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Committee for Human Medicinal Products

Overview of comments received on ICH M13B Guideline on bioequivalence for immediate-release solid oral dosage forms - additional strengths biowaiver

EMA/CHMP/ICH/85092/2025

Please note that comments will be sent to the ICH M13B 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
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	0	0	Decimal places	It is not expressively stated how to handle decimal places (or significant digits) and whether intermediate values are to be rounded. We propose 3 significant digits because precision and accuracy of the applied methods are in the range of a few percent. Intermediate values should not be rounded as this may introduce a bias. For illustration, in example 2 the total value of changes is given as 1.2 (0.7+0.3+0.1+0.1). If no intermediate rounding is applied, this value is 1.28 (0.76+0.31+0.13+0.09; rounded to 2 decimals for presentation not for calculation).	Please add: "Assessments should be conducted based on values rounded to 3 significant digits. For calculation of derived values such as total absolute values no rounding of the intermediate numbers should be applied"
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	0	0	Example results	In example 2 the % for Drug A in the real 5mg formulation is given as 6.2%. The amount of drug substance A is 5.0mg and the total core mass is 80 and there is no intermediate result included, thus percentage is 6.25 or 6.3 if rounded to 1 decimal place.	Please correct, if necessary.

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Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences	0	0	0	The Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences consists of members representing academic and industry sectors in the area of pharmacy and biotechnology. We are pleased to have been given the opportunity to comment on the draft guideline released by the ICH. The draft guidance on biowaivers for additional strengths in bioequivalence studies is an important step to systematize and standardize methodology which was dispersed in other documents. Adding flowcharts increases readability of the guideline and is highly appreciated.	

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences	21	22	1.2	This sentence better suits Section 1.3 Scope.	Move to Section 1.3 Scope
Medicines for Europe	23	23	1.3	It is clearly stated that the scope of M13B guideline is to provide recommendations on obtaining BE waivers for additional strengths. However, the overall requirements for in-vitro dissolution studies are not described either in M13A or in M13B, nor it seems to be planned for M13C. Would you consider adding a paragraph in M13B guideline to include the following requirements for in-vitro dissolution studies? a. Complementary to BE studies (paragraph 4.2.1 of former EMA guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) and b. Proving the representative nature of the selected biobatch (paragraph 4.1.2, d) of former EMA guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)	Adddition of a paragraph describing the expectations with regards to dissolution profiles complementary to BE studies (test vs reference biobatch) and for proving the representative nature of selected test biobatch
Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences	24	26	1.3	This paragraph better suits Section 1.2 Background.	Move to Section 1.2 Background
Medicines for Europe	37	40	1.3	IVIVCs to be considered if the biowaiver criteria mentioned in this guideline aren't fulfilled. To be clarified.	
Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences	39	40	1.3	Duplicates lines 10-11.	Delete lines 39-40

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Medicines for Europe	43	44	2.1	" As detailed in ICH M13A, the selection of biobatch strength(s) is based on the proportionality in PK of the drug (or drugs in the case of an FDC) (see ICH M13A, Section 2.1.6). " According to ICH M13A section 2.1.6, the determination of biobatch strength(s) may be influenced by the solubility of the drug substance in addition to pharmacokinetic (PK) considerations. We like to have some clarification on whether ICH M13B should indicate that the selection of biobatch strength(s) is influenced by both pharmacokinetic (PK) considerations and the solubility of the drug substance like ICH M13A section.	As detailed in ICH M13A, the selection of biobatch strength(s) is based on the proportionality in PK of the drug (or drugs in the case of an FDC) and the solubility of the drug substance (see ICH M13A, Section 2.1.6). "
Medicines for Europe	54	56	2.2.1	The M13B draft states that in justified cases, deviations from direct proportionality for core compositions can be accepted. This strategy is concurred and the industry welcomes the possibility of deviating from proportional composition in line with the proposed rules (per Annex I.).	No changes needed, deviations from direct proportionality should be allowed.
Medicines for Europe	57	58	2.2.1	The M13B draft states: 'Excipients present only to provide colour or flavour that are not expected to affect bioavailability may generally vary between strengths.' To avoid any interpretation issues, the wording should specifically mention that qualitative and quantitative changes are possible.	Proposed new test: 'Excipients present only to provide colour or flavour that are not expected to affect bioavailability may generally vary qualitatively and quantitatively between strengths.'
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	57	58	2.2.1	It is stated that "excipients present only to provide colour or flavour that are not expected to affect bioavailability may generally vary between strengths". This refers to the core formulation/composition defined (line 249ff) as the drug product without film coating or capsule shell. Our understanding is, that for the calculation of percentages, based on calculation of the total mass of the core, such excipients are then to be ignored. Colour/flavour should then also not be considered in the calculation of the core mass for proportionality assessments. Such excipients are likely to vary or (even more likely) may remain relatively constant between strengths, and inclusion of such a constant would automatically introduce an excipient change (%) (then "total mass" will deviate also in case of perfect proportionality for all other excipients).	Please add: "Excipients present only to provide colour or flavour that are not expected to affect bioavailability may generally vary between strengths. If such excipients are part of the core formulation, they should not be included in the calculation of the core mass and %w/w of excipients or drug substance."
Medicines for Europe	59	62	section 2.2.1	if the film coating/capsule shell is non-functional, qualitative differences should be possible/allowed	Qualitative differences in non-functional tablet coating / caspule shell (other than colourants or flavours) should be justified
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	59	62	2.2.1	Qualtitative but not quantitative differences are mentioned for the non-functional tablet coating/capsule shell. In line with the preceeding paragraph, „flavoring agents" should be added in the bracket.	Please add that "Deviations from proportionality in non-functional coating/capsule shell composition are generally acceptable". Also please add: „(other than colourants and flavoring agents)

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Medicines for Europe	64	65	2.2.2	"When the amount of drug substance in a formulation is not more than 5% of the drug product core weight in all strengths, a biowaiver for additional strength(s) may be possible if one of the following conditions is met:" • The term "core weight" may lack precision, so it is recommended to use the glossary-defined term to enhance clarity. • Propose to indicate that "all strengths" means all strengths which are considered to be included in the biowaiver of strengths • Please clarify whether the 5% value represents only the drug substance or includes the salt form as well.	"When the amount of drug substance in a formulation is not more than 5% (w/w) of the drug product core ~~weight~~ formulation in all considered strengths, a biowaiver for additional strength(s) may be possible if one of the following conditions is met:"
Medicines for Europe	75	75	2.3	"2.3 Dissolution Conditions (including Optimisation and Validation)" • It is unclear what is meant with "(including Optimisation and Validation)". Those terms are nowhere addressed in the section text. Validation in the text refers to validation of the analytical method, not of the dissolution conditions. We propose deleting the text in parenthesis in the section header.	2.3 Dissolution Conditions ~~(including Optimisation and Validation)~~
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	75	153	2.3	It appears as if there is no proposal on how many batches of the new strength should be investigated. It is assumed, that the same requirements as for the choice of a test product/batch outlined in chapter 2.1.4 of ICH M13A apply, therefore a reference to that chapter for the selection of a test batch should be made.	Please add: "For the selection of the batch of the additional strength to be investigated, reference is made to ICH M13A with the biobatch to be considered as the "comparator".

