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

Step 5

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M13B document history

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1. Introduction

1.1. Objective

This guideline is intended to provide recommendations on obtaining waivers of bioequivalence (BE) studies (biowaivers) for one or more additional strengths of a drug product in an application where *in vivo* pharmacokinetic (PK) BE or efficacy/safety has been demonstrated for at least one of the strengths, thereby reducing the need for additional *in vivo* PK BE studies. This guideline is applicable during both development and post-approval phases of orally administered immediate-release (IR) solid dosage forms designed to deliver drugs to the systemic circulation, such as tablets, capsules, and granules/powders for oral suspension. Deviations from the recommendations in this guideline may be acceptable if appropriate scientific justification is provided.

1.2. Background

BE for IR solid oral dosage forms with systemic action is largely established via *in vivo* PK BE studies or comparative *in vitro* dissolution studies. For drug products with multiple strengths, if BE has been demonstrated for at least one of the strengths via *in vivo* BE study(ies), waivers of *in vivo* BE study(ies) may be possible for one or more of the additional strengths based on formulation proportionality to the strength for which BE has been demonstrated, *i.e.*, the biobatch strength. The principles in this guideline can also be applied for drug development relating to the introduction of a new strength(s) relative to the strength used in a pivotal clinical trial, which can be considered as the biobatch strength.

1.3. Scope

The scientific and technical aspects of study design and data analysis to support BE assessment based on PK endpoints for orally administered IR solid dosage forms have been described in ICH M13A, *Guideline on Bioequivalence for Immediate-release Solid Oral Dosage Forms*.

ICH M13B, the second guideline in the series, describes the scientific and technical aspects of demonstrating BE for additional strengths of a drug product, *i.e.*, obtaining a biowaiver for one or more strengths in an application with multiple strengths when BE has been demonstrated for at least one of the strengths following ICH M13A.

ICH M13B describes the additional strength(s) biowaiver criteria as they relate to a) the PK dose proportionality of the drug (or drugs in the case of fixed dose combination (FDC) drug products), b) the formulation proportionality of the drug substance(s) and excipients in the additional strength(s) compared to the biobatch strength(s), c) the similarity of the method of manufacture, and d) the similarity in dissolution profiles between the additional strength(s) and the biobatch strength(s) as demonstrated in the dissolution conditions described in this guideline.

Alternative approaches to demonstrating BE of additional strength(s) such as *in vitro-in vivo* correlations (IVIVCs) or other modelling approaches are not discussed in detail in ICH M13B. Applicants are encouraged to consult the regulatory authority(ies) when an alternative approach is proposed or taken.

The third guideline in the series, ICH M13C, will include: 1) data analysis and BE evaluation for highly variable drugs and drugs with narrow therapeutic index, and 2) complex BE study designs and data analysis considerations, *e.g.*, adaptive BE study design.

2. Biowaiver criteria for additional strengths

To be eligible for an additional strengths biowaiver, the following criteria and requirements should be appropriately addressed.

2.1. Selection of biobatch strength(s)

As detailed in ICH M13A, the selection of biobatch strength(s) is based on the PK proportionality of the drug (or drugs in the case of an FDC) (see ICH M13A, Section 2.1.6).

2.2. Qualitative and quantitative composition between strengths and manufacturing aspects

When multiple strengths of a drug product are proposed, a biowaiver for additional strengths may be possible based on the qualitative and quantitative relationship between the formulation(s) of the additional strength(s) and the formulation(s) of the biobatch strength(s).

2.2.1. Product composition

The size of the additional strength(s) batch(es) should meet the same criterion as the biobatch strength(s), as indicated in ICH M13A, Section 2.1.4.

For a biowaiver for additional strength(s), the core formulation(s), *i.e.*, the active and inactive ingredients that make up a drug product, not including tablet film coating or capsule shell, of the additional strength(s) should be qualitatively the same as that of the biobatch strength(s). Further, the core formulation(s) for the additional strength(s) should be quantitatively proportional to that of the biobatch strength(s), *i.e.*, each strength contains the same ingredients in the same proportion. Deviations from direct proportionality of the core formulations between the additional strength(s) and the biobatch strengths(s) can be considered as exceptions with appropriate scientific justification (see Annex I).

For the purpose of this guideline, the composition of the core formulation(s) of the additional strength(s) and biobatch strength(s) can be considered proportional when the amount of drug substance in the formulation, as calculated based on the drug substance form, *e.g.*, the salt, present in the formulation, is not more than 5% of the drug product core weight in all strengths and the total core weight remains similar for all strengths (the 5% criterion). Specifically, in this case, a biowaiver for additional strength(s) may be possible if one of the following conditions is met:

- The amount of each excipient in the product core is constant between the additional and biobatch strength(s) and only the amount of drug substance is different.
- The amount of diluent/filler varies to account for the difference in the amount of drug substance between the additional and biobatch strength(s), while the amount of other excipients remains constant.

Excipients included in the core formulation solely to impart colour or flavour, and which are not expected to affect bioavailability (BA), can generally vary between strengths.

Qualitative differences in non-functional tablet coating/capsule shell composition (other than colourants or flavours) between the additional strength(s) and the biobatch strength(s) are discouraged and, if used, should be justified with data to support that the change in tablet coating/capsule shell composition will not impact BA. Coating (including colourants and flavours) and capsule shell components do not need to meet the quantitative proportionality conditions.

2.2.2. Manufacturing process

The manufacturing process for the additional strength(s) should be representative of that used for the biobatch strength(s). Specifically, equipment should be of the same type and operating principle, and differences in process parameters should be limited to those that may be necessary due to a change in equipment and/or manufacturing scale.

