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M13 Expert Working Group

ICH M13B Guideline:

BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS:
ADDITIONAL STRENGTHS BIOWAIVER

Questions and Answers

ICH M13B Q&As

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In order to facilitate the implementation of the ICH M13B Guideline, the ICH M13 Experts have developed a series of Q&As:

ICH M13B Q&As

Document History

Code	History	Date
ICH M13B Q&As	Adoption by the ICH Assembly under *Step 4.*	04 August 2026

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PREFACE

In response to questions posted to ICH M13B comment period, several Questions and Answers have been developed to provide clarity around some of the concepts related to additional strengths biowaiver for immediate-release solid oral dosage forms covered in ICH M13B.

This Question and Answer (Q&A) document is intended to provide additional clarification and improve harmonisation of additional strengths biowaiver for immediate-release solid oral dosage forms.

The scope and organisation of this Q&A document follow that of ICH M13B.

M13B Questions and Answers

1. INTRODUCTION

#	Date of Approval	Questions	Answers
1.1	04 August 2026	How is ICH M13B different from ICH M9 in principle?	ICH M13B and ICH M9 deal with different issues although using some common principles. ICH M9 relies on comparisons between the test product and a comparator product, while ICH M13B is focused on comparison of strengths within a product line. The biowaiver for additional strengths relies on *in vivo* data (bioequivalence (BE) study(ies)), formulation, and *in vitro* data (dissolution), instead of only formulation and *in vitro* data as recommended for a Biopharmaceutics Classification System (BCS)-based biowaiver as described in ICH M9. For this reason, a BCS Class II or BCS Class IV drug can be considered for an additional strengths biowaiver under ICH M13B, because ICH M13B is not limited by BCS class. For BCS-based waivers, each strength of the product line should be independently demonstrated to meet the BCS biowaiver criteria according to ICH M9. If a strength has been accepted based on a BCS-based biowaiver according to ICH M9, a waiver of an additional strength based on its relationship to this strength is not acceptable, as this would be considered a waiver on a waiver based on *in vitro* data, which introduces a higher uncertainty regarding BE. This is in contrast to an ICH M13B-based waiver of an additional strength for which BE was shown *in vivo* according to ICH M13A, for at least one strength of the product line. The determination of the solubility of the drug substance is aligned between ICH M9 and ICH M13B. However, ICH M13B allows for further justification of high solubility in cases where instability of the drug substance is observed (see Q&A 3.1).

2. BIOWAIVER CRITERIA FOR ADDITIONAL STRENGTHS

#	Date of Approval	Questions	Answers
2.1	04 August 2026	What scientific justification is appropriate to explain deviations from compositional proportionality?	ICH M13B generally acknowledges that direct compositional proportionality provides the confidence to ensure BE between strengths. The deviations allowed in Annex I are intended to only cover scenarios where small quantitative deviations in excipients are necessary for a robust manufacturing process. For instance, for extremes of tablet sizes when there is a wide range of strengths, small excipient adjustments may be needed to, for example, facilitate compression or mitigate sticking. As outlined in Annex I, the rationale for these deviations arises from the pharmaceutical development programme and thus should be explained and justified as part of the relevant submission sections. In any scenario, these deviations should be limited to the ranges outlined in Annex I. Deviations beyond those outlined in Annex I would require additional information to support BE for additional strengths. Other deviations such as a change in drug load of for instance 6% instead of 5% or less (Section 2.2.1) while still fulfilling the deviations from compositional proportionality, or incorporation of excipient proportionality changes only to facilitate dissolution similarity between strengths, are not considered appropriate.
2.2	04 August 2026	ICH M13B states "The same batch(es) used in the BE study(ies), or in the pivotal clinical trials for a new drug development, should be used for comparative dissolution testing". In a case where the biobatch is not available, are other batches acceptable and under which conditions?	The same batch(es) used in the BE study(ies) should be used for comparative dissolution testing, with forethought into retaining sufficient quantities of the biobatch(es) for all anticipated dissolution testing. At the initial submission stage, in exceptional cases where the biobatch(es) is unavailable, batches representative of the formulation and manufacturing process/scale of the biobatch(es) may be considered with appropriate scientific justification. It is recognised that there may be practical limitations of applying for a biowaiver after initial approval of the drug product, *e.g.,* depletion, expiry, or age of biobatch(es). In such cases, it would be acceptable to use representative commercial batch(es) or batch(es) manufactured using the commercial process that meet the final drug product specifications for comparative dissolution testing, ensuring the dissolution data are representative of the product that demonstrated BE.