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Genepharm S.A	76	77		should it be considered that the dissolution profiles for proving batch to batch consistency for the bio-strength batches and comparison between test and reference biobatches can deviate from the dissolution conditions described for strengths biowaiver?	
Medicines for Europe	76	78	2.3	The same batch(es) used in the BE study(ies) should be used for comparative dissolution testing. If the BIO batch has exceeded its expiry date, is it permissible to use a representative batch? Since the guideline is also to apply to post-approval changes and dissolution profiles of biobatch according to the proposed guideline are not always available, additional provisions of the guideline are needed. Some products have been developed more than 10 years ago and may lack dissolution data in standard conditions without use of surfactants.	The same batch(es) used in the BE study(ies) or representative batch (if appropriate dissolution profiles are not available) should be used for comparative dissolution testing.
Krka	77	78	2.3	Considering Objective of this guideline and application also for post-approval phase, in cases where in vitro dissolution testing of the biobatch was not performed as per ICH M13B and the biobatch has expired, a bridging batch (new representative/comparable batch from the same manufacturer produced by the same manufacturing process) can be used for in vitro dissolution testing for biowaiver of additional strengths.	If the batch used in the bioequivalence study has expired and in vitro dissolution testing of the biobatch was not performed as per this guideline, a comparable and representative batch from the same manufacturer, produced by the same manufacturing process as the biobatch (bridging batch) can be used for in vitro dissolution testing for biowaiver of additional strength.
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	77	78	2.3	The guideline states that "The same batch(es) used in the BE study(ies) should be used for comparative dissolution testing". In certain cases, e.g. if new strengths are added a long time after the initial marketing authorization, biobatches have expired and/or are no longer available and historical dissolution data of the biobatch may not meet current standards. In situations like this use of current batches of the strength used in the BE should be acceptable. It should be added that in such situations current batches can be used as reference.	Please add after "The same batch(es) used in the BE study(ies) should be used for comparative dissolution testing." “In case bio-batches or data generated in line with this guideline are not (longer) available, dissolution investigated in a recent batch of the biobatch’s strength may be used as reference".
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	82	82	2.3	In order to be consistent with current guidelines such as ICH M9.	Please add: “Volume of dissolution test is : 900 mL or less (it is recommended to use the volume selected for the quality control (QC) test”

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Genepharm S.A	84	85		Do rotation speed limitations apply for the QC method? It should be clarified	
Genepharm S.A	86	86		The term “at least 12 units” may create a confusion with regards to heterogeneity in number of units tested between the several comparisons	
Medicines for Europe	86	88	2.3	It is stated that "at least 12 units" should be used for BioWaiver dissolution comparisons. It needs clarification, as currently description allows the comparison could be performed ie between 12 units of biobatch and 18 or 24 or even 36 units of the additional strength. If there is a limit or a rationale that should be followed, criteria and limits should be provided. Otherwise the clarification that "The same number of units should be used for both strengths" could be added.	The same number of units should be used for both strengths.
Genepharm S.A	96	96		Filtration may be proven unsuitable in specific cases	To add at the end of the sentence: “and unless otherwise indicated through the filter suitability evaluation in method validation”
Krka	99	100	2.3	While full validation of the QC method is reasonable, non-QC methods should be sufficiently supported only by qualification (reduced-scope validation).	The comparative in vitro dissolution experiments in the QC medium should use validated analytical methods that are suitable for specific use and conditions for the determination of the drug substance. Reduced validation is sufficient for other media.
Medicines for Europe	99	100	2.3	Generally, the quality control (QC) dissolution methods for routine manufacturing testing are developed and designed to be state-of-the-art, by selecting the most suitable dissolution media with respect to discriminative power, reproducibility, robustness, accuracy & precision, etc., and taking into the account the dissolution behaviour of the product and the containing active pharmaceutical ingredient (API). In contrast, dissolution in non-QC media (e.g., physiologically-relevant media of pH between 1.2 to 6.8 intended to compare additional strengths with biobatch to support the strength biowaiver) may result in measurements with technical difficulties due to e.g., potential analyte degradation, precipitation, solid state transition, poor solubility, incompatibility of excipients (or drug form) with the given media. Consequently, unlike for the QC-methods, a full scope validation and compliance of all required validation parameters with acceptance criteria defined in the 'ICH Q2(R2) Guideline on validation of analytical procedures (EMA/CHMP/ICH/82072/2006)' may simply be not possible. For example, in media where sink conditions are not achievable, measurement of accuracy on 100% release will not be possible due to combination of physical-chemical nature of the drug substance and the dissolution media (e.g., low solubility of API, low ionic strength of media, etc.). Additionally, in case of low solubility, preparation of reference standards solution in adequate concentration may be difficult and consequently, e.g., evaluation of its stability would be challenging. Furthermore, whereas high variability in dissolution does not prevent evaluation of similarity (via bootstrapping approach), it can cause issues in fullfiling strict acceptance criteria in analytical method validation. Finally, requirement for full validation for non-QC (in case of biowaiver at least 3 pH conditions) accross all product strengths brings disproporionate burden on applicant's analytical laboratories.	The scope of the validation and acceptance criteria for non-QC dissolution methods may be justified and can differ from the full scope validation of QC-methods according to the 'ICH Q2(R2) Guideline on validation of analytical procedures (EMA/CHMP/ICH/82072/2006)'. Reduced validation scope should be accepted for non-QC methods provided emphasis is given to parameters critically influenced by dissolution media pH (including system suitability test and evaluation of sample matrix pH influences, intermediate precision, stability, and specificity) and validation of drug product exteremes (e.g., lowest & highest strength) shall be permitted when justified.
Genepharm S.A	103	105		There are cases that multiple units of a smaller strength cannot make up for the biobatch strength, for example for biobatch strength of 125mg and a smaller strength of 100mg. In these cases the option of modifying the dissolution volume, to equalize the concentration between the two strengths, could be an option. On the contrary, comparing the additional strength to the respective strength of the innovator product may not assist the strength biowaiver proof, since there are many cases where the test and reference biobatches are already non similar, however proven equivalent in vivo. In such an instance the smaller strengths of test and reference product are expected to be non similar as well. Proving strength biowaiver is therefore not feasible following this experimental design	Such differences in dissolution may be due to the absence of sink conditions, which can be demonstrated by similar dissolution profiles when testing the same dose per vessel, e.g., three tablets of 5 mg versus one tablet of 15 mg, or ensuring the same concentration per vessel for the two strengths