2.3. Comparative dissolution

2.3.1. Dissolution conditions

Similarity of *in vitro* dissolution should be demonstrated under all conditions between one representative batch of the additional strength and the biobatch strength. The same batch(es) used in the BE study(ies), or in the pivotal clinical trials during development of a new drug, should be used for comparative dissolution testing. In cases where this is not feasible, batches representative of the formulation and manufacturing process of the biobatch(es) can be considered with appropriate scientific justification.

The following conditions should be employed in the comparative dissolution studies to characterise the *in vitro* dissolution profiles of all strengths of the drug product:

- Standardised multimedia, *i.e.*, three compendial media covering the range of pH 1.2 - 6.8 (at or about pH 1.2, 4.5, and 6.8) under the following conditions:
    - Apparatus: Compendial paddle or basket apparatuses
    - Volume of dissolution medium: 900 ml or less
    - Temperature of the dissolution medium: 37±1°C
    - Agitation: paddle apparatus - 50 rpm
basket apparatus - 100 rpm
- Using the quality control (QC) method (unless the method is identical to that described above in one of the three compendial media).

At least 12 replicates of the additional strength and biobatch strength should be used for each dissolution profile determination. For IR oral dosage forms other than tablets or capsules, aliquots of at least 12 finished product preparations should be evaluated. The same number of replicates should be used for both strengths being compared.

For suspensions, a rotation speed of 50 rpm is recommended with the paddle apparatus, although a different rotation speed may be used, if justified.

Surfactant may be used only in the QC method and only when appropriately established as part of dissolution method development. For gelatin capsules or tablets with gelatin coatings where cross-linking has been demonstrated, the use of enzymes may be acceptable if appropriately justified.

Samples should be filtered during collection, unless *in situ* detection methods are used.

Dissolution studies as described above should be conducted and presented even if condition-related issues are expected or observed, *e.g.*, coning. In these cases, other dissolution conditions, *e.g.*, compendial apparatuses and agitation speeds, may be considered to overcome specific issues, if scientifically justified.

Should the initial dissolution studies demonstrate that a complete profile cannot be generated in a medium, *e.g.*, due to degradation or insolubility of the drug substance, a case-by-case assessment of the data in that medium is needed. It needs to be determined if the results from that medium can be excluded from the similarity assessment, *e.g.*, if a profile cannot be generated. Partial profiles may be assessed if they are demonstrated to be meaningful, *e.g.*, if degradation is evident in the profiles only after at least three meaningful time points have been collected.

Dissolution conditions should consider the solubility of the drug substance. At pH values where solubility is limited, complete dissolution may not be achievable for all strengths, and dissolution profiles may therefore differ between strengths. Such solubility-related differences in dissolution can be demonstrated by similar dissolution profiles when testing the same dose per vessel, *e.g.*, three tablets of 5 mg *vs.* one tablet of 15 mg. If this is not feasible, *e.g.*, due to an excessive number of individual units in the vessel, the same dissolution behaviour/trend in the comparator product at the same strengths, *e.g.*, the 5 mg strength of the comparator product *vs.* the 15 mg strength of the comparator product compared to the 5 mg strength of the test product *vs.* the 15 mg strength of the test product, is considered suitable for confirmation that intrinsic properties of the drug substance, such as pH-dependent solubility, rather than formulation factors are the cause of the observed initial differences in dissolution profiles of the different strengths.

The comparative *in vitro* dissolution experiments should use validated analytical methods that are suitable for specific use and conditions for the determination of the drug substance. Beyond full validation in the QC medium, if the analytical method does not employ chromatographic separation of the analyte from the media components, specificity, linearity, and accuracy should be verified in all non-QC media. In media where lack of solubility, as established based on solubility data, will prevent measurable dissolution in a 900 ml volume, verification of the analytical method in that medium is not necessary.

Dissolution profile similarity testing and any conclusions drawn from the results (see Section 2.3.2), can be considered valid only if the dissolution profiles have been properly characterised. Dissolution tests and sampling need not exceed two hours in duration. The additional strength and biobatch strength dissolution profiles should be composed of identical time points. Sampling time points should be chosen to adequately describe the complete dissolution profile and have meaningful contribution to the calculated estimate of the difference between the additional strength and the biobatch strength, such that the range of measured differences between the profiles is not over-representing areas where the difference between the additional strength and the biobatch strength dissolution profiles is small and/or not changing. More frequent sampling during the period of greatest change in the dissolution profile should be employed. The number of sampling time points will depend on the time it takes to reach a plateau to estimate dissolution profile similarity. At least three time points are necessary (zero excluded), although more than three time points are preferred, to describe a dissolution profile, with the final time point occurring when dissolution reaches ≥85% for either the additional strength or biobatch strength, or just after both strengths have reached a plateau (of <85%). A plateau is defined by three successive time points differing by 5% or less in mean absolute values of dissolution across the three points.

Normally, only the first time point of a plateau should be included in the similarity calculation. However, in cases where dissolution is slow, care should be taken not to conclude prematurely that the dissolution profile has reached a plateau. In these cases, dissolution profiles up to two hours should be collected to assess whether dissolution has truly plateaued or if plateaus, as defined above, are artefacts related to the slow dissolution behaviour. If a calculated plateau is found to be an artefact, data points through the artefact and up to a true plateau or completion of dissolution should be considered in similarity assessment. If, due to limited solubility, a plateau is reached very rapidly, the

time points from the plateau needed to assess similarity should be employed, *e.g.*, if plateau is reached at the second through fourth sampling time, the first three sampling points should be included in the similarity assessment.

In principle, not more than six time points should be included in the calculation of similarity.