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2.3	04 August 2026	Do you need to consider the characteristics of the comparator product when assessing an additional strengths biowaiver for a drug product?	Generally, the characteristics of the comparator product are not relevant to an additional strengths biowaiver for a drug product since the relationship with the comparator product is established through a BE study. The merits of any additional strengths of the drug product are based on their relationship to the biobatch strength as described in ICH M13B. The exception to this would be if there are bioavailability differences between the respective strengths of the comparator product beyond dose proportional differences related to strength, *e.g.*, if it is reported in publicly available information, such as comparator product labeling or public assessment reports, that a strength of the comparator product has improved bioavailability compared with a different strength in the product line. In such a case, it may be necessary to consider each of the strengths of a drug product developed to be interchangeable with these comparator product strengths independently, *i.e.,* each respective strength of the drug product may need to be compared to the respective strength of the comparator product in a BE study(ies). This can only be assessed on a case-by-case basis in the rare instances when this type of information is available for a comparator product line of strengths.
2.4	04 August 2026	If differences in dissolution profiles between strengths are due to solubility limitations, ICH M13B recommends testing the same dose per vessel to demonstrate similarity in profiles under those conditions. A. What options are available in cases where equivalent doses cannot be achieved by comparing multiple units of a lower strength to a single unit of the higher strength being compared?	A. In cases where equivalent doses cannot be achieved by comparing multiple units of a lower strength to a single unit of a higher strength, it may be possible to achieve equivalent doses through combinations of multiple units in each vessel, *e.g.*, three tablets of 10 mg *vs.* two tablets of 15 mg. In rare cases, an alternative approach may be to adjust the volume of medium employed in the dissolution vessels for each respective strength to achieve equivalent solubility conditions for each strength. In both cases, *i.e.,* adjusting the number of tablets or adjusting the volume of dissolution medium for each strength, the possible impacts on the hydrodynamics within the dissolution vessels should be considered on a case-by-case basis. A dissolution volume in the range of 450 – 900 mL depending on the strength may be acceptable.

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		B. ICH M13B indicates that the use of multiple units in a dissolution vessel may not be feasible due to an excessive number of individual units in the vessel. How many units are considered to be excessive?	B. The determination of the number of units of a drug product in a dissolution vessel that would be considered excessive should be made on a case-by-case basis. Setting an absolute limit to the number of individual units is not possible. Factors to be considered include the volume of dissolution medium employed and the size of the units. When using multiple units to achieve equivalent doses, two to three units is generally considered to be acceptable. Beyond that number of units, a justification addressing the possible impact on vessel hydrodynamics should be provided.
2.5	04 August 2026	If differences in dissolution profiles between strengths are due to solubility limitations, ICH M13B recommends testing the same dose per vessel to demonstrate similarity in profiles under those conditions, or if that is not feasible, to demonstrate the same dissolution trend in the comparator product at the same strengths. What is needed to demonstrate similarity in dissolution in these situations?	In the case of comparing dissolution performance at the same dose per vessel for each strength, similarity should be established between the same dose profiles using an f_2 similarity calculation as described in Section 2.3.2. In the case of demonstrating the same dissolution behaviour in the comparator product at the same strengths, a case-by-case assessment will be needed. Ideally, each strength of the test product will show similar dissolution to the same strength of the comparator product based on an f_2 calculation as described in Section 2.3.2. This is the most straightforward case but, should not be considered a requirement. Alternatively, the magnitude of differences in dissolution between the comparator product strengths should be sufficiently consistent with that observed between the strengths of the test product to demonstrate the same trend for both products. There is no set metric to evaluate these trends beyond visual inspection at the time of assessment.
2.6	04 August 2026	Can centrifugation be employed instead of filtration?	ICH M13B recommends that samples should be filtered during collection to stop the dissolution of analyte particles in the samples at the time of collection. If samples are filtered post-collection, dissolution can continue in the samples thus biasing the biowaiver results. In the same way, dissolution can continue in samples during the time between sample collection and the completion of the centrifugation process. Therefore, centrifugation would only be considered for dissolution studies conducted for a biowaiver if significant problems are