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Medicines for Europe	105	106	2.3	1) To be clarified if the same dose per vessel allows multiple doses for both strengths under comparison in the case where it is not feasilbe to compare with 1 tablet of the biostrength. For instance, comparison of the additional strength 10mg versus the 45mg of the biostrength. 2)To be confirmed that comparison with corresponding strength of the comparator product should be permitted as an alternative approach.	
Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences	106	106	2.3	The term "excessive" is vague and should be avoided	
Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences	110	110	2.3	Other, noncompendial apparatuses and media are often used in the formulation development process to help identify undesidered, that is – different from the comparator product, drug product performance	"compendial apparatuses, agitation speeds, or biorelevant media and apparatuses, may be considered to overcome specific issues, e.g. coning, if scientifically justified"
Krka	110	111	2.3	Standardized deviations from current guidelines (different basket mesh sizes, peak vessels and sinkers) are also scientifically sound and almost standardly used, while only higher agitational speeds are singled out here. We propose broadening of examples of modifications.	Other dissolution conditions, e.g., compendial apparatuses, standardised modifications (e.g. different basket mesh size, peak vessels), agitation speeds, sinkers etc. may be considered to overcome specific issues, e.g., coning, sticking, floating, if scientifically justified.
Medicines for Europe	110	111	2.3	Other dissolution conditions, e.g., compendial apparatuses and agitation speed, may be considered to overcome specific issues, e.g., coning, if scientifically justified. However, use of other non-compendial apparatuses (e.g., apex/peak vessels) and/or methods should be allowed in justified cases.	Proposed new text: 'Other dissolution conditions, e.g., compendial and non-compendial apparatuses and agitation speed, may be considered to overcome specific issues, e.g., coning, if scientifically justified.'
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	110	111	2.3	In order to be consistent with current guidelines such as ICH M9.	Please add: "e.g. compendial apparatuses and agitation speeds as well as the use of sinkers or other appropriately justified approaches may be considered"

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Medicines for Europe	111	112	2.3	Following requirements are proposed: 'For suspensions, a rotational speed of 50 rpm is recommended with the paddle apparatus. A different rotation speed may be used, if justified. All experimental conditions and results shoudl be provided.' Comments: (1) It shall be confirmed that the above text is applicable to suspensions only or applies to all formulations (e.g., the need to present data from all experimental conditions). (2) Altough different rotation speed seems permitted, the requirement for suspensions to use 50 rpm in a paddle apparatus appears too prescriptive. Suspensions typically contain excipients increasing high viscosity and upon introduction of the sample into the dissoution vessel, aggregates may be formed (e.g., observed in suspensions containing xanthan gum). These aggregates prevent release of the active substance even in case of highly-soluble APIs. Consequently, artefacts and high variability is obsereved in dissolution.	Delete text: 'For suspensions, a rotational speed of 50 rpm is recommended with the paddle apparatus. A different rotation speed may be used, if justified. All experimental conditions and results shoudl be provided.'
Medicines for Europe	115	151	2.4	2.4 Assessment of Similarity section: There is no clear distiction between sampling points that should be measured and sampling points that should be included in the similarity assessement. E.g. a plateau should be defined based on three time points however, presumably, not all three of those should be included in the similarity assessment. Please clearly distinguish between sampling points that should be measured to adequately describe the profile and sampling points that should be included in the similarity assessment.	"A plateau is defined by three successive time points differing by less than 5% in mean absolute dissolution. Only the first timepoint of the plateau is then to be included in the similarity calculation. Dissolution tests and sampling need not exceed two hours..."
Medicines for Europe	119	133	2.4	There is a lack of discussion and guidance on selecting the initial time points during which the disintegration of a tablet or capsule is ongoing. For example, if a drug product has a disintegration time of more than one minute, the five-minute time point should be excluded. The first sampling points should include those time points where the disintegration process is almost complete. The only exceptions should be drug forms that erode but do not disintegrate. The 5 minute sampling point is characterised by excessive variability when disintegration takes place. Similarly, the degree of cross-linking is not uniform within one capsule or among different capsules. As consequence, there is a higher variability in the dissolution results if the gelatin capsules are cross-linked. In such cases bootstrap methodology should be used, which is overdiscrimatory. Introducing the standard deviation instead of the relative standard deviation is a step in the right direction, but assigning the same criteria for variability at early and later time points is not appropriate. Time points above 5 minutes characterize the release profile sufficiently well and are not expected to affect bioavailability.	Supplement lines with a following wording: The exclusion of early sampling time points at which the disintegration of a drug form occurs may be justified, for example, by reports of disintegration time studies or study of the time needed for the digestion by enzyme the cross-linked gelatin.
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	119	133	2.4	A time point at 15 minutes or the time of reaching 85% in case of very rapid release is essential.	Please add, e.g., line 131: In case of very rapid release, a sampling time point at the time, where 85% of dissolution are reached, e.g. 15 min, should be included.

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Medicines for Europe	124	125	2.4	The definition of "plateau" in dissolution using "three successive time points" is more than welcome. However a clarification is needed on the "differing by less than 5% in mean absolute dissolution": does it mean that the NMT 5% difference is between two sequential points (ie 73%, 77%, 82% is considered as plateau) or between all of them (ie 73%, 78%, 75%)? Also, the limit should be tightened. An example should be provided to erase ambiguity.	124 A plateau is defined by three 125 successive time points differing by less than 5% in mean absolute dissolution *(e.g. 73%, 78%, 75%)* .
Medicines for Europe	124	125	2.4	A definition of the "mean absolute dissolution" should be provided to erase ambiguity. Currently it can be read as both the mean (=average of all units for this time point) percentage release of the label claim for each time point and as the mean of the dissolution release of the three consecutive time points (e.g. sum of the three consecutive time points divided by three).	A plateau is defined by three successive time points differing by less than 5% in mean absolute dissolution*, where mean absolute dissolution is the average (of all units) release for that time point expressed as a percentage of the label claim.*
Medicines for Europe	124	125	2.4	The definition of "plateau" in dissolution using "three successive time points" is more than welcome. However a clarification is needed on the "successive time points": is there any specific frequence of these time points? The values 72% - 75% - 78% is not the same if these are from samplings at 10min - 15min-20min than if these are from samplings at 15min - 30min - 45min.	A plateau is defined by three successive time points *(with at least 10 minutes difference for Apparatuses I and II and appropriately justified frequency for other apparatuses)* differing by less than 5% in mean absolute dissolution.
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	124	125	2.4	The guideline should define which point of the (two) plateau phases should be used for f2 calculation, the first in the plateau or the last one.	Please rephrase: "...to describe a dissolution profile, with the final time point occuring when dissolution reaches ≥ 85% for either the additional strength or biobatch strength, or or just after both strengths have reached a plateau (of <85%), i.e. the first time point of the posterior plateau.