2.3.2. Assessment of similarity

The process for determining dissolution profile similarity for orally administered IR solid dosage forms is described in the decision tree in Figure 1.

As described in Figure 1, regardless of dissolution variability, 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.

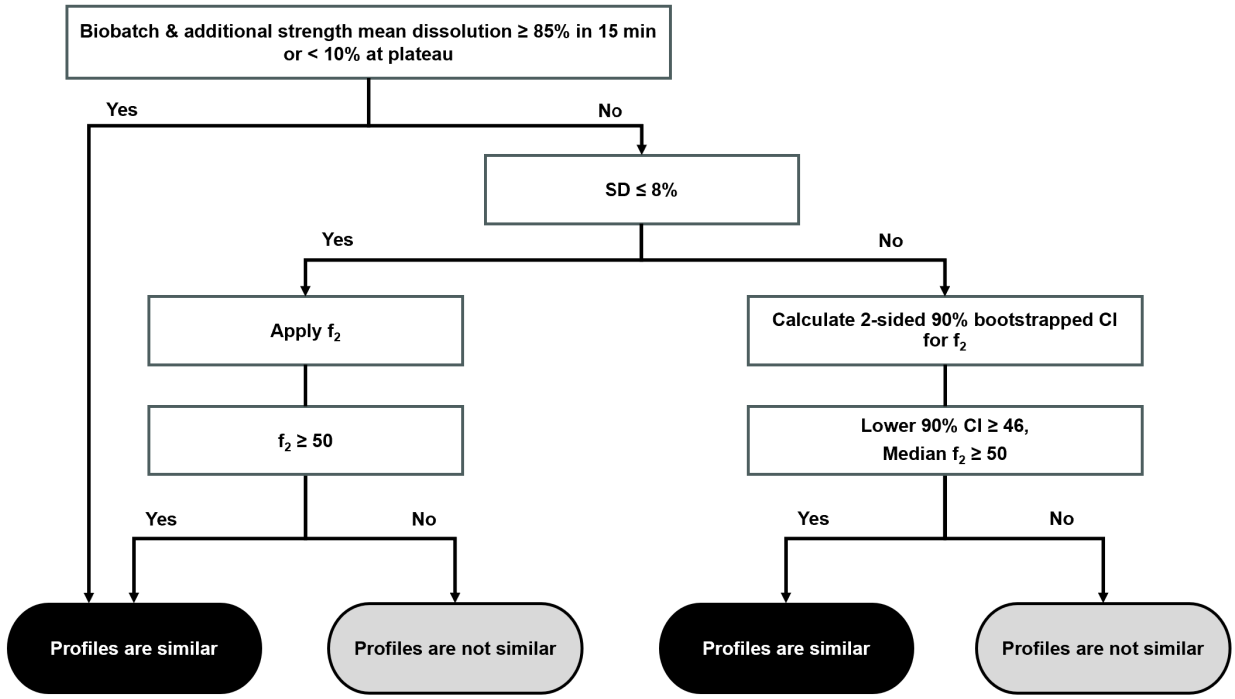
When less than very rapid dissolution is observed for either the additional strength or biobatch strength and the standard deviation (SD) is ≤8% across all time points for both strengths, dissolution similarity can be determined using f_2, the estimate of the similarity factor. An f_2 value of ≥50 suggests that the two mean dissolution profiles are similar.

In cases where one strength has mean dissolution ≥85% within 30 minutes (rapid dissolution) and the other strength has very rapid dissolution, similarity of the profiles should be demonstrated using f_2.

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. To demonstrate dissolution similarity, the lower bound of the two-sided 90% bootstrapped CI for the similarity factor should be ≥46 and the median f_2 from the bootstrapped samples should be ≥50.

The methods and criteria described above can also be applied when dissolution is incomplete, *i.e.*, not achieving 85% within two hours. However, when mean dissolution of both the additional strength and biobatch strength plateau below 10%, no similarity test needs to be applied and similarity can be assumed.

Figure 1: Decision tree for determining mean dissolution profile similarity



3. Specific topics

3.1. Fixed dose combination drug products

For orally administered IR fixed dose combination drug products (FDCs) that consist of multiple strengths, BE for each individual drug substance should be demonstrated for the strength(s) as identified in ICH M13A Section 2.1.6. A biowaiver may be possible for the additional strength(s).

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 if it were an excipient(s), *i.e.*, as if it were a separate diluent(s)/filler(s) (see Annex II, Example 5 for an illustration of this principle). The proportionality conditions should still be fulfilled (see Section 2.2.1 and Annex I).

When an FDC is formulated with the individual drug substances separated, *e.g.*, in separate layers of a tablet or separate particles of a multiparticulate dosage form, 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), and should be considered independently for each component, *e.g.*, each layer or particle.

When the strengths (or components, if applicable) in an FDC are not proportionally formulated (see Section 2.2.1 and Annex I), it may be possible to apply a bracketing approach to demonstrate BE for all strengths (see Section 3.2).

Dissolution data should be submitted for each individual drug substance in the FDC (see Section 2.3). When it is sufficient to show BE with one FDC strength, this strength is the biobatch strength for dissolution comparison, and dissolution similarity between the additional strength(s) and the biobatch

strength should be demonstrated. The dissolution examples in Section 3.2 for single component drug products are also applicable to FDC drug products.

3.2. When In Vivo BE is needed at multiple strengths

In vivo BE assessment at multiple strengths is needed when one or more of the following conditions apply:

- Dissolution dissimilarity between strengths (see Section 2.3.2);
- Deviations from direct proportionality in core formulation exceeding those described in Annex I; or
- Non-dose proportional PK under certain circumstances described in ICH M13A, Section 2.1.6.