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			observed during filter suitability evaluation in method validation, *e.g.*, significant and unavoidable analyte adsorption to the filter is observed.
2.7	04 August 2026	When would it be appropriate to employ more than 12 replicates in a dissolution test?	In general, more than 12 replicates of each strength may be used across any scenario. More than 12 replicates is particularly beneficial when the variability in dissolution is expected to be elevated and greater power is desired for similarity assessment.
2.8	04 August 2026	ICH M13B indicates that other dissolution conditions, *e.g.*, compendial apparatuses and agitation speeds, may be considered to overcome specific issues, *e.g.*, coning, if scientifically justified. Can you provide some examples of when other dissolution conditions might be accepted?	Dissolution studies should be conducted under the conditions described in ICH M13B. These studies may reveal methodological issues that need to be addressed to collect meaningful dissolution profiles. Evidence of the issue observed under the original conditions should be provided to establish the need for methodological modifications. For example: 1. If coning is observed in one of the dissolution media while employing the paddle apparatus at 50 rpm, a methodological change should be made to address this, such as the use of the basket apparatus at 100 rpm. Alternatively, the use of an apex vessel could be considered for use with that medium if apex vessels are compliant with the pharmacopoeia applicable to the region(s) where the data will be submitted. An increase in rotation speed could also be considered as a possible last-resort solution. However, because a loss of discriminatory power is anticipated in this scenario, its use should be thoroughly justified. An increase in rotation speed solely to reduce variability or to achieve complete dissolution is not acceptable. The original dissolution conditions should be maintained for the media where there is no coning observed. 2. If the units of the test product are observed to be floating in a dissolution medium, a sinker could be considered for use with that medium.
2.9	04 August 2026	ICH M13B indicates that comparative dissolution studies should be conducted in three compendial media covering the	Minor deviations within ±0.05 pH units are generally considered acceptable at the time of preparation, reflecting normal variability in buffer preparation and pH measurement. The pH should be controlled, documented, and consistent across strengths being compared.

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		range of pH 1.2 – 6.8 (at or about pH 1.2, 4.5, and 6.8). How far and under what circumstances can the pHs of the dissolution media deviate from pH 1.2, 4.5, and 6.8?	Other circumstances when dissolution media pH may vary are, if the drug substance has specific pKa characteristics, a rapidly changing solubility gradient around the specified pH, or stability characteristics that necessitate testing at different pH values to adequately characterise dissolution behaviour across the physiological pH range; or when using official compendial buffers that may have slightly different pH values than those specified, provided they cover the intended pH range. Any deviation from the specified pH values should be scientifically justified based on the drug substance or drug product characteristics and should be clearly documented in the dissolution study report. For significant deviations or alternative pH selections, a rationale demonstrating that the chosen conditions adequately assess the dissolution profile across the physiological pH range should be provided.
2.10	04 August 2026	ICH M13B states that sampling time points should be selected to have meaningful contributions to the calculated estimate of the difference between the additional strength and the biobatch strength. How should this be interpreted in selecting sampling time points for a dissolution experiment?	The selection of sampling time points is dependent on the performance characteristics of the products under investigation. The sampling protocol should be designed to capture the profiles up to completion of dissolution, *i.e.*, the time taken to reach 85% dissolution (or a plateau), with approximately six time points when feasible. The following scenarios are provided for consideration during the design of a dissolution study, but as noted above, the final design is dependent on the dissolution characteristics of the drug product being investigated and different sampling times could be used, provided the conditions for evaluable time points are met. Inclusion of the 15-minute sampling time point in the protocol is of strategic importance for profile similarity determinations (except in cases of slow dissolution as in scenario 3 below). 1. The dissolution is completed within 30 minutes (rapidly dissolving). • The suggested sampling times are 5, 10, 15, 20, 30 and 45 minutes. 2. The dissolution is not rapidly dissolving (> 30 minutes) but completed within 45 minutes.

