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

Step 2b

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS

ADDITIONAL STRENGTHS BIOWAIVER

M13B

Draft version

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At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

M13B
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ICH HARMONISED GUIDELINE

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ADDITIONAL STRENGTHS BIOWAIVER
M13B

ICH Consensus Guideline

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1 INTRODUCTION

1.1 Objective

This guideline is intended to provide recommendations on obtaining waivers of bioequivalence (BE) studies for one or more additional strengths of a drug product in an application where *in vivo* BE has been demonstrated for at least one of the strengths. The 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. Applicants are encouraged to consult the regulatory authority(ies) when an alternate approach is proposed or taken.

1.2 Background

BE for IR solid oral dosage forms with systemic action is largely established via *in vivo* pharmacokinetic (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 comparative *in vitro* dissolution studies between the additional strength(s) and the strength that has demonstrated BE, *i.e.*, the biobatch strength. To be eligible for this biowaiver of additional strengths, specific criteria apply in terms of dose proportionality in PK, formulation proportionality, and dissolution profile similarity in specific dissolution conditions.

M13B is intended to reduce the need for *in vivo* BE studies for additional strengths by recommending the specific criteria needed to pursue a biowaiver of such studies.

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*.

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 waiver(s) 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.

M13B describes the additional strength(s) biowaiver criteria as they relate to a) the dose proportionality in the PK of the drug (or drugs in the case of fixed dose combination (FDC) products), b) the formulation proportionality of the drug substance(s) and excipients in the additional strength(s) compared to the biobatch strength, and c) the similarity in dissolution profiles between the additional strength(s) and the biobatch strength 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 M13B. Applicants are encouraged to consult the regulatory authority(ies) when an alternate approach is proposed or taken.

2 CRITERIA FOR BIOWAIVER OF ADDITIONAL STRENGTHS

2.1 PK Dose Proportionality of the Drug

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).

2.2 Qualitative and Quantitative Composition Among Different Strengths (Manufacturing and Formulation Aspects)

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

2.2.1 Product Composition

For a biowaiver, the core formulation(s) of the additional strength(s) should be qualitatively the same as that of the biobatch strength(s). Further, the composition of 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 for core composition between strengths can be considered as exceptions with appropriate scientific justification (see Annex I).

Excipients present only to provide colour or flavour that are not expected to affect bioavailability may generally vary between strengths.

Qualitative differences in non-functional tablet coating / capsule shell composition (other than colourants) 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 bioavailability.

2.2.2 High-potency Drug Products

When the amount of drug substance in the 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 amounts of each excipient in the product core are constant between the additional and biobatch strength(s) and only the amount of drug substance is changed.
- The amount of diluent/filler varies to account for the change in the amount of drug substance (or solid dispersion intermediate if applicable) between the additional and biobatch strength(s), while the amounts of other excipients remain constant.

2.2.3 Manufacturing Process

The manufacturing process used for the additional strength(s) should be the same as that used for the biobatch strength(s).

2.3 Dissolution Conditions (including Optimisation and Validation)

Similarity of *in vitro* dissolution should be demonstrated under all conditions between the additional and biobatch strengths. The same batch(es) used in the BE study(ies) should be used for comparative dissolution testing.

The following conditions should be employed in the comparative dissolution studies to characterise the *in vitro* dissolution profile of the product:

- 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
- At least 12 units 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 unit preparations should be evaluated.
- Dissolution testing should be conducted for all strengths across the pH range (covering physiological conditions). Dissolution should be tested for all strengths in 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) and in the quality control (QC) medium (unless the medium is identical to one of the three compendial media as described above).
- Surfactant may be used in only the QC medium and only when appropriately established as part of dissolution method development.
- Samples should be filtered during collection, unless *in situ* detection methods are used.
- For gelatin capsules or tablets with gelatin coatings where cross-linking has been demonstrated, the use of enzymes may be acceptable if appropriately justified.

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.

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 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. 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 is considered suitable for confirmation that intrinsic drug properties, such as pH-dependent solubility, rather than formulation factors are the cause of the observed initial differences in dissolution profiles.

Other dissolution conditions, *e.g.*, compendial apparatuses and agitation speeds, may be

considered to overcome specific issues, *e.g.*, coning, if scientifically justified. 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 should be provided.

For details on sampling timepoint selection, refer to Section 2.4.

2.4 Assessment of Similarity

Dissolution profile similarity testing and any conclusions drawn from the results, can be considered valid only if the dissolution profiles have been properly characterised as discussed in more detail below.