Where *in vivo* BE assessment is needed under both fasting and fed conditions and at multiple strengths, it may be sufficient to assess BE for only one strength under both conditions. For the other strengths, a non-high-risk situation may be assumed, and a waiver of either the fasting or fed BE study may be justified based on prior knowledge and/or PK BE data from studies conducted with the first strength. The condition selected (fasting or fed) to conduct BE for the second strength should follow the principles described in ICH M13A, Section 2.1.5.

3.2.1. Bracketing

Assuming qualitative similarity is maintained across strengths, a bracketing approach may be used to support additional strengths biowaivers when *in vivo* BE assessment at multiple strengths is needed, as described above. Under this approach, the strengths selected for *in vivo* BE assessment represent the extremes in deviation, such that any differences in the remaining strength(s) are covered by these extreme strengths. It is therefore sufficient to conduct *in vivo* BE studies on these extreme strengths, *i.e.*, biowaiver(s) for the intermediate strength(s) is possible.

For example, in a scenario with three strengths where BE should be demonstrated for more than one strength due to non-proportional composition, the highest and lowest strengths are considered the extremes in deviation from direct proportionality, and the intermediate strength is in between with regard to composition. A bracketing approach may be applied, and *in vivo* BE studies conducted with the highest and lowest strengths may be sufficient. The results of these BE studies can be extrapolated to the intermediate strength based on *in vitro* dissolution data, where dissolution profile comparison demonstrates similarity under QC and standardised multimedia conditions appropriate to the situation under consideration. Both the highest and lowest strengths will serve as biobatch strengths for dissolution comparison with the intermediate strength. The intermediate strength should demonstrate similar dissolution to either of the biobatch strengths. Alternatively, the mean dissolution profile of the intermediate strength should fall between the mean dissolution profiles of the two biobatch strengths, which may be achieved without demonstrating similarity to either biobatch strength profile individually.

3.3. Drug substance instability

In some cases, drug substance instability may preclude its classification within the Biopharmaceutics Classification System (BCS), as described in ICH M9, *Biopharmaceutics Classification System-based Biowaivers* Sections 2.1 and 2.2. However, for the purpose of an additional strengths biowaiver and to assign acceptable Level 1 or Level 2 deviations from direct proportionality (see Annex I), applicants can provide additional data to justify time-dependent high solubility. This can include concentration *vs.* time measurements for the drug substance and any degradation products of the drug substance for the same duration as for the dissolution experiment. If sufficient information cannot be provided to

demonstrate time-dependent high solubility, the drug substance should be considered low solubility within this context.

4. Documentation

Applicants should develop a biowaiver report that includes the following:

- A rationale for additional strengths biowaiver strategy and biobatch strength(s) selection.
- A tabular listing of the biobatch strength(s) and the additional strength(s) with their qualitative and quantitative compositions, excipient quantity per unit, and quantity of each ingredient as a percentage of the total core weight. If deviations from direct proportionality are present, a scientific rationale should be provided.
- A prospective analysis plan for dissolution profile comparison detailing the following:
    - Objective of the study;
    - Description of all test methods and media with a thorough description of experimental settings and analytical methods, including information on the dissolution conditions such as apparatus, de-aeration, filtration during sampling, volume, etc. The analytical method employed should be described, including, where necessary, validation and qualification of the analytical parameters;
    - Batch information for the additional and biobatch strengths [unit dose (strength and assay), batch number, manufacturing date, batch size, and expiry date (or retest date as appropriate)];
    - Total number of units per strength. Data from at least 12 replicates of each of the additional and biobatch strengths should be employed;
    - Number and distribution of sampling time points; and
    - Detailed description of method to be used for evaluation of similarity (see Section 2.3.2 and Figure 1).
- The measured pH of each medium at the beginning and end of each dissolution run.
- Dissolution results with tabulated individual and mean values with standard deviation, as well as mean dissolution profiles of the additional and biobatch strengths.
- Dissolution similarity assessment.
- Conclusions.

5. Glossary

Biobatch:

A specific batch of a drug product used in BE or pivotal clinical study(ies).

Biobatch strength(s):

The strength(s) of the drug product used in BE or pivotal clinical study(ies).

Bootstrapping:

A resampling procedure that uses data from one sample to generate a sampling distribution by repeatedly taking random samples with replacement from the known sample.

Bracketing approach:

An approach of conducting BE studies on extreme strengths to support the demonstration of BE for all strengths.

Core formulation:

The active and inactive ingredients that make up a drug product, not including tablet film coating or capsule shell.

Core weight:

The total mass of the core formulation.

f_2 (estimated similarity factor):

F_2, the similarity factor, is a model-independent measure for the comparison of two dissolution profiles.

$$f_2 = 50 \cdot log \frac{100}{\sqrt{1 + \frac{1}{P}\left[\sum_{j=1}^{P}(R_j - T_j)^2\right]}}$$

where f_2 is the estimated similarity factor, P is the number of time points, R_j is the sample mean percent biobatch (reference) strength dissolved at j^{th} time after initiation of the study, and T_j is the sample mean percent test strength dissolved at j^{th} time after initiation of the study.

Fixed dose combination:

A single dosage form that contains two or more drug substances.

IVIVC:

A predictive mathematical model describing the relationship between an *in vitro* property of a dosage form (usually the rate or extent of drug dissolution or release) and a relevant *in vivo* response, *e.g.*, plasma drug concentration or amount of drug absorbed.

Non-functional coating:

A coating that does not alter the dissolution and/or release characteristics of the dosage form. For the purpose of this guideline, coatings designed for functions such as appearance, taste masking, stability, or strength differentiation are considered non-functional for BE assessment.