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			• The suggested sampling times are 10, 15, 20, 30, 45 and 60 minutes. 3. The dissolution is slow, being completed only after 45 minutes. • The suggested sampling times are 15, 30, 45, 60, 90, and 120 minutes.
2.11	04 August 2026	Why does ICH M13B recommend including not more than six sampling time points in the f_2 calculation for similarity?	The f_2 similarity factor assesses if the average difference between the test and reference mean profiles is within 10%, which corresponds to an f_2 value of at least 50, to support a conclusion of similarity for two dissolution profiles. The similarity limit, *i.e.*, $f_2 \geq 50$, for f_2 is defined independent of the number of sampling time points to be used in the assessment of dissolution similarity. However, using an excessive number of time points, *e.g.*, more than 6 or more than 1 after the profile reaches the >85% plateau, for f_2 calculations could bias the similarity assessment. Despite some individual timepoints on the profiles showing large differences, *e.g.*, 20%, the data can still meet the similarity limit of $f_2 \geq 50$ if many points are included. Further, it is unlikely that more than 6 time points are needed to describe a profile for immediate-release drug products and additional time points would not provide additional information but may overly emphasise certain parts of the dissolution curve, *e.g.,* those with small differences, thereby smoothing the overall difference. The recommendation of no more than 6 time points is a practical recommendation and does not prohibit the use of more time points for f_2 calculation, provided that adequate justification is provided.
2.12	04 August 2026	When determining dissolution profile similarity using f_2, ICH M13B defines high variability as an SD >8% at any time point. How was this decided, and why was SD used in the definition instead of CV?	If $f_2 > 50$ is observed when the variability in the dissolution profiles is small, this does not guarantee that f_2 is truly greater than 50, however, it is unlikely to be greatly different from the observed value. When the variability is high, there is large uncertainty around the observed value of f_2. As such, if $f_2 > 50$ is observed, there is a reasonable chance that the true value of f_2 is substantially smaller, *i.e.*, the true difference between the profiles is much larger than was observed. Therefore, a variability cut-off is necessary to indicate when it is reasonable to decide on dissolution similarity using the observed f_2 without using bootstrap to calculate a confidence interval (CI).

