proportionality is unknown, BE studies should generally be conducted at both the lowest and highest strengths.	Would it be possible to clarify the type of data needed to support saturation of absorption versus solubility please? The root cause of less than proportional PK can be difficult to discern in vivo as dose/250mL is an over simplification of gut drug concentrations and/or the transporter responsible for absorption may be unknown.
EUFEPS Network on Bioavailability and Biopharmaceutics	236	241	2.1.6	If studies both at the lowest and highest strength are required and the respective product is deemed high risk - it is not clear, if studies will be needed for both strengths on fasting AND fed conditions (4 trials). If not, which studies can be waived.	
ORBIS project	236	241	2.1.6	Implementing the necessity to study two doses for a drug product which also requires fasting/fed condition and pH-dependence study results in 6 clinical BE studies what limits (or precludes) generic competition. To limit additional costs and promote generic competition, we suggest that if the two doses are studied for drug products that require also fasted and fed conditions and/or pH-dependency verification, the fed conditions and pH-dependency are checked only for the highest dose.	If the reason for non-dose proportionality is unknown, BE studies should generally be conducted at both the lowest and highest strengths. A single BE study for the highest dose is recommended. Study in highest strength should be conducted in fasting conditions, except drugs administered only with meal which should be studied in fed conditions.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	240	241	2.1.6	Currently it is assumed that full bracketing is acceptable, but what if "intermidate strengths" behave differently from lowest and highest strengths. In case of non-dose proportionality, ICH should advise BE studies at all strengths	
EUFEPS Network on Bioavailability and Biopharmaceutics	240	241	2.1.6	The last sentence clearly concerns only this paragraph. Therefore, "non-dose proportionality" should be replaced by "less than dose proportionality" to avoid confusion with more than proportional non-dose proportionality.	
Medicines for Europe	241	241	2.1.6	It should be considered whether a clause could be added at the end of section 2.1.6 allowing the use a lower strength in all cases where studies in the highest strength are in general required if there are safety and/or tolerability concerns	Add: In all cases where studies in the highest-to-be-marketed strength are generally required, it is acceptable to select a lower strength if the highest strength cannot be administered to healthy subjects for safety and/or tolerability reasons.
Gilead Sciences	242	265	2.1.7	Consider adding a note in this section (or elsewhere) that if metabolites need to be measured, wash out and sampling times may need to be adjusted to enable adequate characterisation of the PK profile of the metabolite.	
ORBIS project	242	242	2.1.7	The section title 'Moieties to be measured' should be changed to increase readability and understanding.	"Moieties to be measured" => "Selection of Analyte"
SciencePharma, Poland	244	250	2	According to the guideline, there is no possibility to use the metabolite as a surrogate for an active parent compound in case it is not possible to reliably measure the parent compound. It is acceptable only in case of prodrugs. This issue had been widely discussed before the current CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** guideline came into force.	It is suggested to add the following sentences, as per current CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** guideline: "The use of a metabolite as a surrogate for an active parent compound is not encouraged. This can only be considered if the applicant can adequately justify that the sensitivity of the analytical method for measurement of the parent compound cannot be improved and that it is not possible to reliably measure the parent compound after single dose administration."
EFPIA	250	252	2.1.7.1	It would be helpful to clarify and define the threshold for when the metabolites have to be measured and demonstrate bioequivalence.	"In cases where a metabolite contributes to safety or efficacy that constitutes at least X% of total activity, demonstration of BE should be based on the parent drug and primary active metabolite".
Adamed Pharma SA	251	255	2.1.7.1.	To avoid ambiguity, we suggest adding a statement that if the active metabolite appears after the absorption stage, there is no need to measure its level to demonstrate bioequivalence.	
EUFEPS Network on Bioavailability and Biopharmaceutics	251	253	2.1.7.1	*It is not clear why assessment of the parent drug does not suffice if any active metabolites are formed through gut wall metabolism. This resembles First-Pass in the liver and should not be of concern. It may also not be only seen in rare cases. * Formation in the gut lumen obviously is different as direct interaction with the formulation may have an impact on the local formation. * Cases where both the parent compound and a primary active metabolite have to be considered for BE assessment should be limited to situations where it is known that a relevant amount of pre-systemic metabolism occurs and where the metabolite has a significant contribution ot efficacy and/or safety.	
Krka, d.d., Novo mesto	251	255	Section 2.1.7.1	Formation of metabolites in GIT lumen is extremely rare. Distinction of metabolite forming in the GUT wall and in the liver is very difficult. Therefore it may make sense to define cases when additional analyses of metabolites are necessary in product specific guidelines and thus avoid misinterpretations.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	251	253		"In rare cases, demonstration of BE based on the parent drug alone may not be sufficient and the primary active metabolite should also be considered, e.g., drugs that have metabolites formed through gut wall or gut lumen metabolism that contribute to efficacy or safety" Comment: This should only be relevant for the metabolites that significantly contribute to E/S. The cases where both the parent compound and a primary active metabolite have to be considered for BE assessment should be limited to situations where it is known that significant pre-systemic metabolism occurs and where the metabolite has a significant contribution to efficacy and/or safety.	In rare cases, demonstration of BE based on the parent drug alone may not be sufficient and the primary active metabolite should also be considered, e.g., drugs where it is known that they have a relevant amount of metabolites formed through gut wall or gut lumen metabolism that contribute significantly to efficacy or safety.
ORBIS project	251	255	2.1.7.1	It may not be possible for an applicant to decide whether a generic drug under development meets the criteria for a "rare case" or not. The term "contribute to efficacy or safety" is not clear and may be interpreted by regional Regulatory Agencies in a different way. Harmonised list of drugs and respective analytes should be added to the guideline. This list may be periodically updated, thus it may be suitable to include list in the appendix to the guideline.	Add harmonised list of drugs and respective analytes.
EUFEPS Network on Bioavailability and Biopharmaceutics	260	261		A stereoselective assay should be required only if a) the enantiomers exhibit different pharmacodynamic properties, b) the enantiomers exhibit different PK properties, and... Comment: This should only be relevant in case of significant difference.	
Krka, d.d., Novo mesto	260	261	2.1.7.2	Conditions under points a and b should only be relevant in case of significant difference.	"a) the enantiomers exhibit significantly different pharmacodynamic properties, b) the enantiomers exhibit significantly different PK properties, and"
Medicines for Europe	260	261		"a) the enantiomers exhibit different pharmacodynamic properties, b) the enantiomers exhibit different PK properties, and" Comment: This should only be relevant in case of significant difference.	Proposed change: "a) the enantiomers exhibit significantly different pharmacodynamic properties, b) the enantiomers exhibit significantly different PK properties, and"
EFPIA	264	265	2.1.7.2	It is sufficient to demonstrate BE for only the active enantiomer in cases where one enantiomer is inactive (or makes a low contribution) with respect to both safety and efficacy.	Is there a threshold value for % of enantiomer below which it can be considered a 'low contribution enantiomer'?
ORBIS project	264	265	2.1.7.2	The term 'low contribution' is not clear.	Define "low contribution"
Adamed Pharma SA	265	265	2.1.7.2.	The term "low contribution" could be more precise. The guideline should provide specific criteria by which "low contribution" can be assessed.	
EFPIA	265	265	2.1.7.2	How is the "low contribution" defined? Keeping this wording could open the path to different intepration of what is "low" for same molecule by both the applicant and by different regulatory authorities revising the study protocol, leading to unecessary study repetition.	
EFPIA	267	273	2.1.8	In general, it is recommended to take at least 12-18 samples after single dose administration to fully characterize the PK profile	Please consider this wording (line 270), "...sufficient samples after Tmax to ensure are liable estimate of the extent of exposure,which is achieved when AUC(0-t)covers at leas t80% of AUC(0-inf). In general it is recommended to take at least 12-18 samples...."
ORBIS project	277	280	2.1.8	It may not be possible to calculate Kel for drugs exhibiting enterohepatic circulation. There may be problems with calculation of Kel for individual subjects too. Both situations should be acknowledged in the guideline.	Add acknowledgement that in some cases (e.g. drugs exhibiting enterohepatic circulation, individual semi-log profiles not showing linearity in terminal phase) it may not be possible to calculate kel. Add confirmation that such situations (if explained) do not influence validity of the study.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	278	280	2.1.8	Suggest specifying a minimum span for calculation of kel	"To reduce these inaccuracies, it is recommended that three or more data points in the terminal log-linear phase of the concentration-time curve be used to estimate kel and that the sampling interval used to calculate kel be at least 1.5-times the half-life of the drug."
EFPIA	281	283	2.1.8	It is not clear what is the "pre-dose" mentioned here. If it is the pre-dose before the first dose, then 5 min before dosing is not necessary and normally within 15 min before dosing is considered adequate. If it is the pre-dose before the last dose, then the sampling time window should be the same as the time window for the last sample within the dosing interval (here specified in 10 min).	In multiple-dose studies, the pre-dose sample before the first dose should be taken immediately before dosing, i.e., within 15 ~~5~~ minutes of dosing, and the sample before the last dose is recommended to be taken within 10 minutes of the nominal time for the dosage interval to ensure an accurate determination of AUC(0-tauSS).
EFPIA	281	283	2.1.8	In multiple dose studies, recommendation of sampling within 10 min nominal time point for last sample may not be relevant for compounds with long half-life.	
EFPIA	281	283	2.1.8	In multiple-dose studies, the pre-dose sample should be taken immediately before dosing, i.e., within 5 minutes of dosing, and the last sample is recommended to be taken within 10 minutes of the nominal time for the dosage interval to ensure an accurate determination of AUC(0-tauSS).	For compounds with a long t1/2 specifying that the pre-dose sample is take 5 minutes prior to dosing may be overly stringent, suggest this could be wriiten more flexibly. Same principle applies to the timings of the last PK sample during the dosing interval. Pre-dose and Ctau should have the same level of flexibility e.g. both 5 or both 10 minutes.
Krka, d.d., Novo mesto	282	282	Section 2.1.8	Proposed time-span seems too short (for practical reasons). We suggest the same time window for pre-dose and for the last sample (10 minutes). E.g. based on internal data analyses from typical BE study the introduced 5 minutes difference in the predose window is estimated to be less than 0.5% percent of the AUC0-24. Such small contribution in AUC evaluation does not justify the possible errors and protocol deviations that would occure at the clinical site if such condition would to be introduced.	"the pre-dose sample should be taken immediately before dosing, i.e., within 10 minutes"
Medicines for Europe	282	282		"the pre-dose sample should be taken immediately before dosing, i.e., within 5 minutes" Comment: This time-span is too short (for practical reasons). We suggest the same time window for pre-dose and for the last sample (10 minutes).	Proposed change: "the pre-dose sample should be taken immediately before dosing, i.e., within 10 minutes"
Adamed Pharma SA	288	290	2.1.8.1.	It suggests the situations when the datasets of Cmax occurring at the first post-dose sampling time may not result in exclusion of the data from affected subjects from the analysis. We believe, it is worth specifying whether and in which circumstances it is necessary to exclude a participant(s) and what criteria should be met in such case.	