Annex I: Considerations for deviation from direct compositional proportionality

Deviations from direct proportionality in core formulations between strengths can be considered as exceptions with appropriate scientific justification. The rationale for deviations from direct proportionality should be supported by the pharmaceutical development program for the drug product. The justification for deviations from direct proportionality should consider the biopharmaceutical properties of the drug substance(s), the complexity of the formulation and manufacturing characteristics of the drug product, as well as the dissolution characteristics of the drug product strengths.

When a rationale for deviation from direct proportionality arises from the pharmaceutical development program, the BCS-defined solubility characteristics of the drug substance(s) (see ICH M9) will be a primary factor in determining whether such a deviation can be justified within the context of an additional strengths biowaiver or whether additional BE data will be necessary to support the deviation.

Deviations from direct proportionality in core formulation for additional strengths containing high solubility drug substances are lower risk with respect to potential effects on relative BA. 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 for non-high-risk products (as described in ICH M13A), provided the absolute value of deviation in total core weight of the additional strength does not exceed 20% from the theoretical total core weight of the additional strength assuming direct proportionality, and similarity in mean dissolution profiles is demonstrated with the QC method and under standardised multimedia conditions (Annex III, Figure 2).

Deviations from direct proportionality in core formulation for additional strength(s) containing low solubility drug substances are higher risk with respect to potential effects on relative BA and are, therefore, generally discouraged and need a strong scientific justification. In such a justification, applicants should explain the pharmaceutical development needs necessitating such a deviation, the complexity of the drug product, as well as a risk-based evaluation of the mean dissolution profiles between the additional and biobatch strengths under both QC and standardised multimedia conditions, as described below.

Non-high-risk drug products

For non-high-risk drug products, deviations from direct proportionality for additional strength(s) can be accepted if properly justified based on the following:

1) Deviations up to Level 2 differences (see Table 1) can be considered for drug products containing BCS low solubility drug substance(s) if:
    a. similar dissolution is demonstrated with the QC method;
    b. rapid or very rapid dissolution is demonstrated in at least one of the standardized media conditions (see Section 2.3.1). If the QC method is identical to one of the standardized media conditions, then demonstration of rapid or very rapid dissolution under that one set of dissolution conditions is sufficient; and
    c. 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 assuming direct proportionality.
2) Deviations up to Level 1 (see Table 1) can be considered for drug products containing BCS low solubility drug substance(s) if:

a. similar dissolution is demonstrated with the QC method;

b. sufficient, i.e., at least 10%, mean dissolution is observed to allow f2 profile comparison under at least one standardised multimedia condition other than the QC condition; and

c. the total core weight of the additional strength does not deviate by more than 10% from the theoretical total core weight of the additional strength assuming direct proportionality.

In all cases, mean dissolution profile comparison should demonstrate similarity in QC and standardised multimedia conditions.

Refer to Annex III, Figure 2 for biowaiver criteria for non-high-risk drug products.

High-risk drug products

Deviations from direct proportionality for additional strength(s) for drug products containing low solubility drug substance(s) with formulation-manufacturing (process/technology) enhanced PK performance are of significant risk with respect to potential effects on relative BA (see ICH M13A Section 2.1.5). For these high-risk drug products, because of the complexity of the formulations, excipients functioning as the solubilizing or carrier matrix in the formulation, *e.g.*, the dispersing excipient(s) in a solid dispersion formulation, should be directly proportional to the drug substance(s) between the additional and biobatch strengths. For drug products using a solid dispersion intermediate, proportional amounts of the same intermediate should be used in the different strengths. Deviation from proportionality for the remaining excipients should only be considered with strong justification and, if justified, these deviations should fall within Level 1 (see Table 1), provided rapid or very rapid dissolution is demonstrated in at least one standardised multimedia condition and with the QC method, and the total core weight of the additional strength does not deviate by more than 10% from the theoretical total core weight of the additional strength assuming direct proportionality. Mean dissolution profile comparison should demonstrate similarity in the standardised multimedia conditions and with the QC method.

Table 1: Acceptable Level 1 and Level 2 deviations in core formulation excipient content relative to the biobatch strength to be considered with appropriate scientific justification for a biowaiver, expressed as percent (w/w) of the core formulation weight *

Function of excipient	**Deviation (%w/w)**	
	Level 1	**Level 2**
Diluent/Filler	5	10
Disintegrant		
Starch	3	6
Other	1	2
Binder	0.5	1
Lubricant		
Stearate salts	0.25	0.5
Others	1	2
Glidant (Fluidizing agent)		
Talc	1	2
Other	0.1	0.2
Total absolute value of excipient changes (%)	5	10

*** Note to Table 1** - This table provides levels of allowable differences in excipient content when direct proportionality between the additional and biobatch strengths cannot be achieved. Excipients with functions not described in the table, *e.g.*, surfactants, should be present in direct proportion between strengths. For excipients with multiple functions, the most conservative allowable deviation should apply to that excipient. Deviations from proportionality for these excipients or excipient differences outside of those described above, are generally not allowed and will need additional supporting information to provide adequate bridging to the biobatch strength.

Annex II: Examples of application of additional strengths biowaiver principles

The following cases are theoretical examples meant to illustrate the principles described in the guideline.

Example 1: Direct proportionality of core formulations

5 mg and 10 mg strengths of a drug product have been developed. A BE study has been conducted with the 10 mg strength (biobatch strength) comparing it to the 10 mg strength of the accepted comparator product. As illustrated in the following table, the formulation of the additional strength (5 mg) is directly proportional to the core formulation of the biobatch strength, *i.e.*, each strength contains the same ingredients in the same proportion. If other biowaiver criteria, including dissolution similarity, are satisfied, a biowaiver for the 5 mg strength is possible.