Sampling time points should be chosen to adequately describe the complete dissolution profile. 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 less than 5% in mean absolute dissolution. Dissolution tests and sampling need not exceed two hours. Sampling time points should be selected to 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 not changing. More frequent sampling during the period of greatest change in the dissolution profile should be employed. The additional strength and biobatch strength dissolution profiles should be composed of identical time points. In principle, not more than six time points should be included in the calculation 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.

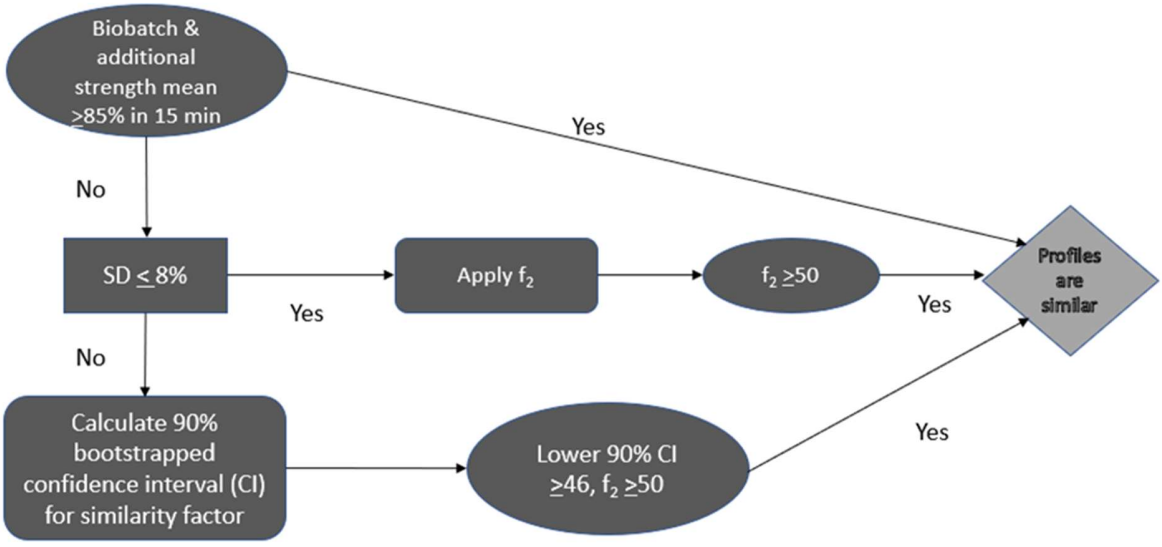
As described in Figure 1, when ≥85% of the drug is dissolved within 15 minutes (very rapid dissolution) for both the additional strength and biobatch strength mean dissolution profiles, no further mathematical evaluation is needed, and similarity can be concluded.

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

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 90% bootstrapped CI for the similarity factor should be ≥46 and the point estimate (f_2) 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 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.

Figure 1: Decision tree for determining dissolution profile similarity using f_2



3 SPECIFIC TOPICS

3.1 Fixed Dose Combination Products

For oral IR 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 applied 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 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).

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 other dissolution examples in Section 3.2 for single component products are also applicable to FDC products.

3.2 Bracketing Where the Above Criteria Are Not Met

Assuming qualitative similarity is maintained between strengths, a bracketing approach may be used when BE assessment at more than two strengths is needed due to one or more of the following:

- Dissolution dissimilarity between strengths (see Section 2.4);

- Deviations from direct proportionality in core composition exceeding those described in Annex I; or
- Non-dose proportional PK (see ICH M13A, Section 2.1.6).

If the strengths selected for BE assessment represent the extremes so that any differences in the remaining strength(s) are covered by these extreme strengths, it is sufficient to conduct BE studies on these strengths, *i.e.*, a waiver of BE study(ies) on the strength(s) in between can be applied.

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. For the other strength, a waiver of either the fasting or the fed study may be justified based on prior knowledge and/or PK data from the studies conducted with the one strength. The condition selected (fasting or fed) to test the other strength should follow the principles described in ICH M13A Section 2.1.5.

Dissolution profile comparison should demonstrate similarity in QC and multimedia conditions based on the situation under consideration.

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.

As a further example, in a situation with three strengths and a bracketing approach is used such that BE studies are conducted with the highest and lowest strengths, both the highest and lowest strengths will be considered the biobatch strengths for dissolution comparison with the middle strength. If the biobatch strengths show similar dissolution, then the middle strength should show similar dissolution against either of these biobatch strengths. 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.