EFPIA	288	290	2.1.8.1	Why Cmax if collected at first sampling time after dose is to excluded ? This is contrary to the principle that data cannot be excluded just based upon PK consideration. While the study per se cannot be considered adequate to show BE if the study design is flawed by incorrect sample collection, the data cannot be excluded.	Delete the last sentence: "Datasets where Cmax occurs at the first post-dose sampling time may result in exclusion of the data from affected subjects from the analysis."
EUFEPS Network on Bioavailability and Biopharmaceutics	288	290	2.1.8.1	It should be considered that requirements of this guideline will be considered as clear and hard criteria during evaluation of market authorisation applications Thus, clear criteria how to treat datasets with first time Cmax should be provided. We suggest that such datasets be considered, but that observations question the validity of the results if first time Cmax occurs too frequently. For practical reasons the language in the current FDA guidance may by considered, which accepts first time Cmax as long as sufficient sampling at an early time point was done.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	288	290	2.1.8.1	Clear criteria how to treat datasets with first time Cmax should be provided.This is especially relevant for fast release/absorption products.	Datasets where Cmax occurs at the first post-dose sampling time may not result in exclusion of the data from affected subjects from the analysis, but may question the validity of the trial if such observations are made in more than 20% of all profiles determined in a study.
ORBIS project	288	290	2.1.8.1	The phrase 'may result in exclusion' is ambiguous and may preclude harmonisation. The exclusion of data is critical for validity of the study, and the rule should be 0/1 decision. Please consider adding statement that single occurrences of Tmax at a first post-dosing sampling time are acceptable. However, a rule similar to AUC0-t/AUCinf ratio may be applicable, for example "In case Tmax is observed at a first post-dosing sampling time in at least 20% of subjects after administration of particular product (test or comparator) then validity of the study need to be discussed in the submission."	Add specific and clear criteria for exclusion of data. Specify recommended action if criteria are not met.
Arab Pharmaceutical industry Consulting	291	296	2.1.8.2	how to handle missing values at 72 hours for truncated designs is not discussed. For long-half life, normally samples will be 24, 48 and 72 so missing 72 time point will lead to loosing one third of the profile.	Add to paragraph: If the subject didn't show up at the clinic for the sampling of 72 hours or 72 hours sampling had concentration less than LLOQ then this subject data should be excluded from statistical analysis of AUC0-72 provided to end with a minmum of 12 readings for AUC0-72
ORBIS project	291	305	2.1.8	The content of paragraphs 2.1.8.2 and 2.1.8.3 does not match the main title of section 2.1.8. Sampling, and it may be more matched with Pharmacokinetic analysis section. To increase readability, please consider re-writing the whole section as a step-by-step general guidance of sampling points to be selected, i.e. pre-dose, 1-2 samples before Tmax, well-characterised Tmax (usually 5-10 sampling points), distribution phase (3 points), elimination phase (at least three sampling points), the last sampling point (3 times half-life or 72 h, whichever is shorter).	The content of sub-sections should match the section title.
EFPIA	292	296	2.1.8.2	The long elimination half-lives could apply to drugs with low intrasubject availability	Please clarify if this applies to drugs with low intrasubject variability
EUFEPS Network on Bioavailability and Biopharmaceutics	292	296	2.1.8.2	Half-lives differ between subjects included in a study. However, use of truncated AUC should be acceptable in any case, even if only a part of the subjects meets certain critieria related to half-life, e.g. if there are both slow and fast metabolizers. For clarification a sentence could be added to this paragraph which says that sampling beyond 72 h is not considered necessary for any immediate release formulation (such as in the current EMA guideline). Basically, as the "threshold" of 24 hours has no real purpose, if truncated area is anyway accepted, the "24h" could be omitted in order to avoid establishing a "potentially misinterpreted threshold".	
Medicines for Europe	292	296	2.1.8.2	Half-lives differ between subjects included in a study. However, use of truncated AUC should be acceptable in any case, even if only a part of the subjects meets certain critieria related to half-life, e.g. if there are both slow and fast metabolizers. Therefore, a concrete definition of a half-life where the use of truncated AUC is acceptable should be avoided. For clarification a sentence could be added to this paragraph which says that sampling beyond 72 h is not considered necessary for any immediate release formulation (such as in the current EMA guideline).	Truncating AUC for orally administered IR drug products known to exhibit longer elimination half-lives, i.e., 24 hours or longer, mitigates the clinical challenge of prolonged sampling and follow-up. Therefore, For such products, AUC(0 72h) may be used in place of AUC(0-t) for comparison of the extent of absorption. Seventy-two hours is considered to be adequate to ensure completion of GI transit of the drug product and absorption of the drug substance. A sampling period longer than 72 h is not considered necessary for any immediate release formulation irrespective of the half life of the drug.
EFPIA	293	293	2.1.8.2	24h as a threshold for a "Long half-life drug" is defined too late in the guideline. This should be added under definition or stated previously in the document (i.e. first time when this term is used)	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Krka, d.d., Novo mesto	293	296	Section 2.1.8.2	Opting for using AUC(0-72h) should be based on whether all subjects are expected to exhibit measurable concentrations at 72 hours post-dose. While this is largely dependent on the drug's terminal half-life, other factors (e.g. shape of the entire plasma concentration-time curve) might also play a role, making some drugs with half-lives < 24 h suitable candidates for AUC(0-72h). Additionally, half-lives can differ significantly between subjects included in a study, which should not preclude the use of truncated AUC. Therefore, an exact limit for the half-life, above which to use truncated AUC, should not be set in the guideline. Since GI transit is completed in 72 h and sampling beyond that point is not considered necessary for immediate release products, this should be clearly stated to avoid unnecessary prolongation of clinical activities.	Truncating AUC for orally administered IR drug products known to exhibit longer elimination half-lives, i.e., 24 hours or longer, mitigates the clinical challenge of prolonged sampling and follow-up. For such products, AUC(0-72h) may be used in place of AUC(0 t) for comparison of the extent of absorption. Seventy-two hours is considered to be adequate to ensure completion of GI transit of the immediate-release drug product and absorption of the drug substance. A sampling period longer than 72 h is therefore not considered necessary for any immediate release formulation irrespective of the half-life of the drug.
EUFEPS Network on Bioavailability and Biopharmaceutics	297	305		It is recognised that partial AUC is introduced to have a reasonable alternative fo an evaluation of tmax. As tmax, early exposure is only relevant in rare cases. Partial AUC is a variable parameter and depends on the cut-off value, so has impact on the study design and cannot be considered additionally retrospectively. The draft guideline neither defines clearly when partial AUC is required, nor how the cutoff value is to be set. But without clear criteria its is not possible to design a study properly. It is therefore suggested to remove this section from M13A (see also next bullet) or refer to product-specific requirements separate from this general guideline. For an example of increased variability see Boily et al 2005 "The impact of new partial AUC parameters for evaluating the bioequivalence of prolonged-release formulations", although MR products are considered). * In addition it may be necessary to allow different statistical approaches for partial AUC, such as scaling (although not yet harmonised, unlimited scaling may be appropriate). Alternatively ,a requirement that only the point estimate must be within 80 to 125% could be considered for such a parameter. May also affect 2.2.4.	
Krka, d.d., Novo mesto	297	305	Section 2.1.8.3	In very rare cases early onset of action is proven to be clinically relevant and in many times importance of early onset of action is not supported by clinical studies. Additional PK parameters to assess bioequivalence of the products should therefore be applied only when clinical relevance of early onset is uniformly recognized. In order to unify approaches of different sponsors and assure comparability of studies and thus products, clear and concise guidelines for each product under question should be available. This is only possible through Product specific guidelines, therefore ommition of this section in the guideline should be considered.	Deletion of pAUC throughout the guideline.
Medicines for Europe	297	305		Early exposure (pAUC) Comment: Early exposure is only relevant in rare cases, therefore, it should be part of Bioequivelence product specific guidance.	Propose change: Deletion of pAUC as PK parameter for IR products
EFPIA	298	305	2.1.8.3	for rapidly absorbed compound AUC0-tmax maybe interesting parameter: it is the reflect of the rate of absorption	AUC0-tmax to be added for rapidly absorbed compound
SciencePharma, Poland	300	301	2	The information regarding the medicinal products with early onset has been added. However, the term "early onset" was not specified.	It is suggested to define (or at least provide an example of) the meaning of "early onset": *"(…) e.g., when the early onset (i.e. 15 minutes) of action is clinically relevant (…)"*
Arab Pharmaceutical industry Consulting	301	302	2.1.8.3	pAUC maybe used when the early onset of action is clinically relevant. what will be the acceptance criteria? Is it based on point estimate alone or on confidence intervals as well especially that not much published data on pAUC to support sample size calculations. Any suggestions for time to calculate early exposure in relation to tmax?	
Adamed Pharma SA	303	304	2.1.8.3.	In our opinion the phrase "predetermined time-point that is related to a clinically relevant pharmacodynamic measure" should be more precise. A clinically relevant pharmacodynamic measure may result in very different value for specific drugs, e.g. for analgesics should this measurement be related to Tmax? Furthermore, we wonder if the groups of medicines, for which pAUC should be determined, have been identified. If so, it would be helpful if the list of these drugs would be publicity available. □	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ORBIS project	306	333	2,2	Exclusion of data is a critical decision during BE study. Thus, a separate section consisting of all possible reasons for data exclusion would increase readability. Please consider placing all reasons for subject / data exclusion in one section, e.g. Lines 414-416 on exclusion of data due to pre-dose concentration > 5% Cmax could be moved to subsection 2.2.1.2.	Add dedicated section describing all possible reasons for subject / data exclusion.
EFPIA	308	311	2.2.1	It is mentioned " all criteria for study subject inclusion into the BE analysis population be clearly defined in the study protocol. Any exclusions from the BE analysis population should be documented prior to bioanalytical analysis, e.g., subjects that are withdrawn from the study, have protocol violations, or experience GI disturbances potentially affecting absorption." The GI disturbance may be related to characteristics of the test formulation (e.g., dose dumping) which would preclude the exclusion of the period from the analysis.	Please consider deleting the following from line 311: "…or experience GI disturbances potientially affeting absorption," as GI disturbances could be from the test formulation.
ORBIS project	309	311	2.2.1	The term "BE analysis population" should be defined. If BE analysis population consists of all subjects included in analysis of PK endpoints, then exclusion of subjects according to section 2.2.1.1. or with pre-dose concentration > 5% Cmax prior bioanalysis (lines 414-416) is not possible.	Define BE analysis population.