Component	Function	Strength (label claim)				Absolute % difference relative to core weight of additional strength
		10 mg		5 mg		
		Biobatch strength		Additional strength		
		Quantity per unit		Quantity per unit		
		mg	%*	mg	%*	
Dry Mixing						
Drug A	Active ingredient	10.0	6.7	5.0	6.7	--
Lactose monohydrate	Diluent/filler	128.8	85.9	64.4	85.9	0.0
Pregelatinised starch	Binder	7.4	4.9	3.7	4.9	0.0
Talc	Glidant	3.0	2.0	1.5	2.0	0.0
Lubrication						
Magnesium stearate	Lubricant	0.8	0.5	0.4	0.5	0.0
Total		150.0	100.0	75.0	100.0	
Total absolute value of excipient changes (%)						0.0
Absolute value of deviation in total core weight of additional strength (%)					0.0	

*each ingredient expressed as a percentage of the total core weight

Example 2: Acceptable Level 1 deviation from direct proportionality of core formulations

5 mg and 10 mg strengths containing a low solubility drug substance have been developed. A BE study has been conducted with the 10 mg strength (biobatch strength) comparing it to the 10 mg strength of the accepted comparator product. Similar mean dissolution has been demonstrated with the QC method and the three standardised multimedia (more than 10% mean dissolution observed in at least one of the multimedia) but rapid dissolution is not observed in any of the multimedia.

Component	Function	Strength (label claim)						Absolute % difference relative to core weight of additional strength
		10 mg		5 mg		5 mg		
		Biobatch strength		Additional strength; directly proportional theoretical formulation		Additional strength; actual formulation		
		Quantity per unit		Quantity per unit		Quantity per unit		
		mg	%*	mg	%*	mg	%*	
Dry mixing								
Drug A	Active ingredient	10.0	6.7	5.0	6.7	5.0	6.2	--
Lactose monohydrate	Diluent/filler	128.8	85.9	64.4	85.9	69.3	86.6	0.7
Pregelatinised starch	Binder	7.4	4.9	3.7	4.9	3.7	4.6	0.3
Talc	Glidant	3.0	2.0	1.5	2.0	1.5	1.9	0.1
Lubrication								
Magnesium stearate	Lubricant	0.8	0.5	0.4	0.5	0.5	0.6	0.1
Total		150.0	100.0	75.0	100.0	80.0	100.0	
Total absolute value of excipient changes (%)								1.2
Absolute relative value of deviation in total core weight of additional strength (%) **						6.67		

*each ingredient expressed as a percentage of the total core weight

**Absolute relative value of deviation in total core weight between the proposed additional strength and the directly proportional theoretical formulation of that strength divided by the total weight of the directly proportional theoretical formulation multiplied by 100, *e.g.*, (80.0-75.0)/75.0 * 100 = 6.67%.

As illustrated in the above table, the formulation of the additional strength (5 mg) deviates from direct proportionality in core formulation compared to that of the biobatch strength. The %w/w differences for each excipient comply with the acceptable Level 1 deviations as described in Table 1 and the total core weight of the additional strength does not deviate by more than 10% from the directly proportional theoretical total core weight of the additional strength. As illustrated in Annex III, a biowaiver for the 5 mg strength is possible.

Example 3: Level 1 deviation from direct proportionality of core formulation that does not meet criteria

5 mg and 10 mg strengths containing a low solubility drug substance have been developed. A BE study has been conducted with the 10 mg strength (biobatch strength) comparing it to the 10 mg strength of the accepted comparator product. Similar mean dissolution has been demonstrated with the QC method and the three standardised multimedia (more than 10% mean dissolution observed in at least one of the multimedia) but rapid dissolution is not observed in any of the multimedia.

Component	Function	Strength (label claim)						Absolute % difference relative to core weight of additional strength
		10 mg		5 mg		5 mg		
		Biobatch strength		Additional strength; directly proportional theoretical formulation		Additional strength; actual formulation		
		Quantity per unit		Quantity per unit		Quantity per unit		
		mg	%*	mg	%*	mg	%*	
Dry mixing								
Drug A	Active ingredient	10.0	6.7	5.0	6.7	5.0	5.6	--
Lactose monohydrate	Diluent/filler	128.8	85.9	64.4	85.9	77.6	87.5	1.6
Pregelatinised starch	Binder	7.4	4.9	3.7	4.9	4.0	4.5	0.4
Talc	Glidant	3.0	2.0	1.5	2.0	1.5	1.7	0.3
Lubrication								
Magnesium stearate	Lubricant	0.8	0.5	0.4	0.5	0.6	0.7	0.2
Total		150.0	100.0	75.0	100.0	88.7	100.0	
Total absolute value of excipient changes (%)								2.5
Absolute value of deviation in total core weight of additional strength (%) **						18.3		

*each ingredient expressed as a percentage of the total core weight

**Absolute relative value of deviation in total core weight between the proposed additional strength and the directly proportional theoretical formulation of that strength divided by the total weight of the directly proportional theoretical formulation multiplied by 100, *e.g.*, (88.7-75.0)/75.0 * 100 = 18.3%.

As illustrated in the above table, the formulation of the additional strength (5 mg) deviates from direct proportionality in core formulation compared to that of the biobatch strength. The %w/w differences for each excipient comply with the acceptable Level 1 deviations as described in Table 1, however, the total core weight of the additional strength deviates by more than 10% from the directly proportional theoretical total core weight of the additional strength**.** As illustrated in Annex III, a BE study should be provided to support the 5 mg strength. Alternative approaches such as an IVIVC or other modelling approaches to support the 5 mg strength may be considered if agreed by the relevant regulatory authority(ies).