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Medicines for Europe	125	126	2.4	"need not exceed two hours": clarifications are needed. As per Ph. Eur. monograph 5.17.1: "typically, a single-point acceptance criterion is sufficient to demonstrate that the majority of the active substance has been released, although in certain circumstances it may be necessary to test at additional time point(s), in order to demonstrate adequate dissolution", where the total duration of the test is not specified. Since there is the possibility to have an IR formulation exceeding two hours (QC media), would you reconsider amending this point? Also for such products, which are the requirements applied for the duration of multimedia testing?	….not exceed two hours (*unless otherwise justified*)
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	125	125	2.4	The requirement of "by less than 5% in mean absolute dissolution" should be defined in more detail as we asee that here percentage points are intended. (40%, 42% and 44% should indicate a plateau, although 44/40 is 10% change).	Please change the wording to underline that the percentage points are meant to: "differing by less than 5% (percentage points) in mean absolute dissolution"
Krka	130	131	2.4	Sampling intervals shorter than 5 minutes could potentially allow calculation of similarity factor in some cases of rapid dissolution in initial time points up to 15 minutes. However, it is well known that in cases of formulations with very rapid dissolution, absorption is controlled with gastric emptying rate, therefore sampling intervals shorther than 5 minutes wouldn't provide additional meaningful information regarding product performance *in vivo* , while shorter sampling intervals could lead to more variabile dissolution results due to small differences (e.g. tablet disintegration) which have no impact on *in vivo* performance of the product.	More frequent sampling during the period of greatest change in the dissolution profile should be employed, but sampling intervals shorter than 5 minutes are generally not necessary.
Medicines for Europe	130	131	2.3	When there is knowledge of delayed disintegration that indicates a slow release of the active substance, it is acceptable and quite rational to have first dissolution sampling time point after 10min. In the same time there is the term "frequent sampling during the period of greatest change on the dissolution profile should be employed". For instance, is it acceptable to perform sampling at 15, 20, 25, 30, 35 & 45min for a product that reaches and excheeds 85% at about 30min?	More frequent sampling during the period of greatest change in the dissolution profile should be employed.*The initial timepoint should be selected taking into account previous product knowledge (e.g. from preliminary experiments)*

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Krka	136	138	2.4	As already stated in Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017), similar dissolution of two batches may be assumed in cases when difference in their mean result is less than 10%. F2 calculation is based on the same approach - dissolution profiles with ≤ 10% difference will exhibit f2 ≥ 50, which is also described in Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). Below is an example where one can't calculate f2 factor with classical sampling approach, because results of batch of lower strength are above 85% after 10 and 15 minutes, respectively (2 time-points > 85%), while dissolution results of BEQ batch are slightly below 85% after 15 minutes (don't meet criterion >85% in 15 minutes). F2 dissolution profile comparison could be performed using more frequent sampling before 10 minute time-point (e.g. 2.5min, 7.5min); however, with this sampling approach too much emphasis is given on initial part of the dissolution profiles, where differences are greatest but not important for in vivo performance as absorption is controlled with gastric emptying rate. In such cases proposed approach with difference < 10% of drug dissolved after 15 minutes would enable similarity assesment.	As described in Figure 1, when ≥85% of the drug is dissolved within 15 minutes (very rapid dissolution) for both the additional strength and biobatch strength mean dissolution profiles, no further mathematical evaluation is needed, and similarity can be concluded. Additionally, when less than very rapid dissolution is observed for one of the strengths, similarity between two batches may be concluded when difference between their mean dissolution results at 15 minutes does not exceed 10% of the label claim.
Medicines for Europe	136	138	2.4	As already stated in GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) and Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017), similar dissolution of two batches may be assumed in cases when difference in their mean result is less than 10%.	As described in Figure 1, when ≥85% of the drug is dissolved within 15 minutes (very rapid dissolution) for both the additional strength and biobatch strength mean dissolution profiles, no further mathematical evaluation is needed, and similarity can be concluded. Additionally, when less than very rapid dissolution is observed for one of the strengths, similarity between two batches may be concluded when difference between their mean dissolution results at 15 minutes does not exceed 10% of the label claim.
Genepharm S.A	139	141		There are cases that only one of the batches under comparison presents a release >85% from the second time point. For example, for the dissolution profiles presented in the table below: Time pointsBiobatchAdditional strength 5’ 75 81 10’ 80 86 15’ 82 90 30’ 88 96 The two batches don’t release >85% at 15’, therefore an f2 comparison should be followed. However 3 time points with only one point >85% are not available. Sampling points earlier than 5’ cannot be added due to instrumental restrictions. Advice therefore is needed on how to compare the batches in these cases. Could the “10% difference per time point” rule be followed in such a case?	
Medicines for Europe	139	147	section 2.4	Clear definition of standard deviation (SD) should be provided (in Glossary). It should be clarified what is referred here, because in other EMA document i.e. Reflection paper EMA/CHMP/CVMP/QWP/336031/2017, RSD is to be considered for dissolution analysis.	
Medicines for Europe	141	142	2.4	Statistically, similarity in dissolution profiles of two batches can be assumed in case of differences of less than 10% in their mean dissolution results. Is visual assessment of results acceptable/sufficient in that case, or f2 calculation is necessary anyway?	An f2 value of ≥50 suggests that the two dissolution profiles are similar. *In case of differences ≤10% in the mean dissolution result for each time point, profiles can be considered similar without any statistical evaluation.*