EFPIA	311	311	2.2.1	This section would benefit from introducing the concept of intercurrent events - as one of the 5 attributes of an estimand (ICH E9(R1)) - and clearly state sound intercurrent event strategies for GI events affecting absorption. In particular, it would be beneficial to distinguish between GI events that are related to drug/comparator and those that are not as this would potentially inform how much subject data was to be excluded.	
EFPIA	312	312	2.2.1.1	It should be mentioned somewhere that subjects who vomit after dosing should be removed from the analysis	
EFPIA	320	329	2.2.2.1	MINOR COMMENT	We encourage the ICH to provide further clarification: It is not entirely clear in this paragraph whether all of the data for the subject should be excluded, or just the data within the period with the low concentrations.
EUFEPS Network on Bioavailability and Biopharmaceutics	327	329	2.2.1.1	Definition of a maximum number of subjects who can be excluded due to very low measurable concentrations makes limited sense, since the impact depends on the sample size of the study, e.g., if exclusion of 1 subject in a study with N=24 is acceptable, why would exclusion of 2 subjects in a study with N=96 be a concern? Text now: The limitation of no more than 1 subject should be omitted.	The exclusion of data for this reason will only be accepted in exceptional cases ~~(in general with no more than 1 subject in each study)~~ and may bring the reliability of dose administration into question.
Krka, d.d., Novo mesto	327	329	Section 2.2.1.1	Setting an acceptable number of such cases to 1 is not considered scientifically justified, as one should account for the sample size.	The exclusion of data for this reason will only be accepted in exceptional cases ~~(in general with no more than 1 subject in each study)~~ and may bring the reliability of dose administration into question.
Medicines for Europe	327	329	2.2.1.1	Definition of a maximum number of subjects who can be excluded due to very low measurable concentrations makes limited sense, since the impact depends on the sample size of the study, e.g., if exclusion of 1 subject in a study with N=24 is acceptable, why would exclusion of 2 subjects in a study with N=96 be a concern?	The exclusion of data for this reason will only be accepted in exceptional cases ~~(in general with no more than 1 subject in each study)~~ and may bring the reliability of dose administration into question.
ORBIS project	327	329	2.2.1.1	The possibility of exclusion of fixed number of subjects seems to be too strict, because the number of subjects varies between studies. Please consider removing this part of the sentence.	The exclusion of data for this reason will only be accepted in exceptional cases ~~(in general with no more than 1 subject in each study)~~ and may bring the reliability of dose administration into question.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Richter Gedeon Plc	327	329	2.2.1.1	Definition of a maximum number of subjects who can be excluded due to very low measurable concentrations seems extremely strict and it does not seem logical. The sample size can be extremely different (from n=12 upto even hundreds), therefore saying that only 1 volunteer data can be removede means very different real weight (from 8% to 0,3% if the sample size 12 or 320).	The exclusion of data for this reason will only be accepted in exceptional cases ~~(in general with no more than 1 subject in each study)~~ and may bring the reliability of dose administration into question.
EFPIA	330	331	2.2.1.1	This sentence needs clarification. : "Data from redosing studies are not considered evidence to support removal of extreme values from the statistical analysis."	We highly encourage the ICH to please provide further clarification as the meaning of this sentence is unclear. What does this mean exactly? Redosing of the subject with high values within the same study?
ORBIS project	330	330	2.2.1.1	The term 'redosing study' is not clear.	Add definition/description of 'redosing study'.
EFPIA	339	342	2.2.2.1	The protocol should include plans to minimize missing data. The trial protocol should prospectively define anticipated causes of missing data, the corresponding statistical assumptions about reasons for the missing data, and how missing data will be treated in the statistical analysis	Please consider adding for clarity (line 341), "...identified. The trial protocol should prospectively define anticipated causes of missing data, the corresponding statistical assumptions about reasons for the missing data, and how missing data will be treated in the statistical analysis."
EFPIA	343	344	2.2.2.1	As BE studies can be relatively large, creating a test vs reference plot for each subject may not be informative; having individual profiles in the same plot would greatly reduce the number of outputs and make the comparison at the study level easier. In this case the x-axis could be based on nominal time and then the figure would directly correspond to the by timepoint summary table of concentrations for comparison.	Plot individual profiles in the same plot for better visualization of what is going on in the study. X-axis will be nominal time to correspond to the summary table of concentrations by timepoint.
EUFEPS Network on Bioavailability and Biopharmaceutics	343	349	2.2.2.1	In line with the commonly seen evaluations, overlays/spaghetti plots may be included as a requested presentation of data.	
EFPIA	344	346	2.2.2.1	In addition, two concentration-time graphs (linear and log-linear) should be provided for both the test and comparator products for the mean drug concentrations of all subjects.	Please specify arithmetic mean or geometric mean.
EUFEPS Network on Bioavailability and Biopharmaceutics	345	345	2.2.2.1	Use of "mean" alone normally indicates the "arithmetic mean", however, in general a clear definition (arithmetic and/or geometric mean) is encouraged.	
ORBIS project	346	349	2.2.2.1	Clarification on plots is greatly appreciated.	None
ORBIS project	350	359	2.2.2.2	The use of brackets in PK parameters abbreviations decreases readability. Bullet points or numbered list would increase readability.	Remove the brackets in abbreviations of PK parameters. Use bullet points or numbered list.
EFPIA	352	352	2.2.2.2	The term AUC(0-t) can be confusing, hence, suggest using AUC(0-last) instead throughout the document.	"… primary parameters for analysis: AUC(0-last),…"
EFPIA	352	355	2.2.2.2	1) primary parameters for analysis: AUC(0-t), Cmax, and, where applicable, pAUC, and 2) additional parameters for analysis to assess the acceptability of the bioequivalence study: AUC(0-inf), AUC(0-t)/AUC(0-inf), Tmax, kel, and t1/2.	What is the rationale for AUC0-inf being included as an additional parameter not primary please? AZ assumption: BE studies aim to evaluate formulation differences affecting the absorption, not elimination, and sampling should cover 80% of AUC. Residual AUC may add variability. One exception could be if 80% of AUC is not covered due to delayed absorption in rare cases

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUFEPS Network on Bioavailability and Biopharmaceutics	353	354		Secondary parameters should not be considered as additional parameters for analysis to assess the acceptability of the bioequivalence study. Revise wording, i.e. primary parameter should be "for BE analysis".	
ORBIS project	354	355	2.2.2.2	To increase readability, please consider using consequent terms "AUC(0-t)/AUC(0-inf)" or "AUC(0-t)/AUC(0-inf) percentage".	Consequent use of "AUC(0-t)/AUC(0-inf)" or "AUC(0-t)/AUC(0-inf) percentage".
Arab Pharmaceutical industry Consulting	355	357	2.2.2.2	If the AUC(0-t)/AUC(0-inf) percentage is less than 80% in more than 20% of the observations, then the validity of the study may need to be discussed in the submission. Previous was expressed as residual area which is a direct output from Winnonlin and a reflection of AUC0-t/AUC0-inf and thus no calculations is required through excel	If the residual area is greater than 20% in more than 80% of the observations, then the validity of the study may need to be discussed in the submission
EFPIA	360	361	2.2.2.2	In addition to reporting CV%, the geometric mean CV% should be reported as well since the data are log normally distributed	
EFPIA	360	361	2.2.2.2	Summary statistics to be reported include geometric mean, median, arithmetic mean, standard deviation, coefficient of variation, number of observations, minimum, and maximum	Please specify arithmetic CV and/or geometric CV as both arithmetic and geometric means are recommended.
EUFEPS Network on Bioavailability and Biopharmaceutics	360	361	2.2.2.2	The order of the statistical parameters may be re-ordered. The "coefficient of variation" is located behind the arithmetic mean/arithmetic SC. If this is, therefore, intended as the arithmetic CV%, the geometric CV% is missing as ist a very common part of data presentation indicating directly a measure of total variability.	
EUFEPS Network on Bioavailability and Biopharmaceutics	364	364	2.2.2.2	It was already observed, that the given example was interpreted as a recommendation/requirement and the guideline was used as an argument for specific choices of methods. As the given example is maybe also not the optimal algorithm, this may be changed to "e.g., linear trapezoidal or other algorithm for AUC" or analogously implementing an alternative algorithm such as "linear/log trapezoidal" or "lin up/ log down trapezoidal". To underline: it is well recognised that these are identified as examples ("e.g.", however, in reality, the wording will be taken "as is" for future trials.	
EFPIA	370	372	2.2.2.2	Consider to softend up this requirement to allow for alternative strategies for handling concentrations below LLOQ, e.g. appropriate censoring methods.	
EFPIA	370	372	2.2.2.2	This recommendation can affect the calculation of the AUC using non-compartmental methods.	For the calculations of area under the curve (AUC) and terminal rate constant (z), if a result is below the lower limit of quantification (LLOQ) the result should be set to 0 for the pre-dose PK sample as well as for all other samples being LLOQ and occurring before Tmax. For subsequent time points, the result should be set to missing.
EUFEPS Network on Bioavailability and Biopharmaceutics	370	372	2.2.2.2	It is recognised that this rule to set all values reported as BLOQ to "0" would be consistent with the handling of the differences calculated in case of endogenous substances and also with some regulations (ANVISA) and would support an easier/less error-prone approach in NCA. Due to logarithmic transformation, also omission from calculation of Lz is then automatically achieved. However, despite other algorithms also having drawbacks, this seems to be inferior to other very basic approaches (e.g., set to "0" prior to Cmax and keep it as text/missing for interpolation after tmax). Therefore, this may be replaced by a request to clearly define the chosen approach. If this approach is kept, it should be defined that except for endogneous substances, the last triangel (from tlast to the first sample time with a BLOQ value) should NOT be included in the calculation of AUCs.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Jazz Pharmaceuticals	370	371	2.2.2.2	Regarding treating BLOQ as zero when calculating the PK parameters, this may depend on the time point of that concentration in the concentration-time profile. If the BLOQ is at the beginning or end of the concentration-time curve, then treat it as zero. However, if it is in the middle of the measurable concentrations, then it is more reasonable to treat it as missing.	
ORBIS project	370	372	2.2.2.2	Treating all <LLOQ values as zero suggests that a triangle between Clast and the next sampling point with zero concentration should be included in AUC(0-inf) calculation. It should be clearly stated how to calculate AUC(0-inf). Please consider using a uniform approach for all PK parameters -the same rule for samples after Clast for Kel, T1/2 and AUC calculation (omit values instead of setting them to zero).	Any concentration reported as below the lower limit of quantification (LLOQ) observed before Clast should be treated as zero in PK parameter calculations. Values below the LLOQ observed after Clast are to be omitted from the pharmacokinetic calculations of Kel and t1/2.
EFPIA	373	382	2.2.2.3	Current standards require retainment of batch samples.	Please clarify how long samples of the test and reference should be retained.