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			The basis of the selection of the variability criterion was that it should be stringent enough to protect against a high probability of accepting profiles where there could potentially be very large differences, but at the same time was not so stringent that bootstrap is used frequently in situations where there is little risk. To inform the choice, the probability of concluding similarity, *i.e.,* observed $f_2 > 50$ and variability criterion satisfied, was estimated using simulations for different variability conditions, different true differences between profiles, and different variability cut-offs. Historical data from approved applications were also analysed to support the cutoff. The f_2 statistic is based on additive differences between profiles, and as such, the SD is the natural measure of variability and is independent of the mean of measured dissolution, as opposed to the CV. The CV depends on the mean and has large values when the mean is low, even if the variation around the mean is small, hence, two cut-off values had to be defined reflecting the different mean values at early vs. late time points. In the simulations, criteria based on CV had unattractive properties, with bootstrap f_2 needing to be used in many low variability situations where the difference was small. Use of CV also led to an unsatisfactory lack of symmetry, *i.e.*, the probability of acceptance depended not only on the magnitude of the difference between profiles but also on whether it was test or reference that had the higher values, and situations where the chance of acceptance increased with increasing true difference. It was clear that the cut-off should be based on SD. The cut-off value for SD of ≤8% was chosen based on application of different choices of SD cut-off in simulation studies and on > 100 real dissolution data sets which resulted in a similar frequency of switching from f_2 to an alternative method as for the previously defined CV values.
2.13	04 August 2026	How should dissolution similarity be evaluated if SD >8%, *e.g.*, the type of point estimator and CI, number of bootstrapped data sets,	The use of a two-sided 90% CI for f_2 is the recommended methodology for dissolution comparison in those cases where the variability in the data sets for any drug product results in SD >8% at any time points that are included in the f_2 calculation, since in these cases the f_2 statistic could differ greatly from the population (true) f_2.

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		and criteria applied to each individual bootstrapped data set?	The bootstrap analysis should be performed using at least 5,000 data sets, and the number of samples should be reported. The calculation of the 90% CI should be conducted using a percentile method. In each bootstrap dissolution data set, all sampling times pre-defined in the dissolution study protocol until the sampling time where one of the products dissolves at least 85%, or a plateau is reached, should be considered for the calculation of f_2. The estimation of the f_2 value on each bootstrapped dissolution data set should be performed using the f_2 formula described in ICH M13B. Any commercial or in-house developed programmes could be used for the calculation of the 90% CI of f_2. In all cases, the software should be adequately documented. The selected options should be described in detail, such as the method of the bootstrap, *e.g.*, not including the zero time point value, using whole vector as bootstrap unit, the algorithm to determine that in each bootstrap data set there is only one time point is used where the dissolution is at least 85% or at plateau, the inclusion of at least 3 data points, the number of bootstrap data sets, and seed number (if available). The report should be sufficiently detailed to enable the analysis to be repeated.
2.14	04 August 2026	Why does ICH M13B specify 46 as the cut-off for acceptability for the lower bound of the bootstrapped CI for f_2 when determining dissolution profile similarity using f_2? Why was 50 not used?	If high variability is seen in a dissolution profile ICH M13B recommends that a bootstrapped CI for f_2 should be calculated. In these cases, dissolution profile similarity is in part determined by considering the lower bound of the 90% CI, which should be above a cut-off. If a lower bound cut-off of 50 were used, in high variability situations this would be requiring that it is shown to be almost certain that the true f_2 is 50 or greater. However, in low variability situations there is no such requirement and a value of f_2 very close to 50 results in a positive outcome, although if the CI were to be calculated it would certainly be below 50. Therefore, to avoid an unfair double penalty in high variability situations, *i.e.*, observing high variability not only means having to perform bootstrapping but also having to meet a much stricter criterion, it was necessary to use a CI threshold lower than 50 when using bootstrap f_2.