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences	143	147	2.4	The specifics of the boostrapping method are not provided, e.g. the minimum number repetitions of boostrapping (e.g. 5000), time point selection (e.g. should the last time point be the time when both strengths exceed 85% or only one of them), or the curve selection (e.g. should whole dissolution profiles be bootstrapped, or would bootstrapping be possible from the individual time points)	Provide more specific recommendations regarding the bootstrapping procedure.
Gedeon Richter plc.	143	143	2.4	High variability is defined as an SD >8% at any time point- up to now high variability has been defined when relative standard deviation or coefficient of variation of any product was less than 20% for the first point and less than 10% from second to last time point (GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) , the definition was the same for waiver for additional strenghts as well as for bioequivalance study (to evaluate the in vitro results of test and reference products), if the M13B guidline change the definition of variability for additional strength will it be different for the bioequivalence? Does this mean that for cases where SD>8%, regardless of time point, the bootstrap method should always be used?	
Krka	143	143	2. 4.	The limitation of SD > 8% can be unneccessarily strict at early time points or rapidly releasing formulations. Since 15 minute time point is deemed crucial, we propose widening of SD for time points up to 10 minutes as per EMA Q & A (3.13.) and Reflection paper (Section 2.1.1) and ICH M9 guideline on biopharmaceutics classification system-based biowaivers.	High variability is defined as SD > 10% at timepoints up to 10 min and SD >8% at any time point >10 min.
Medicines for Europe	143	143	2.4	Kindly clarify that "SD>8%" refers to the "at least 12 units" that are used for comparison, meaning that it might also apply as a criterion to 24 (or more) units that will be officially presented. - linked with comment for line 86	High variability is defined as an SD>8% at any timepoint, *irrespectively of the number of units involved in the analysis for this timepoint* .
Medicines for Europe	143	145	2.4	Clarification needed regarding the definition of point estimate f2. Is this the typical f2 value? Or is the average of the f2 values of the bootstrap comparisons? Furthermore, is the expected f2 value still needed to be calculated in the case of bootstrapping as it was mentioned in section 3.11 of Clinical pharmacology and pharmacokinetics: questions and answers (from August 2023)? In this section was mentioned that ''In case of bootstrapping, similarity in dissolution profiles will be concluded when the lower limit of the 90% confidence interval for the Expected f2 is ≥ 50''.	If high variability is observed for either the additional strength or biobatch strength, then calculation of the 90% confidence interval (CI) for the similarity factor using bootstrapping methodology is recommended. The confidence intervals and point estimate should be calculated for the parameter of "estimated similarity factor" as defined in page 11.
Medicines for Europe	143	143	2. 4.	High variability is defined as an SD >8% at any time point. The limitation can be unneccessarily strict at early time points or rapidly releasing formulations. Since 15 minute time point is deemed crucial, we propose that limitation of 20% RSD for time point up to 10 minutes as per EMA Q & A (3.13.) and Reflection paper (Section 2.1.1) and ICH M9 guideline on biopharmaceutics classification system-based biowaivers	High variability is defined as RSD > 20% at timepoints up to 10 min and SD >8% at any other time point.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Ms. Miral Sindhav, Aspire Pharma Ltd.	143	147	2.4 Assessment of Similarity	"High variability is defined as an SD >8% at any time point. If high variability is observed for either the additional strength or biobatch strength, then calculation of the 90% confidence interval (CI) for the similarity factor using bootstrapping methodology is recommended." This requirement can be particularly stringent at initial time points in the following situations: Low absolute drug release due to poor solubility: When the drug has low solubility, absolute release values are low at initial time points. Even minor variability can result in a high percentage standard deviation (SD), despite well-controlled conditions. Formulation-related variability: Minor differences in disintegration time or capsule opening can introduce early-stage variability, which often reflects formulation characteristics rather than inconsistent dissolution behavior. These factors can lead to a classification of high variability based solely on early time points, unnecessarily triggering the need for a more complex bootstrapping approach, even when overall dissolution profiles are visually and quantitatively similar.	We would link to recommend inline to current EMA and FDA guidance for dissolution similarity as below: The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	143	143	2.4	Definition of high variability in dissolution is different from the one in M9, should be aligned	
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	143	147	2.4	Methodology should be defined more in details (f.i. f2-factor to be used such as the estimated f2, percentile CI (any?), approach of bootstrapping such as selection of wole profiles, the number of bootstraps to be done, seed used in the bootstrapping needs to be fixed).	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Gedeon Richter plc.	146	147	2.4	In case of bootsraping function in M13B: the lower bound of the 90% bootstrapped CI for the similarity factor should be ≥46 and the point estimate (f2) should be ≥50 The acceptance criteria has changed from the: In case of bootstrapping, similarity in dissolution profiles will be concluded when the lower limit of the 90% confidence interval for the Expected f2 is ≥ 50. (3.11 Expectations for bootstrapping to calculate the 90% CI for the f2 similarity factor (Q& EMA). Does that mean that the acceptance criteria for the same statistical test (bootstrap method) will be different in different cases: waiver for additional strenghts' study (M13B) and bioequivalance study ((GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE London, 20 January 2010 Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **))	
Medicines for Europe	146	147	2.4	The M13B draft states: 'To demonstrate dissolution similarity, the lower bound of the 90% bootstrapped CI for the similarity factor should be ≥46 and the point estimate (f2) should be ≥50.' It shall be clarifed whether the applicants may choose any type of point estimator (e.g., the estimated f2, bias-corrected f2, expected f2, etc.) and associated confidence intervals (e.g., percentile, basic, normal, BCA, etc.) or whether particular type is preferred. E.g., in the EU, currently, the expected f2 and percentile intervals are recommended by the Clinical pharmacology and pharmacokinetics: Q&A (Section 3.13).	Clarification of the preferred type of f_2 point estimator and associated bootstrapped confidence intervals shall be given in the M13B guideline.
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	146	147	2.4	A limit of 46 is set for the lower bound of the 90% bootstrapped CI. From a formal perspective it should be specified that this is a two-sided CI.	Please change to: "…the lower bound of the two-sided 90% bootstrapped CI…"
Krka	147	148	2.4.	In case of dissolution profiles with different lag-time and comparable release kinetics (e.g HPMC capsules where different strengths contain the same content e.g. granules, pellets, however between capsules of different strengths differences in lag time can occur), standard similarity evaluation easily results in non-similar dissolution profiles, which is not relevant in-vivo due to the same release kinetics. Differences occur only in the time of start of the dissolution process. The dissolution curve adjustment with the lag time should be considered. See example below. Both profiles were simulated using Weibull function (alpha=2, betha=10) with different lag-times 2 and 5 minutes. Resulting f2 factor is below 50 (46) and dissolution profiles are deemed not-similar. Lag time adjustment rendes these profiles identical.	If dissolution profiles exhibit significant lag time (time at which up to 5 % of API is dissolved), the curves can be adjusted for lag time and similarity criteria are applied after the lag time adjustment.
Medicines for Europe	147	148	2.4	•In case of dissolution profiles with lag time (e.g HPMC capsules where different strengths contain same intermediate product e.g. granules, however between capsules of different strengths differences in lag time can occur), standard similarity evaluation could result in non-similar dissolution profile, which is not relevant in-vivo as dissolution kinetics of all strengths remains the same, differences can occur only in the time of start of the dissolution process. The dissolution curve adjustment with the lag time should be considered.	If dissolution profiles exhibit lag time (time at which up to 5 % of API is dissolved), the curves can be adjusted considering the lag time for assessment of similarity. Similarity criteria are applied after the lag time adjustment.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	147	147	2.4	The rationale for a threshold of 46 (in contrast to the more common 50) should be given. The f2 values/CI values should be compared considering no decimal places (after rounding to integer) as this is currently incidcated by the use of >46<.	
Medicines for Europe	148	151	2.4	It is not clear why 10% was assigned as a cut-off value. For products with limited solubility, the dissolution plateau value should be set at below 20%. The 20% cut-off is appropriate to assess the similarity with a maximum difference of 10% between the additional strength and biobatch strength dissolution profiles. The maximum difference of 10% has been used to establish acceptance criteria to statistical methods like the f2 value to assess profile similarity, therefore values above 10% maximum portion dissolved should also be considered.	Change to: However, when the maximum portion dissolved of both the additional strength and biobatch strength plateau below 20%, no similarity test needs to be applied, and similarity can be assumed.
Medicines for Europe	149	151	2.4	" However, when the maximum portion dissolved of both the additional strength and biobatch strength plateau below 10%, no similarity test needs to be applied, and similarity can be assumed". Clarification is needed on whether the "plateau below 10%" case is subject to specific SD/RSD requirement.	
Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences	152	152	2.4	Idea of placing a flowchart here is highly appreciated. However, flow is both top-down and left-to-right, which is confusing. Two paths are missing: (1) "f2 ≥ 50" => No; (2)"Lower 90% CI ≥ 46, f2 ≥ 50" => No.	Flowchart should be rearranged as top-down or left-to-right. Missing paths should be added.
Medicines for Europe	152	153	2.4	Figure 1 does not include the plateau below 10% case. It should be revised to ensure completeness by including this case.	
Medicines for Europe	152	152	2.4	*"Figure 1: Decision tree for determining dissolution profile similarity using f2"* The figure caption may require revision to reflect that f2 is not the only method applied in the figure.	"Figure 1: Decision tree for determining dissolution profile similarity ~~using f2~~"
Genepharm S.A	159			There is a reference to monolithic forms. We would need though clarifications for the other complex forms such as multi particulates, sprinkle capsules and if ICHM13B applies also to those cases	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	159	170	3.1	" When an FDC is formulated as a single blend or granulate (monolithic), the recommendations as identified in Section 2.2.1 and Annex I are applicable to the proportionality in the formulation(s) of the additional strength(s). The conditions regarding direct proportionality should be fulfilled for each individual drug substance in the FDC. When considering the amount of one drug substance in an FDC, the other drug substance(s) can be considered as excipient(s), i.e., as diluent/filler. In this case the proportionality rules should still be fulfilled (see Section 2.2.1 and Annex I). When an FDC is formulated with the individual drug substances in separate layers, criteria for proportionality in the formulation(s) of the additional strength(s) should follow those of non-FDCs (see Section 2.2.1 and Annex I) and should be considered independently for each layer. When the strengths (or layers, if applicable) in an FDC are not proportionally formulated (see Section 2.2.1 and Annex I), BE should be demonstrated for all strengths. Alternatively, it may be possible to apply a bracketing approach (see Section 3.2)." •This section does not clearly indicate the applicability of the "5% rule" for fixed-dose combinations (FDCs), as there is no reference to Section 2.2.2. However, the explanation for Example 4 (lines 395-397) specifies that Section 2.2.2 can be applied to FDCs. To ensure clarity, the applicability of the 5% rule for FDCs should be explicitly stated, and the wording revised accordingly. Additionally, all instances of "Section 2.2.1 and Annex I" should be updated to "Section 2.2.1, 2.2.2, and Annex I"	" When an FDC is formulated as a single blend or granulate (monolithic), the recommendations as identified in Sections 2.2.1, 2.2.2 and Annex I are applicable to the proportionality in the formulation(s) of the additional strength(s). The conditions regarding direct proportionality should be fulfilled for each individual drug substance in the FDC. When considering the amount of one drug substance in an FDC, the other drug substance(s) can be considered as excipient(s), i.e., as diluent/filler. In this case the proportionality rules should still be fulfilled (see Sections 2.2.1, 2.2.2. and Annex I). When an FDC is formulated with the individual drug substances in separate layers, criteria for proportionality in the formulation(s) of the additional strength(s) should follow those of non-FDCs (see Sections 2.2.1, 2.2.2 and Annex I) and should be considered independently for each layer. When the strengths (or layers, if applicable) in an FDC are not proportionally formulated (see Sections 2.2.1, 2.2.2 and Annex I), BE should be demonstrated for all strengths. Alternatively, it may be possible to apply a bracketing approach (see Section 3.2). When the amount of drug substance in a formulation is not more than 5% (w/w) of the drug product core formulation in all strengths, a biowaiver for additional strength(s) may be possible if conditions in Section 2.2.2. are met"
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	162	164	3.1	For FDCs reference is made to Sections 2.2.1 and 2.2.3 and Annex I. A reference to Section 2.2.2. should be included. A clarification, that the 5% rule is applied to each drug substance separately is recommended (considering other drug substances as filler).	Please add: "Other drug substance(s) will be considered as excipients(s), i.e. as diluent/filler, in the assessment whether with respect to a specific drug substance the drug product qualifies as high-potency (see Section 2.2.2)"
Krka	165	167	3.1	According to ICH M13A, the IMPs should be administered with water of the same temperature and volume, in the range of 150 to 250 milliliters (ml). Under fasting conditions, the 240 mL of water are emptied from the stomach typically within 15-30 min as shown by published scientific literature.1 Therefore, in tablets that disintegrate within 10 minutes (bilayer or monolithic) all excipients and APIs are mixed within the stomach and potentially interact with each other. 1 D. Mudie, K. Murray, C.L. Hoad, S.E. Pritchard, M. Garnett, G.L. Amidon, P.A. Gowland, R.C. Spiller, G.E. Amidon, L. Marciani, Quantification of gastrointestinal liquid volumes and distribution following a 240 mL dose of water in the fasted state, Mol. Pharm. (2014).	When an FDC is formulated with the individual drug substances in separate layers, criteria for proportionality in the formulation(s) of the additional strength(s) should follow those of non-FDCs (see Section 2.2.1 and Annex I) and should be considered independently for each layer. However, if both layers disintegrate rapidly (within 10 minutes), criteria for proportionality may be considered for a whole tablet.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	165	167	3.1	When FDC is formulated with the individual drug substances in separate layers and has very rapid disintegration, all components from all layers are in vivo mixed in the stomach just the same as in mono-layer tablets. Therefore, it should be acceptable not to consider each layer separately in such cases, but also the tablet as a whole.	When an FDC is formulated with the individual drug substances in separate layers, criteria for proportionality in the formulation(s) of the additional strength(s) should follow those of non-FDCs (see Section 2.2.1 and Annex I) and should be considered independently for each layer. However, if both layers disintegrate within 10 minutes, criteria for proportionalyty can be considered for a whole tablet.
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	165	167	3.1	It is stated that separate layers should be assessed independently regarding proportionality. This should also apply to analogous formulation principles such as mixtures of microtablets with a powder or multiple separate granules.	Please add: "or analogous formulations, e.g. core-coat, mixtures of separate granules or mixtures of micro-tablets and powders in a capsule"
Genepharm S.A	176			How IVIVC or modelling can be used in those cases	
Medicines for Europe	176	176	3.2	*"3.2 Bracketing Where the Above Criteria Are Not Met".* Clarification and corretion are needed to explain what does "the above criteria" mean here.	
Krka	186	188	3.2	Deviation from direct proportionality for core compositio may be misleading, as the guideline suggests that this is the only option for bracketing approach. Assessment of fasting and fed condition on one dosage strength only should be applicable to other reasons (dissolution dissimilarity, disproportional PK).	Where BE assessment is needed under both fasting and fed conditions, and at two strengths due to ~~deviations from formulation proportionality~~ bracketing, it may be sufficient to assess BE for one of the strengths under both fasting and fed conditions.
Medicines for Europe	186	188	3.2	"Where BE assessment is needed under both fasting and fed conditions, and at two strengths due to deviations from formulation proportionality, it may be sufficient to assess BE for one of the strengths under both fasting and fed conditions." The way it is specified now, the wording limits the application of this possibility ("may be sufficient to assess BE for one of the strengths under both fasting and fed conditions") only if dose-proportionality conditions is not met.	Where BE assessment is needed under both fasting and fed conditions, and at two strengths due to deviations from formulation proportionality, non-dose proportional PK or dissolution dissimilarity, it may be sufficient to assess BE for one of the strengths under both fasting and fed conditions