EUFEPS Network on Bioavailability and Biopharmaceutics	373	382	2.2.2.3	In case, potency is not known at the time of protocol submission, the concept of potency correction as a potential necessity should still be acceptable, if the intention is clearly defined in the protocol. However, content potency then needs to be documented prior to initiation of the trial.	
EUFEPS Network on Bioavailability and Biopharmaceutics	373	382	2.2.2.3	A reference to chapter 2.1.4 is recommended to clarify, that content assay is always acceptable based on the procedure proposed for the routine quality testing of the test product.	
Medicines for Europe	373	382	2.2.2.3	No example how potency correction should be performed. Secondly, this should also be acceptable postfestum, as this is unbiased mathematical calculation.	It is advised to add an explanation re how potency correction should be performed or refer to a relevant guidance. Deletion of denoted text "If potency correction is to be used, this intention should be pre-specified in the study protocol. Analysis should be provided for both uncorrected data and for potency-corrected data."
EUFEPS Network on Bioavailability and Biopharmaceutics	374	382	2.2.2.3	Potency correction is a much better approach than using the assay of both investigational products as it was determined a priori and limiting the maximum difference to 5%. Thus, the 5% criterium should be substituted by acceptance of dose normalisation procedure.	It is a basic principle of BE testing that the results obtained in a BE study should be representative for the general quality of the products tested and compared - and not only specific pbatches of these products. The "5% rule" opens room for certain adjustment/"compensation" of BA deviations of the products by selected potency differences between the batches.
ProPharma <Bertine Vorstenbosch - de Wijs>	374	379	2.2.2.3	The results from the potency assay of the test and comparator products should be submitted and the test product batch should be within 5% of the comparator product batch. In exceptional cases where a comparator product batch with a measured drug content within 5% of a test product batch cannot be obtained, a potency correction may be accepted with supporting justification, e.g., potency data from multiple lots of comparator product, pending market availability, and considering the totality of evidence.	Please consider to add "+/-": "... within +/- 5% of the comparator product batch".
Krka, d.d., Novo mesto	379	381	Section 2.2.2.3	Potency correction should also be acceptable postfestum, as this is unbiased mathematical calculation.	If potency correction is to be used, this intention should be pre-specified in the study protocol. Analysis should be provided for both uncorrected data and for potency-corrected data.
EFPIA	385	386	2.2.3.1	This statement should refer and align to section 2.2.1 above	
EFPIA	386	388	2.2.3.1	It is not always possible to document exclusions before the bioanalytical assay of samples as data pertaining to exclusions may only be available after the database from the study has been locked. It would be more apt to document the exclusion of any data prior to any statistical analyses to determine BE.	Decisions made to exclude subjects from the BE analysis population, e.g., due to incomplete sampling or protocol violation, should be documented prior to statistical analysis.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Jazz Pharmaceuticals	389	389	2.2.3.1	Regarding the minimum sample size of 12, is it reasonable for the sponsor to justify a sample size below 12 where products have low inter-individual variability? Please consider including clarification or additional advice for this case.	
EUFEPS Network on Bioavailability and Biopharmaceutics	392	393	2.2.3.1	The calculation of the 90% confidence interval (CI) of the mean test/comparator ratio for the primary PK parameters should not be confused with the two one-sided t-tests employed to reject the null hypothesis of non-equivalence. The end result is the same, but these are not the same calculations.	
Medicines for Europe	392	393	2.2.3.1	The calculation of the 90% confidence interval (CI) of the mean test/comparator ratio for the primary PK parameters should not be confused with the two one-sided t-tests employed to reject the null hypothesis of non-equivalence. The end result is the same, but these are not the same calculations.	The assessment of BE is based on 90% confidence intervals for the geometric mean ratios (test/comparator) for the primary PK parameters under consideration. ~~This method is equivalent to two one-sided t-tests with the null hypotheses of bioinequivalence at the 5% significance level.~~ The data should be transformed prior to analysis using a logarithmic transformation
EFPIA	394	394	2.2.3.1	PK parameters	Consider replacing: 'The data should be transformed prior to analysis...' with 'The PK parameters should be transformed prior to analysis...'
EFPIA	402	408	2.2.3.2	Using a fixed effects ANOVA model only allows inference to be made to the subjects in the study rather than the population. Mixed models (with random subject effect) should be considered so inferene can be accurately applied to the entire population (rather than just subjects in the BE study).	Please align with the FDA draft guidance released in 2022 to allow for mixed models (i.e. random subject effect) and included data from subjects with just one period of evaluable data.
EFPIA	402	408	2.2.3.2	Specific details about stastistical analysis considerations for handling missing data (for example removing subjects whose concentration data is missing in one or both periods in a crossover study) is not provided in this guideline.	It will be helpful to clarify this in the guideline.
EFPIA	403	407	2.2.3.2	Please add a sentence to say which effects are fixed in the model and whether subject within sequence can be treated as a random effect.	Because of the differences in HA statistical analysis for "Subject within formulation," please consider adding “Sequence, period and formulation will be fixed effects and subject within sequence will be a random effect.” or an equivalent.
EUFEPS Network on Bioavailability and Biopharmaceutics	403	404	2.2.3.2	Design should not be limited to 2x2x2 studies.	Conventional ~~two-treatment, two-period, two-sequence~~ randomised crossover design studies should be analysed using an appropriate parametric method, e.g., ANOVA.
Medicines for Europe	403	404	2.2.3.2	Design should not be limited to 2x2x2 studies.	Conventional ~~two-treatment, two-period, two-sequence~~ randomised crossover design studies should be analysed using an appropriate parametric method, e.g., ANOVA.
EFPIA	407	408	2.2.3.2	Given these studies are conducted in HV, the number of subjects with just one period is limited so why not include them in the analysis assuming missing at random and use a mixed effects model (see previous comment as well)?	Align with the FDA draft guidance released in 2022 to allow for mixed models and included data from subjects with just one period of evaluable data
EFPIA	407	408	Section 2.2.3.2	In general, the primary analyses should include all data for all subjects who provide evaluable data for both the test and comparator products	It's stated to include subjects that contribute data from both the reference and test arms. Please can you clarify that if a patient drops out and contributes data to only one treatment, should that patient be included or excluded from the primary analysis? Theoretically, all subjects could be included in the primary analysis set as the BE criteria are based on the statistical model.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Krka, d.d., Novo mesto	407	408	Section 2.2.3.2	The text is not clear, is there an emphasis on "analyses should include all data" (i.e. no exclusions) or on "data for both products" (i.e. only SAS PROCGLM, no SAS PROCMIXED)?	"In general, the primary analyses should include all data for ~~both the test and comparator products~~ all subjects who provide evaluable data for comparisons/analyses as per protocol."
ORBIS project	407	423	2.2.3	Terms "primary analyses", "pivotal statistical analysis", "pre-defined primary statistical analysis" and "primary statistical analysis" are not clear and suggest secondary or pilot analyses. If different types of analyses may be considered during statistical analysis of BE data, they should be specified in the guideline.	Define types of statistical analysis.
EFPIA	408	408	2.2.3.2	See above comment about aligning with section 2.2.1	
EUFEPS Network on Bioavailability and Biopharmaceutics	408	408		"In general, the primary analyses should include all data for all subjects who provide evaluable data for both the test and comparator products." Comment: Not clear, is there an emphasis on analyses should include all data (i.e. no exclusions) or on data for both products (i.e. only SAS PROCGLM, no SAS PROCMIXED)?	"In general, the primary analyses should include all data for all subjects who provide evaluable data for comparisons/analyses as per protocol."
Medicines for Europe	408	408		"In general, the primary analyses should include all data for all subjects who provide evaluable data for both the test and comparator products." Comment: Not clear, is there an emphasis on analyses should include all data (i.e. no exclusions) or on data for both products (i.e. only SAS PROCGLM, no SAS PROCMIXED)?	"In general, the primary analyses should include all data for all subjects who provide evaluable data ~~for both the test and comparator products~~ for comparisons/analyses as per protocol."
EUFEPS Network on Bioavailability and Biopharmaceutics	409	416	2.2.2.3	It shoud be clarified, that the test for carry-over is generally the test for the effect "sequence" in a standard evaluation. It may also be clarified that significant effect for "sequence", "period" and "treatment" have no direct consequence (or clinically relevant) meaning insofar as a appropriate ANOVA was conducted. This may facilitate assessment of BE trials also by authorities in order to reduce discussions about statistically significant effects in the statistical model.	
EFPIA	414	416	2.2.3.3	Entirely or just for that period. Please clarify	
EUFEPS Network on Bioavailability and Biopharmaceutics	414	416	2.2.3.3	Exclusion of a subject vs. subject's data from corresponding/concerned period. In a study with multiple periods, only data from the respective period where the pre-dose concentration was >5% of the Cmax value for that period should be excluded, not all data for the respective subject.	If there are subjects for whom the pre-dose concentration is greater than 5% of the Cmax value for the subject in that period, then the pivotal statistical analysis should be performed excluding the subject's data from the concerned period ~~from that subject~~.
EUFEPS Network on Bioavailability and Biopharmaceutics	414	416	2.2.3.3	It may happen that in individual subjects 5% of their respective Cmax value is below the Limit of Quantitation, in spite of all efforts to lower the LoQ. It would be good if the guideline addresses the question how to proceed in such situations, e.g. as in the proposed change.	Add e.g.: If the pre-dose concentration for a period is below the Limit of Quantitation (LoQ), but the LoQ is >5% of the Cmax value for the respective period, its data should not be excluded from the statistical analysis, as long as there is no risk for a carry-over effect, e.g. due to a sufficiently long washout period or lack of pre-dose values in other subjects.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	414	416	2.2.3.3	Exclusion of a subject vs. subject's data from corresponding/concerned period. In a study with multiple periods, only data from the respective period where the pre-dose concentration was >5% of the Cmax value for that period should be excluded, not all data for the respective subject.	If there are subjects for whom the pre-dose concentration is greater than 5% of the Cmax value for the subject in that period, then the pivotal statistical analysis should be performed excluding the subject's data from the concerned period ~~from that subject~~.
Medicines for Europe	414	416	2.2.3.3	In case a formulation has low bioavailability it may happen that in individual subjects 5% of their respective Cmax value is below the Limit of Quantitation, in spite of all efforts to lower the LoQ. It would be good if the guideline addresses the question how to proceed in such situations, e.g. as in the proposed change.	Add e.g.: If the pre-dose concentration for a period is below the Limit of Quantitation (LoQ), but the LoQ is >5% of the Cmax value for the respective period, its data should not be excluded from the statistical analysis, but if such a situation occurs in more than 20% of the observations then the validity of the study may need to be discussed.
Krka, d.d., Novo mesto	415	416	Section 2.2.3.3	"...excluding the data from that subject." In a study with multiple periods, only data from the respective period where the pre-dose concentration was >5% of the C_{max} value for that period should be excluded, not all data for the respective subject.	If there are subjects for whom the pre-dose concentration is greater than 5% of the Cmax value for the subject in that period, then the pivotal statistical analysis should be performed excluding the subject's data from the concerned period from that subject.