Example 4: FDC direct proportionality of core formulations

320 mg/25 mg and 160 mg/12.5 mg strengths of a drug product have been developed. A BE study has been conducted with the 320 mg/25 mg strength (biobatch strength) comparing it to the 320 mg/25 mg strength of the accepted comparator product. As illustrated in the following table, the formulation of the additional strength (160 mg/12.5 mg) is directly proportional to the core formulation of the biobatch strength, *i.e.*, each strength contains the same ingredients in the same proportion. If other biowaiver criteria, including dissolution similarity, are satisfied, a biowaiver for the 160 mg/12.5 mg strength is possible.

Component	Function	Strength (label claim)				Absolute % difference relative to core weight of additional strength
		320 mg/25 mg		160 mg/12.5 mg		
		Biobatch strength		Additional strength		
		Quantity per unit		Quantity per unit		
		mg	%*	mg	%*	
Dry mixing						
Drug A	Active ingredient	320.0	56.5	160.0	56.5	--
Drug B	Active ingredient	25.0	4.4	12.5	4.4	--
Lactose monohydrate	Diluent/filler	200.0	35.3	100.0	35.3	0.0
Pregelatinised starch	Binder	10.0	1.8	5.0	1.8	0.0
Talc	Glidant	10.0	1.8	5.0	1.8	0.0
Lubrication						
Magnesium stearate	Lubricant	1.0	0.2	0.5	0.2	0.0
Total		566.0	100.0	283.0	100.0	
Total absolute value of excipient changes (%)						0.0
Absolute value of deviation in total core weight of additional strength (%)				0.0		

*each ingredient expressed as a percentage of the total core weight

Example 5: FDC that can be considered proportional for core formulations

320 mg/25 mg and 320 mg/12.5 mg strengths of a drug product have been developed. A BE study has been conducted with the 320 mg/25 mg strength (biobatch strength) comparing it to the 320 mg/25 mg strength of the accepted comparator product. As illustrated in the following table, the formulation of the additional strength (320 mg/12.5 mg) is not directly proportional to the core formulation of the biobatch strength, as the amount of drug substance B and the amount of the filler lactose monohydrate have been changed, while the amount of drug substance A and the amounts of other excipients and core weight have not been changed, resulting in a different percentage of drug substance B and lactose monohydrate compared to the biobatch strength (320 mg/25 mg).

Component	Function	Strength (label claim)				Absolute % difference relative to core weight of additional strength
		320 mg/25 mg		320 mg/12.5 mg		
		Biobatch strength		Additional strength		
		Quantity per unit		Quantity per unit		
		mg	%*	mg	%*	
Dry mixing						
Drug A	Active ingredient	320.0	56.5	320.0	56.5	--
Drug B	Active ingredient	25.0	4.4	12.5	2.2	2.2**
Lactose monohydrate	Filler	200.0	35.3	212.5	37.5	2.2
Pregelatinised starch	Binder	10.0	1.8	10.0	1.8	0.0
Talc	Glidant	10.0	1.8	10.0	1.8	0.0
Lubrication						
Magnesium stearate	Lubricant	1.0	0.2	1.0	0.2	0.0
Total		566.0	100.0	566.0	100.0	
Total absolute value of excipient changes (%)						2.2
Absolute value of deviation in total core weight of additional strength (%)					0.0	

*each ingredient expressed as a percentage of the total core weight

** not included in the calculation of the total absolute value of excipient changes

When considering drug substance B, the amount of drug substance B is less than 5% of the core weight in the biobatch strength and the additional strength. According to Section 3.1, the other active substance, in this case drug substance A, can be considered as if it were an excipient (filler). Hence, considering drug substance A as if it were a filler, drug substance B follows the 5% criterion, as indicated in Section 2.2.1, and the additional strength can be considered proportional to the biobatch strength.

When considering drug substance A, the amount of this active substance is not changed between the biobatch strength and the additional strength, but drug substance B, in this situation considered as if it were a filler as described in Section 3.1, is not constant. The ratio between drug substance B and drug substance A is not the same for both strengths. However, as in this case drug substance B is considered as if it were a filler and its change represents less than 5% of the product core, which is compensated by the addition of the same amount of an actual filler of the formulation, the ratio between drug substance A and 'filler' (actual filler + drug substance B) is the same for both strengths.

As a result, the biobatch strength and the additional strength can be considered proportional. If other biowaiver criteria, including dissolution similarity, are satisfied, a biowaiver for the 320 mg/12.5 mg strength is possible.

Example 6: Example of bracketing approach for an FDC

Four strengths of a monolithic FDC containing 2 drug substances (drug substance A and drug substance B) have been developed. The amount of drug substance A in the strengths remains constant, while the amount of drug substance B varies across strengths. The strengths were all formulated to the same core weight (see table below).