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Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	186	191	3.2	Line 187 mentions "deviations from formulation proportionality" only. Should dissolution dissimilarity and non-dose proportional PK not play a role here?	
Medicines for Europe	192	193	3.2	"Dissolution profile comparison should demonstrate similarity in QC and multimedia conditions based on the situation under consideration" This sentence lacks clarity. The preceding text in the guideline already specifies that QC and multimedia dissolution are required; however, the exact details are not provided. Additionally, the examples included (194 - 197) are limited. It is recommended to expand the guidance by including further details and additional examples to improve clarity.	Dissolution profile comparison should demonstrate similarity in QC and multimedia conditions based on the situation under consideration (see further examples).
Medicines for Europe	194	197	3.2	"For example, in a situation where BE needs to be demonstrated with more than one strength, e.g., with three strengths, in vivo BE studies are conducted with the highest and lowest strengths, and the middle strength is only dose proportional with the highest strength, then the highest strength will be considered the biobatch strength for dissolution comparison with the middle strength." • This example is not applicable, as it does not represent a true bracketing case; the middle strength is dose proportional to the highest one, so a normal biowaiver can be applied, while the lowest strength undergoes a separate BE study, so biowaiver is irrelevant in this case. It is recommended to remove or replace it with a more relevant example	
Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	194	197	3.2	Bracketing may cover deviations in one or more of dissolution, composition and PK. As long as the "extreme" strengths are chosen in a manner that differences in composition and/or dissolution are covered, any strength found “in between” should be valid for application. In the presented scenario the range of acceptable formulations is set by the chosen highest and lowest strength. Sole reference to one of these seems too strict in a bracketing approach.	Please add to the example: "…with the middle strength, unless similarity cannot be shown, but a bracketing approach is also applicable considering dissolution of the highest and lowest strength in this example"