EUFEPS Network on Bioavailability and Biopharmaceutics	418	418	2.2.3.4	Please clarify what is meant with "should reflect independent samples". Does this just mean that the evaluation should be based on an unpaired ANOVA, that is without any matching of subjects?	
Gilead Sciences	419	420	2.2.3.4	"Demographic characteristics or other relevant covariates known to affect the PK should be balanced across groups, to the extent possible." Clarity on what 'balanced' mean would be helpful? For example, does balance mean the expectation is that the characteristics and covariates need to demonstrate comparability across groups?	
EFPIA	421	422	2.2.3.4	If the randomization is already stratified by a known relevant factor, please add one sentence to explain why the factor should still be included in the model.	Clarification is needed to understand why the stratifying factors are being reanalyzed in the statistical plan.
EFPIA	421	422	2.2.3.4	Please make it clear that the formulation by relevant factor interaction term need not be included in the model.	Please consider adding a sentence to say, "The interaction between formulation by relevant factor interaction need not be included in the model."
EFPIA	423	423	2.2.3.4	Here it is stated that post-hoc and data driven analysis are not aceptable in parallel study design. This is not specified for cross-over design. Furthermore, later in multigroup design studies this is accepted if robust scentific justification is provided (see also next comment).	Line 423 should be deleted.
Adamed Pharma SA	424	443	2.2.3.5.	Regarding the group effect, if the Group by Treatment interaction is significant, further analysis and interpretation may be warranted if heterogeneity between groups is observed. However BE should be determined based on the overall treatment effect in the whole study population. In our opinion, more understandable explanation of what is expected in the demonstration of significant Group by Treatment interaction is required. For example, if BE is not proven in one of the two or three groups, but group heterogeneity is not demonstrated, can the Sponsor still apply for registration of the investigational product based on the results for the whole population? What criteria should be met to consider groups to be heterogeneous? Furthermore, in case of the inhalation products, the IMP administration is conducted in many groups with very few subjects in one group. These subjects may be pooled into one group for consideration in the statistical analysis?	
EFPIA	424	427	2.2.3.5	2.2.3.5 Multi-Group Design Studies. Sample size requirements and/or study logistics may necessitate studies to be conducted with groups of subjects.	Please clarify 'groups of subjects' as this terminology can be used for group-sequential/adaptive design. Assume this implies that different groups of subjects are studied on different days and/or diffierent sites?

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUFEPS Network on Bioavailability and Biopharmaceutics	427	427	2.2.3.5	Please clarify the meaning and the impact of the sentence: "The combination of multiple factors may complicate the designation of group."	
Krka, d.d., Novo mesto	427	427	Section 2.2.3.5	Meaning and the impact of this sentence is unclear: "The combination of multiple factors may complicate the designation of group."	Propose to delete the sentence.
Medicines for Europe	427	427	2.2.3.5	Meaning and the impact of this sentence is unclear: "The combination of multiple factors may complicate the designation of group."	Propose to delete the sentence.
Adrian GHITA, 3S Pharmacological Consultation and Research, Romania	428	431	2.2.3.5	It is not clear from the statement if the assessment of the BE (based on the 90% confidence limits) should be based on the residuals from the specified model considering only the mentioned factors for ANOVA as: Sequence, Subject within Sequence, Period, and Formulation effects (as specified in section 2.2.3.2) or to account also for the Group effect but leaving apart from the model only the Group-by-Treatment interaction term.	
EUFEPS Network on Bioavailability and Biopharmaceutics	428	437	2.2.3.5	In accordance with the recommendations described in lines 395-397 of the draft guidance (The statistical analysis should take into account sources of variation that can be reasonably assumed to have an effect on the response variable) we suggest to add a preceding paragraph similar to the one suggested in the next column and include that the recommendations provided in lines 428 ff. apply only in all other cases.	Add e.g.: Since dosing in groups is not reasonably expected to have an effect on the response variable, no group related factors should be included in the statistical model used for evaluation in case of all of the following criteria are met for the subjects randomized: - Same subject pool - Same selection critieria - Same site/center - Same timeframe (first dosing less than xxx apart)
EUFEPS Network on Bioavailability and Biopharmaceutics	428	437	2.2.3.5	It makes sense that in the assessment of BE the group by treatment interaction term should not be included, but it's weird that applicants could also select a model including such an interaction term. The sentence "However, the appropriateness of the statistical model should be evaluated to account for the multi-group nature of the BE study." seems to be out of place since the sentences before and after talk about the group by treatment interaction.	
EUFEPS Network on Bioavailability and Biopharmaceutics	428	437	2.2.3.5	"The assessment of BE in the whole study population should be done without including the Group by Treatment interaction term in the model, but it should be evaluated. " Please explain how the evaluation of the Group by Treatment interaction term should be performed. And which terms should be included in this evaluation. It may be reasonable to refer to the model discussed for the evaluation (theoretically) of a two -stage design in the EMA-PKWP-Q&A (3.2), although it is stated there that "A term for a formulation*stage interaction should not be fitted" and no poolabbility criterion is considered. However, if this is requested, at least testing at the 5% criterion only should be requested. Also, a clearer statement what encompasses the "root cause of the Group by Treatment interaction should be investigated to the extent possible" would be helpful to avoid unsatisfying communication between applicants and assessors. A descriptive presentation of comparisons in each group may be of interest?	
EUFEPS Network on Bioavailability and Biopharmaceutics	428	437	2.2.3.5	Inclusion of a group-term may substantially compromise power: in a meta-study (320 multi-group studies) a group-by-treatment interaction was "detected" at approximately the level of the test (8.81% AUC, 10.3% Cmax).; in well-controlled trials likely false positives. Impossible to detect a true treatment effect by statistics, i.e., subsequent investigation of root causes is futile. See also https://bebac.at/lectures/Brussels2023.pdf	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Krka, d.d., Novo mesto	428	437	Section 2.2.3.5	The BE studies are in general already designed to minimize/eliminate the group effect in the study taking into account the following measures: - All groups are dosed at the same clinic within short time interval - Subjects are enrolled from the same enrolment pool - Randomization is performed at the study initiation - Same study protocol and procedures are followed. Therefore, in accordance with recommendation "The statistical analysis should take into account sources of variation that can be reasonably assumed to have an effect on the response variable" (lines 395-397 of this draft guidance), no adjustment of statistical model should be needed if above conditions are fulfilled. Additionally, evaluation of G*T interactions is redundant in such cases. BE studies are not powered enough to correctly test these interactions; to overcome this study's sample size should be much larger. Furthermore, in many cases there will be falsely detected positive interaction (from 5 to 10%, depending on the level of testing).	Addition of: Since dosing in groups is not reasonably expected to have an effect on the response variable, no group related factors should be included in the statistical model used for evaluation in case of all of the following criteria are met: - All groups are dosed at the same clinic within short time interval (within one month) - Subjects are enrolled from the same enrolment pool - Randomization is performed at the study outset - Same study protocol and procedures are followed in all groups. Text on Group by treatment interaction from lines 432 – 437 should be adjusted to comply with proposed addition (no G*T interaction evaluation if above conditions are met).
Medicines for Europe	428	437	2.2.3.5	In accordance with the recommendations described in lines 395-397 of the draft guidance (The statistical analysis should take into account sources of variation that can be reasonably assumed to have an effect on the response variable) we suggest to add a preceding paragraph similar to the one suggested in the next column and include that the recommendations provided in lines 428 ff. apply only in all other cases. Furthermore, recent analyses do not support the scientific rationale on evaluation of G*T interaction (Schütz H. Statistical challenges and opportunities in ICH M13A. 2nd Bioequivalence Workshop, Medicines for Europe, 26 Apr 2023, Brussels, Belgium. Available online https://bebac.at/lectures/Brussels2023.pdf)	Add e.g.: Since dosing in groups is not reasonably expected to have an effect on the response variable, no group related factors should be included in the statistical model used for evaluation in case of all of the following criteria are met for the subjects randomized: - Same subject pool - Same selection critieria - Same site/center - Same timeframe (first dosing less than 1 month apart)
Medicines for Europe	428	437	2.2.3.5	It makes sense that in the assessment of BE the group by treatment interaction term should not be included, but it's weird that applicants could also select a model including such an interaction term. The sentence "However, the appropriateness of the statistical model should be evaluated to account for the multi-group nature of the BE study." seems to be out of place since the sentences before and after talk about the group by treatment interaction.	BE should be determined based on the overall treatment effect in the whole study population. When dosing in groups can reasonably be expected to have an effect on the response variable, the appropriateness of the statistical model should be evaluated to account for the multi-group nature of the BE study. In general, the assessment of BE in the whole study population should be done without including the Group by Treatment interaction term in the model~~, but applicants may also use other pre-specified models, as appropriate. However, the appropriateness of the statistical model should be evaluated to account for the multi-group nature of the BE study~~. Applicants should evaluate potential for heterogeneity of treatment effect across groups, i.e., Group by Treatment interaction. If the Group by Treatment interaction is significant, this should be reported and the root cause of the Group by Treatment interaction should be investigated to the extent possible. Substantial differences in the treatment effect for PK parameters across groups should be evaluated. Further analysis and interpretation may be warranted in case heterogeneity across groups is observed.
Medicines for Europe	428	437	2.2.3.5	The assessment of BE in the whole study population should be done without including the Group by Treatment interaction term in the model, but it should be evaluated.	Please suggest how the evaluation of the Group by Treatment interaction term should be performed. And which terms should be included in this evaluation.
Krka, d.d., Novo mesto	430	431	Section 2.2.3.5	Inclusion of Group by Treatment interaction into statistical model would give equal weight to groups, even if the number of subjects in each group is very different. That is why the BE comparison result can be misleading and model with Group by Treatment interaction should not be acceptable if groups are not balanced.	In general, the assessment of BE in the whole study population should be done without including the Group by Treatment interaction term in the model~~, but applicants may also use other pre-specified models, as appropriate~~.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Adrian GHITA, 3S Pharmacological Consultation and Research, Romania	431	437	2.2.3.5	In the special case of multiple groups enrolled within a single clinical center (for logistical or safety reasons when small sentinel groups are first enrolled), the analysis of the Group-by-Treatment interaction will not yield any valuable insights. In most cases, the Group-by-Treatment interaction will not be significant, or it may be significant merely by chance when some subjects exhibit abnormal profiles during some periods of the study. Even if we disregard the analytical problems that may occur, such unexplainable outlier profiles do exist among volunteers and they are totally random in nature, so their values are not readily explainable. Accordingly, such subjects must be regarded as members of their formulation group (when all dosed subjects are pooled together) rather than as members of subgroups. Also, if two identical sized groups were used in a study, but one group did not meet the BE criteria, what would be the overall BE conclusion? "Substantial differences in treatment effects for PK parameters" is a vague term. It refers to all PK metrics (e.g. Cmax, AUCt, and AUCinf) or just to "at least one"? As an example, a standard 3x3 crossover design (either two tests and one comparator or two comparators and one test) will yield 18 possible sources of significant Group-by-Treatment effects that may pose difficult interpretation of the results.	As a suggestion, we propose eliminating multigroup investigations and not accounting for the Group effect if all volunteers are dosed in the same facility, subjected to the same protocol conditions regardless of whether they are dosed in different groups. Or, if the elimination is not considered appropriate, to be very clear as to when the BE criteria is passed, for instance, when at least one group proves BE on all PK metrics, if the largest group (as number of volunteers) or if all groups do?