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 Section 2.1 and 2.2. However, for the purpose of additional strength biowaivers 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 strength(s) 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. In case of deviations from direct proportionality, 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 fully described, including validation and qualification of the analytical parameters;
  - Batch information for the additional and biobatch strengths [unit dose (strength and assay), batch number, manufacturing date and batch size, expiry date];
  - Total number of units per strength. Data from at least 12 units of each of the additional and biobatch strengths should be employed;
  - Number and distribution of sampling time points; and
  - Method for evaluation of similarity (see Section 2.4 and Figure 1).
- Dissolution results with tabulated individual and mean values as well as individual and mean dissolution profiles of the additional and biobatch strengths.

- Dissolution similarity assessment
- Conclusions

5 GLOSSARY

Bootstrapping:

Bootstrapping is 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.

Biobatch strength(s):

The strength(s) of the drug product used in the *in vivo* BE study or studies.

Bracketing approach:

Is an approach of conducting BE studies on extreme strengths to support the demonstration of BE for all strengths. For demonstrating BE for all strengths, it is sufficient to conduct BE studies on the extreme strengths, *i.e.*, a waiver of BE studies on the strengths in between can be applied.

Core formulation:

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

Extreme strength(s):

The strength(s) of the drug product that represent the largest difference in composition. Often, but not always, these will be the highest and lowest strengths**.**

f2 (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 Tj 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.

High potency drug product:

A drug product where the %w/w of a given drug substance is ≤5% of the core weight in all strengths.

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/release characteristics of the dosage form. For the purpose of this guideline, coatings designed for functions such as appearance, stability, or strength differentiation are considered non-functional for bioequivalence decisions.

ANNEX I: CONSIDERATIONS FOR DEVIATION FROM DIRECT COMPOSITIONAL PROPORTIONALITY

Deviations from direct proportionality for core composition between strengths can be considered with appropriate scientific justification. The rationale for deviations from direct proportionality should be supported by the pharmaceutical development program for the products. 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 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 strength biowaiver or whether additional BE data will be necessary to support the deviation.

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.

Deviations from direct proportionality for additional strength(s) containing low solubility drug substances are greater risk with respect to potential effects of such deviation on relative bioavailability and are, therefore, generally discouraged and need a strong scientific justification. Applicants should address the pharmaceutical development needs necessitating such a deviation, the complexity of the product, as well as a risk-based evaluation of the dissolution profiles between the additional and biobatch strengths under both QC and multimedia conditions. Deviations can be accepted if properly justified based on the following:

1) Deviations up to **Level 2** differences (see Table 1) can be considered for products containing BCS low solubility drug substance(s) if:
    a. at least rapid dissolution (dissolution ≥85% in 30 minutes) is demonstrated in the QC and at least one multimedia (without surfactant) condition (see Section 2.3); and
    b. 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.
2) Deviations up to **Level 1** (see Table 1) can be considered for products containing BCS low solubility drug substance(s) if:
    a. at least rapid dissolution is demonstrated in the QC medium;
    b. sufficient, *i.e.*, at least 10%, dissolution is observed to allow f_2 profile comparison under at least one multimedia (without surfactant) 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 version assuming direct proportionality.

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

Refer to Annex II to aid in the interpretation of the biowaiver criteria for non-high-risk products.

<u>High-risk products</u>

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 bioavailability (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 between the additional and biobatch strengths. For products using an intermediate solid dispersion, proportional amounts of the same intermediate should be used in the different strengths. Deviation

from proportionality for the remaining excipients will only be considered with strong justification and, if justified, these deviations should fall within Level 1 (see Table 1), provided at least rapid dissolution is demonstrated in the QC and at least one multimedia condition, 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 version assuming direct proportionality. Dissolution profile comparison should demonstrate similarity in QC and multimedia conditions.

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) *

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. 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.

EXAMPLES OF APPLICATION OF BIOWAIVER PRINCIPLES

Example 1: Direct proportionality of composition

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 in composition to the formulation of the biobatch strength. If the criteria for dissolution similarity are satisfied, a biowaiver for the 5 mg strength is possible.