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Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	198	204	3.2	It should be specified what "mean dissolution profile should fall between the dissolution profile of the high and low biobatch strengths" means. Would it be acceptable if certain dissolution points exceed the area between the mean profiles of higher and the lower strength?	
Medicines for Europe	201	202	3.2	"If the biobatch strengths show similar dissolution, then the middle strength should show similar dissolution against either of these biobatch strengths." The word "either" may introduce ambiguity. Line 403 should also state "either one".	If the biobatch strengths show similar dissolution, then the middle strength should show similar dissolution against either one of these biobatch strengths."
Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences	202	204	3.2	It is unclear if in such case, the mean dissolution profile of the middle strength should be similar (e.g. f2 > 50 or lower 90%CI of bootstrapper f2 > 46) to both biobatch strengths or if falling within the profiles is sufficient or if the variability in the dissolution should be similar between intermediate strengths and highest/lowest strengths.	Clarify the requirements on the variability and dissolution similarity accordingly.
Krka	202	204	3.2	Dissolution profiles of biobatches present a "safe space" in terms of ensuring adequate in vivo performance. However, in practice middle strength can fall outside of this space only at the very beginning of the profile where variability is a consequence of disintegration as depicted in Figure a. In addition, similar dissolution profiles of middle strength with either of the biobatches as presented in Figure b should suffice for granting a biowaiver.	Alternatively, if the biobatch strengths exhibit different dissolution profiles between themselves, the middle strength mean dissolution profile should fall between the dissolution profiles of the high and low biobatch strengths or be comparable to either one of them.
Medicines for Europe	202	204	3.2	"Alternatively, if the biobatch strengths have different dissolution between themselves, the middle strength mean dissolution profile should fall between the dissolution profiles of the high and low biobatch strengths." • In such cases, similarity calculation is not required. It is recommended to explicitly state this in the text for clarity. ts or guiding principles should be established to reduce ambiguity. Additionally, lines 404-405 may require revision to reflect these considerations more precisely.	Alternatively, if the biobatch strengths have different dissolution between themselves, the middle strength mean dissolution profile should fall between the dissolution profiles of the high and low biobatch strengths, eliminating the need for similarity calculation
Medicines for Europe	206	214	section 3.3	what are the consequences for dissolution (biowaiver of strengths) for DPs with instable drug substances?	add conclusion regarding expected proceedings for dissolution calculation / calculation of dissolution including degradation products