Richter Gedeon Plc	432	437	2.2.3.5.	What is the scientific question that the Group × Treatment interaction term aims to answer in case of bioequivalence development programs? Is the Group × Treatment interaction of scientific interest for the regulatory decision-making in case of Bioequivalence development programs?	•Bioequivalence studies are not planned and powered to confirm Group × Treatment interactions. •Therefore the sensitivity and specificity of the Group × Treatment interaction term in bioequivalence studies is very low. This means that in case of a significant Group × Treatment interaction the probability of a false positive significance is considerable. •Powering for the interaction term is not straight-forward and would lead to a sample size increase. An increased sample size would lead to an overpowered bioequivalence trial. Therefore we propose to remove it from the guideline.
Richter Gedeon Plc	432	437	2.2.3.5.	What is the exact definition for multi-group design? In what cases shall the Group × Treatment interaction be investigated?	If the whole concept is not removed, than include exact definition into the text
Richter Gedeon Plc	432	437	2.2.3.5.	If the Group × Treatment interaction needs to be investigated, which model, or decision-algorithm shall be applied?	If the whole concept is not removed, than include the model and the decision-algorithm into the text.
EUFEPS Network on Bioavailability and Biopharmaceutics	438	439		"In multicentre BE studies, when there are very few subjects in some sites, these subjects may be pooled into one group for consideration in the statistical analysis." Comment: This is applicable also for monocentric study with several small groups. Is there a minimum number of subject to be considered as separate group (e.g. 12 subject as minimum for BE study)?	"In multicentre or multigroup BE studies, when there are very few subjects in some sites/groups, these subjects may be pooled into one group for consideration in the statistical analysis."
Krka, d.d., Novo mesto	438	439	Section 2.2.3.5	Pooling of groups should also be applicable for monocentric study with several small groups or one group much larger than the other. A minimum number of subject to be considered as separate group should be set to 12 subject as minimum.	In multicentre or multigroup BE studies, when there are very few subjects in some sites/groups (less than 12 subjects), these subjects may be pooled into one group for consideration in the statistical analysis
Medicines for Europe	438	439		"In multicentre BE studies, when there are very few subjects in some sites, these subjects may be pooled into one group for consideration in the statistical analysis." Comment: This is applicable also for monocentric study with several small groups. Is there a minimum number of subject to be considered as separate group (e.g. 12 subject as minimum for BE study)?	"In multicentre or multigroup BE studies, when there are very few subjects in some sites/groups, these subjects may be pooled into one group for consideration in the statistical analysis."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	441	443	2.2.3.5	Suggest to move these 3 lines at the end of the general considerations in section 2.2.3.1, since this concept applies to all designs.	Move after line 401 and before line 402
ORBIS project	444	450	2.2.4.	Criteria for multiple-dose studies are not specified. To avoid problems with harmonisation regarding secondary parameters, please consider adding the statement that results of secondary PK parameters do not influence regulatory decision on BE.	Add criteria for multiple-dose studies. Add the statement that the results of secondary PK parameters do not influence the regulatory decision on BE.
EFPIA	445	445	2.2.4	Extra dash in AUC(0--t)	Remove extra -
EFPIA	445	450	2.2.4	For the majority of drug products, the PK parameters to demonstrate BE include Cmax and AUC(0--t). For drugs with a long elimination half-life, AUC(0 72h) may be used in place of AUC(0-t) (see Section 2.1.8.2). For drugs where it is clinically relevant to assess the early exposure or early onset of action, an additional PK parameter, pAUC, may be used to establish BE (see Section 2.1.8.3). The 90% confidence interval for the geometric mean ratio of these PK parameters used to establish BE should lie within a range of 80.00 - 125.00%.	Would it be possible to mention potential options for flexibility in some cases or refer to ICH M13C? E.g. FDA Generic guidance includes that BE assessment using in vitro data are acceptable for BE (ICH M9), also IVIVC, PD and clinical endpoints.
EUFEPS Network on Bioavailability and Biopharmaceutics	445	445	2.2.4	BEQ citeria for multiple-dose study are missing. The parameters to demonstrate BE in multiple dose studies should be mentioned here (as in line 368).	For the majority of drug products, the PK parameters to demonstrate BE include Cmax and AUC(0-t) in single dose studies and CmaxSS and AUC(0-tauSS) in multiple dose studies.
Krka, d.d., Novo mesto	445	445	Section 2.2.4	BE criteria for multiple-dose study are missing.	For the majority of drug products, the PK parameters to demonstrate BE include Cmax and AUC(0-t) in single dose studies and CmaxSS and AUC(0-tauSS) in multiple dose studies.
Medicines for Europe	445	445	2.2.4	BEQ citeria for multiple-dose study are missing. The parameters to demonstrate BE in multiple dose studies should be mentioned here.	For the majority of drug products, the PK parameters to demonstrate BE include Cmax and AUC(0-t) in single dose studies and CmaxSS and AUC(0-tauSS) in multiple dose studies.
EFPIA	446	448	2.2.4	This section only discusses long elimination half-life.	Please consider adding for clarity (line 446) "…long elimination half-life and low intrasubject variability…."
Medicines for Europe	447	450	2.2.4	Partial AUC [pAUC], are very often highly-variable, however, scaling of limits is not permitted per current draft text, only standard limits are allowed on line 450. pAUC should therefore not be in the scope of M13A.	This should be removed from this guideline and, if necessary at all, included only in M13C (where high variability will be addressed)
EFPIA	449	450	2.2.4	At some stages of development, it may be possible to also conclude based on established product-specific clinical comparability bounds.	
Medicines for Europe	449	450	2.2.4	Since the 80-125% acceptance range does not always apply, it's recommended to add the word "generally" For example, the narrow therapeutic index drug(s) [NTI] and HVD will be dealt with in M13C.	The 90% confidence interval for the geometric mean ratio of these PK parameters used to establish BE should generally lie within a range of 80.00 - 125.00%, unless otherwise justified.
EFPIA	460	461	2.2.5.1	Please explain whether a single higher order crossover designed study will be acceptable, instead of conducting several 2-way crossover studies.	Please consider: "A single study using a higher order crossover may be conducted with the test product and all comparators. However, it is preferred for the statistical analysis to only test two at a time and not all at once, making pairwise comparison within the analysis."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ProPharma <Anna K. Klein>	462	466	2.2.5	It is possible that the results meet the BE acceptance criteria with one region-specific comparator product but not meet BE acceptance criteria with the other region-specific comparator product. In such case, BE is demonstrated with one comparator product and not demonstrated with the other comparator product. The protocol should specify the main objectives of the study and which comparisons are to be performed.	In this case, what will be the criteria of choice of the comparator?
EFPIA	469	481	2.2.5.2	In the previous section on Multiple Comparator Products it states that the analysis should only test two at a time and not all at once. Does this apply to Muliple Test Products as well?	Clarify analysis should be done two at a time.
EFPIA	474	475	Section 2.2.5.2	The need to apply multiplicity correction in pivotal trials depends on the underlying objectives of the trial:	
EFPIA	476	476	Section 2.2.5.3	But nevertheless it would only make senes if a test based on the union of test specific null hypothesis provided type 1 error control	
EFPIA	476	477	Section 2.2.5.4	In this case, the null hypotheses should be rejected for all test formulations. This would require designing the study with a higher power. A statement regarding the needed higher power would be helpful.	Please consider adding a following sentence to say that "As the null hypotheses should be rejected for all hypotheses, the study should be designed with a higher power."
EUFEPS Network on Bioavailability and Biopharmaceutics	476	479	Section 2.2.5.5	Please add that in case of hierarchical testing of BE hypotheses, multiplicity adjustment should not be required.	
Medicines for Europe	476	479	Section 2.2.5.6	Please add that in case of hierarchical testing of BE hypotheses, multiplicity adjustment should not be required.	a) If the objective is to achieve BE for all test formulations versus the comparator product, then no alpha adjustment is needed. b) If the objective is to show BE for any of the test formulations, then multiplicity adjustment may be needed. c) In case of hierarchical testing of BE hypoteses on different formulations, then then no alpha adjustment is needed.
Adamed Pharma SA	478	479	Section 2.2.5.7	According to the ICH M13A the need to apply multiplicity correction in pivotal trials depends on the underlying objectives of the trial and may be needed if the objective is to show BE for any of the test formulations. In our opinion, this section should specify in which cases this correction should be made. The statement "may be needed" is very general and can be interpreted in many ways.	
EUFEPS Network on Bioavailability and Biopharmaceutics	478	479	Section 2.2.5.8	The wording "then multiplicity adjustment may be needed" is very vague. Please provide clarification and examples in which cases a multiplicity adjustment is needed in cases where a BE study is conducted with multiple test products.	
Medicines for Europe	478	479	Section 2.2.5.9	The wording "then multiplicity adjustment may be needed" is very vague. Please provide clarification and examples in which cases a multiplicity adjustment is needed in cases where a BE study is conducted with multiple test products.	
ORBIS project	478	479	Section 2.2.5.10	It is not clear when multiplicity adjustment is needed. Clear rules should be described in the guideline.	Add rules regarding multiplicity adjustment.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	479	479	Section 2.2.5.11	It may be more appropriate to say “alpha adjustment” as given in Rows 476-477. Also, this would require a different level for the confidence intervals. That aspect should be mentioned.	Please consider make the following change: "If the objective is to show BE for any of the test formulations, then multiplicity (alpha) adjustment may be needed. This may require using a different level for the confidence intervals other than 90%."
Adamed Pharma SA	483	504	Section 2.2.5.12	More detailed instructions should be given in the sections as it was presented in the current BE guideline.	