Component	**Function**	**Strength (label claim)**							
		40 mg/20 mg		40 mg/15mg		40 mg/10mg		40 mg/5 mg	
		Quantity per unit		Quantity per unit		Quantity per unit		Quantity per unit	
		mg	%*	mg	%*	mg	%*	mg	%*
Drug A	Active ingredient	40.0	10.0	40.0	10.0	40.0	10.0	40.0	10.0
Drug B	Active ingredient	20.0	5.0	15.0	3.75	10.0	2.5	5.0	1.25
Lactose monohydrate	Filler	320.0	80.0	327.0	81.75	334.0	83.5	341.0	85.25
Pregelatinised starch	Binder	10.0	2.5	10.0	2.5	10.0	2.5	10.0	2.5
Magnesium stearate	Lubricant	10.0	2.5	8.0	2.0	6.0	1.5	4.0	1.0
Total		400.0	100.0	400.0	100.0	400.0	100.0	400.0	100.0

*each ingredient expressed as a percentage of the total core weight

The amount of drug substance B is 5% or less of the core weight in the 4 strengths. According to Section 3.1, the other active substance, in this case drug substance A, can be considered as if it were an excipient (filler). Considering drug substance A as a filler, drug substance B does not follow the 5% criterion, as indicated in Section 2.2.1, because the difference in amount of drug substance B is not compensated by the amount of filler, and the amount of the other excipients, *i.e.,* magnesium stearate, have not been kept the same. Therefore, the strengths cannot be considered proportional.

When considering drug substance A, the amount of this drug substance is not changed between the 4 different strengths, but drug substance B, which in this situation is considered as if it were a filler as

described in Section 3.1, and the other excipients, *i.e.*, magnesium stearate, are not constant, and therefore, also in this case, the strengths cannot be considered proportional.

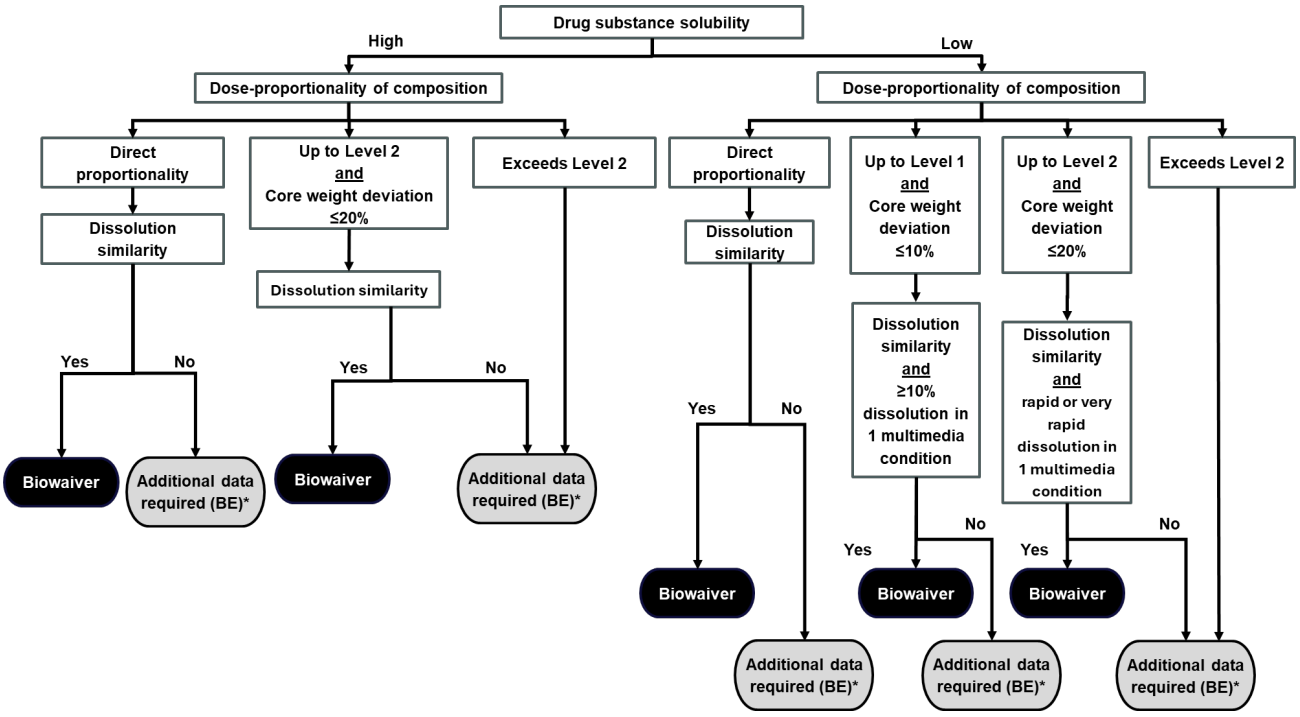
The differences in the formulations of the strengths are bracketed by the highest (40 mg/20 mg) and lowest (40 mg/5 mg) strengths, and if BE has been demonstrated between the 40 mg/20 mg strength and the 40 mg/20 mg strength of the accepted comparator product and between the 40 mg/5 mg strength and the 40 mg/5 mg strength of the accepted comparator product, biowaivers for the intermediate strengths (40 mg/10 mg and 40 mg/15 mg) may be possible.

As discussed in Section 3.2.1, the intermediate strengths should have similar dissolution compared to either of these biobatch strengths. Alternatively, if the biobatch strengths have different dissolution between them, the dissolution profiles of the intermediate strengths should fall within the dissolution profiles of the two biobatch strengths.

Annex III: Decision tree for additional strengths biowaiver for non-high-risk drug products

The decision tree below should be followed to determine whether a biowaiver is possible for an additional strength for non-high-risk drug products.

Figure 2: Decision tree with recommendations for additional strengths biowaiver for non-high-risk drug products



* The additional strength should be supported with a BE study(ies). In some situations, a bracketing approach may be applicable (see Section 3.2.1). Alternatively, additional information including an IVIVC or other modelling approaches to support the additional strength may be considered if agreed by the relevant regulatory authority(ies).

** Core weight deviation – refers to the % deviation of the total core weight of the additional strength relative to the theoretical total core weight of the additional strength assuming direct proportionality (see Annex I).