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Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS) House of Pharma & Healthcare, Frankfurt am Main/Germany German Pharmaceutical Society (DPhG), Frankfurt am Main/Germany Frankfurt Foundation Quality of Medicines (FFQM), Frankfurt am Main/Germany	215	238	4	The prospective protocol for dissolution comparison should also include particularities of testing and potentially applicable bootstrapping.	Please add: "Complete documentation of in vitro dissolution experiments is required including a study protocol, batch information on test and reference batches, detailed experimental conditions, validation of experimental methods, individual and mean results and respective summary statistics in particular on the particularities of the similarity assessment (f2, bootstrap as applicable).
Medicines for Europe	216	216	4	The M13B draft states: 'Applicants should develop a biowaiver report that includes: …' It seems that a separate document (a stand-alone report) would be expected. However, it is not standard practice to prepare stand-alone reports and it should be up to the applicant to prepare a separate report or not.	It shall be the choice of applicant to develop a separate stand-alone biowaiver report or to summarize data in the dossier. Thus, please, modify the proposed text as following, e.g.: 'Applicants should summarize the biowaiver data as following: …'
Krka	227	228	4	We understand that term "qualification" is used as "less than full validation as per ICH Q2", similarly as in M10 guideline. It might be beneficial to include the term qualification into glossary.	The analytical method employed should be fully described, including validation in case of QC method and qualification (reduced scope validation) in case of non-QC methods ~~of the analytical parameters~~;
Medicines for Europe	227	228	4	We understand that term "qualification" is used as "less than full validation as per ICH Q2", similarly as in M10 guideline. in this case validation or qualification should be documented.	The analytical method employed should be fully described, including validation ~~and~~ or qualification of the analytical parameters;
Medicines for Europe	229	230	4.	At the stage of submitting the registration documentation, stability studies are ongoing, therefore the expiry date of the product cannot be clearly stated, only the assumed/expected shelf life of the product. However, providing the current shelf life involves the need to update the entire document (biowaiver report) in the subsequent stages of the registration process solely due to the update of expiry date.	Deletion of „expiry date" or change to „retest date"
Krka	235	236	4	The use of graphic presentation of mean dissolution profiles of different strengths should be sufficient, as they provide a representative overview of the dissolution behavior of each batch and clear comparison between different strengths. Individual values are provided in tabulated form, together with calculated mean dissolution results, SD (and/or RSD), which are needed for calculation of similarity between strengths.	Dissolution results with tabulated individual and mean values as well as ~~individual and~~ mean dissolution profiles of the additional and biobatch strengths.
Medicines for Europe	235	236	section 4	Dissolution results with tabulated individual and mean values, as well as individual and mean dissolution profiles of the additional and biobatch strengths''- By having tabulated representation of individual and mean values together with SD values, mean dissolution profile graphs should be sufficient and with optimal visibility on graphs.	Dissolution results with tabulated individual and mean values, standard deviation (SD), as well as mean dissolution profiles of the additional and biobatch strengths''
Medicines for Europe	239		5	We suggest defining the term "sink conditions" in the guideline, which are specified only in European Pharmacopoeia. It happens that registration Authorities ignore the reference to sink conditions when developing release conditions for sparingly soluble active substances. They require justification that the amount used is the smallest possible without providing a selection criterion for the smallest amount of detergent used.	Sink conditions are in a volume of dissolution medium that is a least 3 – 10 times the saturation volume. Sink conditions should be ensured for the release of the active substance in the QC medium.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	255	261	section 5	f2 calculation is added here in glossary, which seems to be unusual.	f2 calculation should be included in line 147
Medicines for Europe	264	266	5	*"A drug product where the %w/w of a given drug substance is ≤5% of the core weight in all strengths."* The term core weight may be ambiguous and using the terminology defined in the glossary would enhance clarity.	"A drug product where the %w/w of a given drug substance is ≤5% of the core forumulation weight in all strengths."
Medicines for Europe	277	277	Annex I	*"Deviations from direct proportionality for core composition between strengths can be considered……"* It is recommended to use terminology defined in the glossary	"Deviations from direct proportionality for core formulation between strengths can be considered……"
Medicines for Europe	289	295	Annex I	The specified section states: Deviations from direct proportionality for additional strengths containing highly soluble drug substances are lower risk with respect to potential effects on relative bioavailability. Therefore, with proper justification, deviations in amounts of excipients, based on excipient function, up to Level 2 differences as described in Table 1 can be considered, provided the total core weight of the additional strength does not deviate by more than 20% from the theoretical total core weight of the additional strength version assuming direct proportionality, and similarity in dissolution profiles is demonstrated in QC and multimedia conditions. Rationale: High solubility drugs can belong to BCS class I or III. For BCS III the permeability is their limiting bioavailability factor. BCS Class I drugs do not have neither solubility nor permeability constrains. For this class of drugs, consideration of excipient effects should only focus on excipients that may have an influence on the absorption. As compared to the ICH M9, ICH M13B classifies all high solubility drugs (both BCS class I and III) in one group (irrespective of their permeability), applying only the more rigorous limits for deviations in amounts of excipients (applicable for BCS class III in the ICH M9 guideline)	Deviations from direct proportionality for additional strengths containing highly soluble drug substances are lower risk with respect to potential effects on relative bioavailability. Therefore, for BCS class III drugs, with proper justification, deviations in amounts of excipients, based on excipient function, up to Level 2 differences as described in Table 1 can be considered, provided the total core weight of the additional strength does not deviate by more than 20% from the theoretical total core weight of the additional strength version assuming direct proportionality, and similarity in dissolution profiles is demonstrated in QC and multimedia conditions. For BCS class I drugs consideration of excipient effects should only focus on excipients that may have an influence on the absorption (+/- 10% deviation of the concerned excipient content relative to the biobatch strength)
Medicines for Europe	322	322	Annex 1	"Refer to Annex II to aid in the interpretation of the biowaiver criteria for non-high-risk products." The term non-high-risk products is introduced without explanation. We propose to explain the term "non-high-risk product" or refer to the relevant section in M13A	
Medicines for Europe	338	340	Annex I	"Table 1: Acceptable Level 1 and 2 formulation deviations in core excipient content relative to the biobatch strength to be considered with appropriate scientific justification for biowaiver, expressed as percent (w/w)" The text does not explicitly state this, but Example 2 indicates that the deviation is expressed as percent (w/w) of the core formulation weight, rather than of the individual excipient. This should be corrected or clarified in both the table caption and the table header to ensure accuracy.	"Table 1: Acceptable Level 1 and 2 formulation deviations in core excipient content relative to the biobatch strength to be considered with appropriate scientific justification for biowaiver, expressed as percent (w/w) of the core formulation weight"
Krka	347	405	EXAMPLES	More examples in line with EMA Clinical pharmacology and pharmacokinetics Q&A (biowaivers) would be helpful, especially for fixed dose combinations, including triple. Either in the guideline or in Q&A document.	
Medicines for Europe	347	405	EXAMPLES	The number of examples seems rather scarce compared to e.g. those discusses in Clinical pharmacology and pharmacokinetics: questions and answers (section 6 Biowaivers). More examples would help understand the implication of the ICH M13B on different cases, incl. triple combination FDCs	Section EXAMPLES OF APPLICATION OF BIOWAIVER PRINCIPLES should be supplemented by more cases, including biowaiver for various triple combination FDCs
Medicines for Europe	359	359	Annex 1	Example 2, Table last row: The term "Total absolute value of deviation in total core weight of additional strength (%) **" seems incorrect. 5% would be the absolute value of deviation (%), and 6.67% in the example is a relative value (based on the ratio). We propose correction of the text	"Total ~~absolute~~ relative value of deviation in total core weight of additional strength (%) **"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	397	397	Annex 1	"However, the excipient deviations as discussed above for Drug A need to be considered" Example 4, Reference to the excipient deviations as discussed for Drug A is misleading or in conflict with the requirements in section 2.2.2 for high-potency drug products, lines 67-71. We are proposing the replacement of the sentence.	"However, the excipient deviations as discussed above for Drug A need to be considered since the amount of each excipient in the product core are not constant and/or the amount of diluent/filler does not account for the change in the amount of drug substance, the requirements for biowaivers for high-potency drugs are not fulfilled (see Section 2.2.2)."
Genepharm S.A	412			Although in the guideline it is acknowledged that alternative approaches may be considered, IVIVC or modelling is not fully integrated into the decision tree or guidance flow . We need clarifications to this section	
Medicines for Europe	412	412	Annex 2	Figure 2: Scenario low solubility, up to level 1: "Dissolution similarity and ≥ rapid dissolution in QC only and ≥10% dissolution in 1 multimedia condition". Only is incorrect since rapid dissolution must occur at least in QC, ≥10% dissolution would be acceptable in 1 or in more than 1 multimedia conditions. We propose deletion of "only", and state like in proposed text.	Figure 2: Scenario low solubility, up to level 1: "Dissolution similarity and ≥ rapid dissolution in QC ~~only~~ and ≥10% dissolution in ≥ 1 multimedia condition other than QC".
Medicines for Europe	412	412	Annex 2	Figure 2, scenario low solubility, up to level 2: "Dissolution similarity and ≥ rapid dissolutoin in QC + 1 multimedia condition" We propose different text in the box.	"Dissolution similarity and ≥ rapid dissolutoin in QC + **≥** 1 multimedia condition"