EFPIA	483	483	Section 2.2.5.13	an alternative could be supra therapeutic dose can be considered (considering the good tolerance of the drug)	see the proposal in the column F
EFPIA	492	492	Section 2.2.5.14	mutiple baseline endogenous concentration: in order to take into account for fluctuation due to circadian rythms samplings at regular interval throughout 1-2 days prior to administration should be done prior to administration	propose sampling at regular interval throught 1-2 days prior administration
EFPIA	499	500	Section 2.2.5.15	If a baseline correction results in a negative concentration value, the value should be set equal to zero	What is the rationale for this please? Software can usually handle negative values when calculating AUCs. Note: the recommendation has been removed from FDA BA guidance but not BE guidance
EFPIA	501	502	Section 2.2.5.16	If baseline substraction is foreseen in the protocol, then PK and statistical analysis should be conducted only on baseline corrected data, otherwise the corresponding outcome may be heavily influenced by the baseline data (for instance half-life cannot be calculated in presence of a quantifiable baseline) or even biased if the measued baseline is still a relevant part of observed concentrations.	From line 501 delete "…on both baseline uncorrected and …". From line 502 delete "In general, …"
EUFEPS Network on Bioavailability and Biopharmaceutics	503	504	Section 2.2.5.17	*Since the draft guideline offers the opportunity to enrol subjects with low or no production of endogenous compounds and since baseline correction usually increases the variability of the PK parameters, definition fo a threshold where no baseline correction is required would be appreciated. *The recommendation to include subjects with "low" production of an endogenous compound is well established. However, there still is no established rule, under which conditions "low" is low enough to allow omission of baseline correction. In analogy to the consideration, that pre-dose values of not more than 5% of the individual Cmax are considered uncritical, a recommendation would be: "Baselines of not more than 5% of the Cmax observed in a period indicates that the increase is substantial enough to omit baseline correction."	
Medicines for Europe	503	504	Section 2.2.5.18	Since the draft guideline offers the opportunity to enrol subjects with low or no production of endogenous compounds and since baseline correction usually increases the variability of the PK parameters, definition fo a threashold where no baseline correction is required would be appreciated, e.g. according to the proposal in the next column.	Add e.g.: <u>If a baseline correction is expected to affect the reference medicinal product geometric mean AUC by less than 20%, then no baseline correction is required.</u>
Adamed Pharma SA	506	540	Section 2.2.5.19	If the new intended label use/instructions state that the ODT/chewable tablets can be taken with or without water, a 3-arm BE study is recommended to determine BE of the ODT/chewable tablets administered with and without water compared to the comparator product administered as per its labelling. In our opinion in this section, additional information, if multiplicity correction should be applied in such 3-arm BE study might be helpful. Furthermore, additional issues that require clarification are: - if bioequivalence is proven for only one mode of administration, can the product still be registered; - in a case when the labelling of the comparator lacks the statement regarding the intake of water which scheme should be adopted? □	
ORBIS project	506	540	Section 2.2.5.20	Sections 3.2.1 and 3.2.2 are very similar. Please consider merging both of them in one section entitled "Orally Disintegrating Tablets and Chewable Tablets".	Marge sections 3.2.1 and 3.2.2

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
SciencePharma, Poland	517	519	Section 2.2.5.21	There is no option to conduct a 2-period study using the "worst-case scenario" in case an extension to another orally administered IR drug product is considered.	It is suggested to add the following sentence (directly after line 519) as per CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** guideline: ""However, if bioequivalence between ODT taken without water and reference formulation with water is demonstrated in a 2-period study, bioequivalence of ODT taken with water can be assumed."
EUFEPS Network on Bioavailability and Biopharmaceutics	523	523	Section 2.2.5.22	It should also be mentioned that oral powder and granulates can be handled in a similar way to ODTs	
Medicines for Europe	523	523	Section 2.2.5.23	It should also be mentioned that oral powder and granulates can be handled in a similar way to ODTs	
EFPIA	532	536	Section 2.2.5.24	BE assessment without chewing should not be necessary to assess a case that patients take the chewable tablet without chewing.	Please consider removing the need for BE assessment without chewing for this formulation.
SciencePharma, Poland	537	540	Section 2.2.5.25	There is no option to conduct a 2-period study using the "worst-case scenario" in case an extension to another orally administered IR drug product is considered.	It is suggested to add the following sentence (directly after line 540) as per CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** guideline: ""However, if bioequivalence between chewable tablets taken without water and reference formulation with water is demonstrated in a 2-period study, bioequivalence of chewable tablets taken with water can be assumed."
EUFEPS Network on Bioavailability and Biopharmaceutics	541	544	Section 2.2.5.26	For tablets, granules, and powders labelled as being only intended to be dispersed in a liquid before administration as an oral suspension, BE studies should be conducted according to the comparator product labelling. The label may include several options of liquid.	Please add that any iquid/semi liquid listed in the label is appropriate for the BE, and that only one is sufficient.
Medicines for Europe	541	544	Section 2.2.5.27	For tablets, granules, and powders labelled as being only intended to be dispersed in a liquid before administration as an oral suspension, BE studies should be conducted according to the comparator product labelling. The label may include several options of liquid.	Please add that any liquid/semi liquid listed in the label is appropriate for the BE, and that only one is sufficient.
EFPIA	548	558	Section 2.2.5.28	bracketing approach for FDC multiple strength	proposal to add, the bracketing approach in the section
EUFEPS Network on Bioavailability and Biopharmaceutics	548	548	Section 2.2.5.29	It is recognised that local regulations/requirements may preclude more extensive discourse on fixed dose combinations. Would it be possible to clarify that local requirements have still to be considered?	
Medicines for Europe	548	548	Section 2.2.5.30	Clarity for the choice of comparator product (fixed dose combination or concomitant administration of individual components) is missing. ICH M13 does not refer to the guidelines on Clinical development of fixed dose combinations, which is a case with the current EMA BE Guideline.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ORBIS project	551	552	Section 2.2.5.31	Please consider changing wording from "individual component (drugs)" to "individual analytes".	individual component (drug) => analyte
EUFEPS Network on Bioavailability and Biopharmaceutics	556	558	Section 2.2.5.32	Considerating that each component should be evaluated individually, an option that each component can be evaluated in separate studies or in case of different intra-subject variability within the same study in the smaller group should be considered, in particular in case of dug substances with substantially different pharmacokinetics and/or variability. Although this is expected in rare cases only, differences between the APIs may make it feasible and justifiable to investigate an API only in a subgroup of a whole trial or separate investigations into separate trials.	BE should be demonstrated for all components (drugs) in the fixed-dose combination product according to the principles described in this guideline, not necessarily in one/the same study or on the same number of subjects within one study.
Krka, d.d., Novo mesto	556	556	Section 2.2.5.33	Considerating that each component should be evaluated individually, an option that each component can be evaluated in separate studies or in case of different intra-subject variability within the same study in the smaller group should be considered, inparticular in case of dug substances with substantially different pharmacokinetics and/or variability.	BE should be demonstrated for all components (drugs) in the fixed-dose combination product according to the principles described in this guideline, not necessarily in one/the same study or on the same number of subjects within one study.
Medicines for Europe	556	558		Considerating that each component should be evaluated individually, an option that each component can be evaluated in separate studies or in case of different intra-subject variability within the same study in the smaller group should be considered, inparticular in case of dug substances with substantially different pharmacokinetics and/or variability.	BE should be demonstrated for all components (drugs) in the fixed-dose combination product according to the principles described in this guideline, not necessarily in one/the same study or on the same number of subjects within one study.
ORBIS project	559	581	3,4	pH-Dependency study section is unclear. Criteria for selecting cases for the study are not specific; there is no proposition of study design (e.g. proton pump inhibitor dosing scheme). It seems to be unnecessary to conduct clinical BE studies in all cases. Please consider: (1) limiting studies to fasting conditions only (eliminate products taken at fed conditions only) due to food having a greater effect on the pH variation than the drugs, (2) biowaiver for test products with similar dissolution profiles to the comparator in a wide range of pH, (3) elimination of pH-dependency study for products used mainly together with proton pump inhibitors or mainly in achlorhydria population.	Clarifications needed; the limitation of cases where pH-dependency studies need to be conducted would be appreciated.
EFPIA	560	581	3.4.	pH-Dependency	The assumption is that this section applies to pH-modifying or pH-stabilising formulations, i.e. not to all formulations with a pH-dependent solubility. If so, suggest changing the header for clarification.
EUFEPS Network on Bioavailability and Biopharmaceutics	560	573	3.4	According to the current wording this would apply to all cases where there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility. Such situations are very common in generic development due to patent constraints. It should also be considered that such studies are quite burdening on subjects as it requires long confinement at the clinic.	
EUFEPS Network on Bioavailability and Biopharmaceutics	560	560	3.4	The term "ph-dependent solubility" is used without further clarification. A relevant number of substances will show a change in solubility with changes in the media pH. Is this inteded as showing too low solubility in specific conditions, that is, would the classification as BCS II or IV be a working definition here? See also line 172 where reference is made to BCS for low solubility substances in high-risk products.	