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			To inform the choice, the probability of concluding similarity based on the f_2 statistic without CIs, *i.e.*, the observed $f_2 > 50$ and the variability criterion satisfied was estimated. This was accomplished by using simulations for different low variability conditions, *i.e.,* SD=3-6, where decisions will often be made based on non-bootstrapped f_2, and different true differences between profiles. If the true difference between profiles was 10% at each time-point, *i.e.,* f_2=50, the probability of concluding similarity in the simulations tended to be around 50%, as would be expected with a point estimate-based criterion. With bootstrap f_2 requiring the lower bound of the CI to be >50 the success rate in the same scenarios if using bootstrap f_2 would be 5%, showing the harshness and inconsistency of using a limit of 50 for bootstrap f_2, given that the use of f_2 in low variability situations is accepted. If the true difference was 12% at every time-point, *i.e.,* f_2=45.97, the simulated success rates for f_2 were lower, but still generally ≥5%. Therefore, 46 was selected as a reasonably conservative threshold to at least partly match the flexibility of non-bootstrapped f_2 in a low variability situation. Statistically, it might be considered that although the f_2 criteria was originally justified as having an objective to show that $f_2 > 50$, because of the way it has been used based on point estimates in association with variability criteria, it was never truly assessing a null hypothesis that f_2=50, as profiles differing by lower true values of f_2 are considered similar at much higher rates than 5%. The use of a lower threshold than 50 for the CI lower bound when using bootstrap f_2 is a recognition of this point, and it would not be considered a type I error (T1E) if profiles with a true f_2=46 are declared to be similar.
2.15	04 August 2026	Why does ICH M13B not consider other statistical methods to demonstrate dissolution similarity?	Advantages and disadvantages of non-standardised, *e.g.*, Euclidean Distance between the Non-standardised Expected values (EDNE), standardised, *e.g.,* Mahalanobis distance-based, and model-based, *e.g.*, Weibull, methods were evaluated, and it was concluded that f_2 and, in the case of high variability, bootstrap f_2, were suitable since they display sufficient T1E control (bootstrap f_2) and are broadly applied by industry and regulators.

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			Although it is acknowledged that bootstrap f_2 does not use distributional assumptions, unlike EDNE, and hence may bear the risk of lower power, the possibility of an increase in sample size, if necessary, is considered an adequate measure to overcome the lower power without significant added burden. Other methods could be considered suitable, but it was considered that they did not present important advantages over the selected method (bootstrap f_2), and in some cases, the other methods could present a risk of misspecification or if distributional assumptions are not correct then methods using distributional assumptions are inaccurate. Furthermore, recommending one method facilitates a harmonised approach in the different regions. If applicants want to apply a method other than the recommended f_2 or bootstrap f_2 method this needs to be justified and prospectively discussed with the relevant regulatory agency. The results using the recommended f_2 or bootstrap f_2 method should also be submitted.

3. SPECIFIC TOPICS

#	Date of Approval	Questions	Answers
3.1	04 August 2026	For the purpose of BCS solubility classification, ICH M9 expects that stability be maintained over relevant timeframes to accommodate the expected duration of absorption, and instability resulting in >10% degradation precludes classification within the BCS. On the other hand, ICH M13B will accept provisional BCS solubility	The criteria for the determination of the high solubility of the drug substance are aligned between ICH M9 and ICH M13B. However, ICH M13B allows for further justification of high solubility in cases where instability of the drug substance is observed during the solubility experiment, due to the fact that *in vivo* BE has been shown, indicating that the instability of the drug substance does not affect the *in vivo* performance and hence does not impact the additional strengths biowaiver assessment.

		classification for the purpose of application of an additional strengths biowaiver if high solubility is established for the same duration as for the dissolution experiments supporting the biowaiver. Why does this difference exist?	

4. ANNEX

#	Date of Approval	Questions	Answers
A.1	04 August 2026	Q&A 2.1 is also applicable to Annex I.	See Q&A 2.1.

5. APPENDIX: Q&As LINKED TO THE RESPECTIVE SECTIONS OF ICH M13B

Sections of ICH M13B Guideline	1: INTRODUCTION	2.2.1: Product Composition	2.3.1: Dissolution Conditions	2.3.2: Assessment of Similarity	3.3: Drug Substance Instability	ANNEX I: CONSIDERATIONS FOR DEVIATION FROM DIRECT COMPOSITIONAL PROPORTIONALITY	Other ICH Guidelines
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Sections of ICH M13B Guideline	1: INTRODUCTION	2.2.1: Product Composition	2.3.1: Dissolution Conditions	2.3.2: Assessment of Similarity	3.3: Drug Substance Instability	ANNEX I: CONSIDERATIONS FOR DEVIATION FROM DIRECT COMPOSITIONAL PROPORTIONALITY	Other ICH Guidelines
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