EUFEPS Network on Bioavailability and Biopharmaceutics	560	573	3.4	There is a lack of information on the design of studies with PPI co-adminstration.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Krka, d.d., Novo mesto	560	573	Section 3.4	The definition of cases requiering studies with a pH modifiers should be as concise as possible. Proposed text may pose too many different interpretations. According to the current wording requirement would apply to all cases where there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility. Such situations are very common in generic development due to patent constraints. It should also be considered that such studies are quite burdening on subjects as they require long confinement at the clinic. It may make sense to limit the requirements to conduct an additional study with co-administration of a proton pump inhibitor as proposed in column G.	The absorption of drug substances with pH-dependent solubility may be influenced by the gastric pH. This impact on drug absorption can be altered due to the use of, for instance, pH stabilising excipients or a specific salt-form in the formulation. Moreover, the formulation of the final marketed comparator product may be the result of an extensive formulation development program, obtaining for instance a specific formulation without an effect on drug absorption due to gastric pH differences. This is especially relevant in cases where it is foreseen that the product will be taken with acid reducing drug products, e.g., proton pump inhibitors, or is going to be used in certain populations, e.g., patients with achlorhydria. Therefore when, relative to the comparator product, there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility
Krka, d.d., Novo mesto	560	573	Section 3.4	The definition of cases requiering studies with a pH modifiers should be as concise as possible. Proposed text may pose too many different interpretations. According to the current wording requirement would apply to all cases where there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility. Such situations are very common in generic development due to patent constraints. It should also be considered that such studies are quite burdening on subjects as they require long confinement at the clinic. It may make sense to limit the requirements to conduct an additional study with co-administration of a proton pump inhibitor as proposed in column G.	In certain cases, BE under normal fasting conditions between the two products may not ensure BE of the two products in a gastric pH-altered situation, e.g., in the presence of a pH-modifying drug product. In such a situation, an additional BE study with concomitant treatment of a pH-modifying drug product would generally be necessary to demonstrate BE if all of the following criteria are met: -The comparator product administration recommendations/labelling recommend that it should be taken with acid reducing drug products, e.g., proton pump inhibitors, or is intended to be used in certain populations, e.g., patients with achlorhydria - When, relative to the comparator product, there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility - The product is not intended to be administered under fed conditions only, according to the comparator product administration recommendations/labelling - Differences in gastric pH affect absorption
Krka, d.d., Novo mesto	560	573	Section 3.4	Details on studies with the acid suppression agents should be presented as separate guideline or included in individual Product specific bioequivalence guidelines. To avoid significant between study differences in the gastric pH at the time of dosing of investigational product (between the originators as well as between the generic products) a clear guidance should be provided on how PPI interaction study should be designed. Similar as high fat meal is defined for fed studies, uniform approach to PPI study design will guarantee the comparable gastric pH condition at the time of investigation and extrapolation of obtained results between studies.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	560	573	3.4	The scope of situations where an additional BE study with concomitant treatment of a pH-modifying drug product would generally be necessary to demonstrate BE is by far too wide. According to the current wording this would apply to all cases where there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility. Such situations are very common in generic development due to patent constraints. It should also be considered that such studies are quite burdening on subjects as it requires long confinement at the clinic. Please consider limiting the requirement to conduct an additional study with co-administration of a proton pump inhibitor to the following cases: - Only if it is foreseen that the product will be taken with acid reducing drug products, e.g., proton pump inhibitors, or is going to be used mainly in certain populations, e.g., patients with achlorhydria or - Only if it is known that gastric pH affects absorption, e.g. if the formulation of the final marketed comparator product is the result of an extensive formulation development program and - Not if the product is to be taken under fed conditions only and - Optional: only applicable to low-solubility drug substances (BCS class II or IV)	The absorption of drug substances with pH-dependent solubility may be influenced by the gastric pH. This impact on drug absorption can be altered due to the use of, for instance, pH stabilising excipients or a specific salt-form in the formulation. Moreover, the formulation of the final marketed comparator product may be the result of an extensive formulation development program, obtaining for instance a specific formulation without an effect on drug absorption due to gastric pH differences. ~~This is especially relevant in cases where it is foreseen that the product will be taken with acid reducing drug products, e.g., proton pump inhibitors, or is going to be used in certain populations, e.g., patients with achlorhydria. Therefore when, relative to the comparator product, there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility,~~ Thus, in certain cases, BE under normal fasting conditions between the two products may not ensure BE of the two products in a gastric pH-altered situation, e.g., in the presence of a pH-modifying drug product. ~~In such a situation~~
Medicines for Europe	560	573	3.4	The scope of situations where an additional BE study with concomitant treatment of a pH-modifying drug product would generally be necessary to demonstrate BE is by far too wide. According to the current wording this would apply to all cases where there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility. Such situations are very common in generic development due to patent constraints. It should also be considered that such studies are quite burdening on subjects as it requires long confinement at the clinic. Please consider limiting the requirement to conduct an additional study with co-administration of a proton pump inhibitor to the following cases: - Only if it is foreseen that the product will be taken with acid reducing drug products, e.g., proton pump inhibitors, or is going to be used mainly in certain populations, e.g., patients with achlorhydria or - Only if it is known that gastric pH affects absorption, e.g. if the formulation of the final marketed comparator product is the result of an extensive formulation development program and - Not if the product is to be taken under fed conditions only and - Optional: only applicable to low-solubility drug substances (BCS class II or IV)	Therefore, an additional BE study with concomitant treatment of a pH-modifying drug product would generally be necessary to demonstrate BE if all of the following criteria are met: - When, relative to the comparator product, there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility - The product is not intended to be administered under fed conditions only, according to the comparator product administration recommendations/labelling - Any of the following conditions are met: - It is known that differences in gastric pH affect absorption or - The comparator product administration recommendations/labelling recommend that it should be taken with acid reducing drug products, e.g., proton pump inhibitors, or is intended to be used in certain populations, e.g., patients with achlorhydria
Medicines for Europe	560	573	3.4	There is a lack of information on the design of studies with PPI co-adminstration.	In order not to perform such unnecesary study or with inappropriate design, it is requested that the guidance will include reccommendation of PPI, strength, administration, duration etc. as well as to publish a product specific guidance for these kind of products as soon as possible
Richter Gedeon Plc	567	570	3,4	Comment: Information regarding quantitative composition, manufacturing process technology or API -PSD parameter for a product registered in EU are NOT public information. ('"...when, relative to the comparator product, there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing process, or differences in salt form that possess a different pH dependent solubility..")	Companies are not able to collect these information, therefore please reconsider this part of the guideline or competent authorities has to facilitate or share this information with the companies.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUFEPS Network on Bioavailability and Biopharmaceutics	572	573	3.4	It is not clear how to deal with the requirement of additional studies with PPI co-administration in the context of the fed/fasting studies assessment, e.g. - if only studies under fed conditions are required according to chapter 2.1.5, would an additional study on pH dependency still be required, and if yes, what food conditions should be selected for the study with PPI co-administration - if studies both under fasting and fed conditions are required according to chapter 2.1.5, would an additional study on pH dependency still be required, and if yes, what food conditions should be selected for the study/ies with PPI co-administration	
Medicines for Europe	572	573	3.4	It is not clear how to deal with the requirement of additional studies with PPI co-administration in the context of the fed/fasting studies assessment, e.g. - if only studies under fed conditions are required according to chapter 2.1.5, would an additional study on pH dependency still be required, and if yes, what food conditions should be selected for the study with PPI co-administration - if studies both under fasting and fed conditions are required according to chapter 2.1.5, would an additional study on pH dependency still be required, and if yes, what food conditions should be selected for the study/ies with PPI co-administration	
EUFEPS Network on Bioavailability and Biopharmaceutics	591	591	4	*Instead of the manufacturer, the MAH should be stated since the manufacturer is not always known. *It is requested that the name of the manufacturer should be given. However, at least for the EU-SmPC this information is not (always) available. Therefore, the MARKETING AUTHORISATION HOLDER is recommended as alternative. *Instead of country of purchase the "country where the product is marketed" or "country where the product is authorized" should be provided.	Comparator product name, strength, pharmaceutical form, batch number, ~~manufacturer~~, MAH, expiration date, and country/region authorised should be stated.
EFPIA	595	595	4	Typographical error: 'of the' repeated twice. The identity of the of the test product(s) used in the study should be provided, i.e., pharmaceutical	The identity of the test product(s) used in the study should be provided, i.e., pharmaceutical
EFPIA	595	596	4	The identity of the of the test product(s) used in the study should be provided, i.e., pharmaceutical form, strength, batch number, and measured content (% of label claim).	Specifies that measured content (% of label claim) should be provided for the test product, suggest adding this request for the comparator product as well.
Medicines for Europe	597	597		Re-test date should be added as alternative to expiry date, as meaning is different, expiry dates are formally often not yet defined at study conduct	
EFPIA	608	610	4	Submission of data in electronic format is not a requirement in many countries. These should be made available upon request.	Data in a suitable electronic format may be submitted to enable the PK and the statistical analyses to be repeated, e.g., data on actual times of blood sampling, drug concentrations, the values of the PK parameters for each subject in each period, and the randomisation scheme.
EUFEPS Network on Bioavailability and Biopharmaceutics	608	610	4	It is appreciated that a certain flexibility seems to be allowed for submission of the data in a suitable electronic format. However, if it is intended to follow the CDISC standards (SDTM/ADaM), these may be given as a recommendation.	
ORBIS project	608	608	4	The term "suitable electronic format" is not clear.	Define electronic format

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUFEPS Network on Bioavailability and Biopharmaceutics	611	612	4	It is not clear whether module 2.7.1 should also list relevant pilot studies, since the term BE studies is not defined and it's not clear whether pilot studies would fall into this category. It is expected that submission of synopses for pilot studies should be sufficient.	
Krka, d.d., Novo mesto	611	612	Section 4	Additional clarification on which studies are relevant to be listed in Module 2.7.1 would be appreciated, similar as per current EMA guideline.	Module 2.7.1 of the CTD should list all relevant BE studies conducted i.e. BE studies comparing the formulation applied for (i.e. same composition and manufacturing process) regardless of the study outcome.
EUFEPS Network on Bioavailability and Biopharmaceutics	613	614	4	Per current FDA guidance (Submission of Summary Bioequivalence Data for ANDAs), submission of the FDA summary tables is sufficient as opposed to a report synopsis. Recommend to retain this requirement as submission of a synopsis in module 5.3.1.2 will result in datasets needing to be submitted to FDA as well for these studies given the latest validation requirements for FDA submissions.	Add underlined language: For all other studies, synopses of the study reports (in accordance with ICH E3) or model data summary tables (i.e. FDA) are sufficient.
ORBIS project	616	705	5	Test product is not defined.	Add definition of test product
EFPIA	634		5	IR and GI	IR: please spell out GI -gastrointestinal
ORBIS project	636	638	5	The term 'batch number' is confusing. The batch number should not contain letters.	"batch number" => "batch" or "batch ID" or "batch code"
EUFEPS Network on Bioavailability and Biopharmaceutics	645	645	5	For consistency with other defintions	Cmax: Maximum concentration observed after dosing
ORBIS project	645	645	5	Cmax always occurs after administration of the drug, thus phrase 'after dosing' is unnecessary.	Maximum concentration ~~after dosing~~
ORBIS project	666	666	5	Please consider adding the phrase 'calculated as' before the equation. If intended to be expressed in percentages, then multiplication by 100% should be added to the formula.	Calculated as: ⌈(CmaxSS-CminSS) / CavSS⌉*100%
ORBIS project	670	673	5	kcal - as a unit, does not need to be defined. Otherwise, other units like hour, millilitre, etc. should be defined too.	Remove "kcal" from definitions.
Medicines for Europe	671	673	5	The statement that one kcal (kilocalorie) equals 1 calorie in nutrition sounds strange and seems to be incorrect from a mathematical perspective.	A unit used to describe amount of energy in relation to food or energy burned with exercise. Colloqually, w~~W~~hen it comes to nutrition and exercise, the term calorie is often used instead of kilocalories (kcal) ~~and calories equal the same amount of energy. One kcal (kilocalorie) equals 1 calorie in nutrition~~.
ORBIS project	675	675	5	Changing Lambda_Z to Kel is appreciated. Definition of Kel may be extended for metabolites.	The apparent terminal elimination rate constant of the drug or metabolite.
ORBIS project	699	699	5	Please consider adding the phrase 'calculated as' before the equation. If intended to be expressed in percent, Then multiplication by 100% should be added to the formula.	Calculated as: ⌈(CmaxSS-CminSS) / CminSS⌉*100%
EUFEPS Network on Bioavailability and Biopharmaceutics	705	705	5	For consistency with the definition of kel	t1/2: the apparent terminal elimination half-life
ORBIS project	705	705	5	The term 'half-life' is imprecise.	elimination half-life

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA		Throughout	Tmax	Please use lower case t for tmax	Minor