Component	Function	Strength (label claim)				
		10.0 mg		5.0 mg		
				Additional strength; directly proportional		Absolute % difference relative to core weights of additional strength
		Quantity per unit		Quantity per unit		
		mg	%*	mg	%*	
Dry mixing						
Drug A	Active	10.0	6.7	5.0	6.7	--

	ingredient					
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
Total absolute value of deviation in total core weight of additional strength (%)					0.0	

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

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Example 2: Acceptable Level 1 deviation from direct proportionality

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 (the biobatch strength) comparing it to the 10 mg strength of the accepted comparator product. With respect to comparative dissolution, similarity in dissolution has been demonstrated for the QC medium and the three multimedia (more than 10% dissolution observed in at least one of the multimedia) but, at least rapid dissolution is only observed in the QC medium.

Component	Function	Strength (label claim)						
		10.0 mg		5.0 mg		5.0 mg		
				Additional strength; theoretical directly proportional version		Additional strength; deviating from direct proportionality		Absolute % difference relative to core weights of additional strength
		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
Total absolute value of deviation in total core weight of additional strength (%) **						6.67		

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

**absolute difference in total core weight between proposed additional strength and the theoretical directly proportional version of that strength divided by the total weight of the theoretical directly proportional version multiplied by 100, *e.g.*, (80-75)/75 * 100 = 6.7%.

As illustrated in the above table, the formulation of the additional strength (5 mg) deviates from direct proportionality in composition compared to the formulation 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 theoretical total core weight of the additional strength version assuming direct proportionality. As illustrated in Annex II, a biowaiver for the 5 mg strength is possible.

Example 3: Level 1 deviation from direct proportionality 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 (the biobatch strength) comparing it to the 10 mg strength of the accepted comparator product. With respect to comparative dissolution, similarity in dissolution has been demonstrated for the QC medium and the three multimedia (more than 10% dissolution observed in at least one of the multimedia) but, at least rapid dissolution is only observed in the QC medium.

Component	Function	Strength (label claim)				
		10.0 mg		5.0 mg	5.0 mg	
				Additional strength; theoretical directly proportional version	Additional strength; deviating from direct proportionality	Absolute % difference relative to core weights of additional strength
		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
Total absolute value of deviation in total core						18.3		

weight of additional strength (%) **								

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

**absolute difference in total core weight between proposed additional strength and the theoretical directly proportional version of that strength divided by the total weight of the theoretical directly proportional version multiplied by 100, *e.g.*, (88.7-75)/75 * 100 = 18.3%.

As illustrated in the above table, the formulation of the additional strength (5 mg) deviates from direct proportionality in composition compared to the formulation 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 theoretical total core weight of the additional strength version assuming direct proportionality**.** As illustrated in Annex II, a biowaiver for the 5 mg strength is not possible based on the available data. Additional data is needed to support the 5 mg strength.

Example 4: Example of bracketing approach for an FDC

Four strengths of a monolithic FDC containing a low solubility drug substance (Drug A) and a high solubility drug substance (Drug B) have been developed. The amount of Drug A in the strengths remains constant, while the amount of Drug B varies across strengths. The strengths were all formulated to the same core weight.

For Drug A, similarity in dissolution has been demonstrated for the QC medium and the three multimedia (more than 10% dissolution observed in at least one of the multimedia) but, at least rapid dissolution is only observed in the QC medium. For Drug B, similarity in dissolution has been demonstrated for the QC medium and the three multimedia.

Component	Function	Strength (label claim)								
		40 mg/20 mg		40 mg/15mg		40 mg/10mg		40 mg/5 mg		
										Absolute % difference relative to core weight of lowest strength compared to highest strength
		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	3.8	10.0	2.5	5.0	1.2	--
Lactose monohydrate	Diluent/filler	320.0	80.0	325.0	81.2	334.0	83.5	339.0	84.8	4.8

Pregelatinised starch	Binder	10.0	2.5	10.0	2.5	10.0	2.5	10.0	2.5	0.0
Magnesium stearate	Lubricant	10.0	2.5	10.0	2.5	6.0	1.5	6.0	1.5	1.0
Total		400.0	100.0	400.0	100.0	400.0	100.0	400.0	100.0	
Total absolute value of excipient changes (%)										5.8
Total absolute value of deviation in total core weight of additional strength (%) from theoretical directly proportional version considering Drug A		--		0.0		0.0		0.0		

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

The amount of diluent/filler differs incrementally from highest to lowest strength, while the amount of lubricant is present in two differing quantities across the strengths.

Factors to consider for Drug A: The %w/w difference in lubricant between the highest and lowest strengths is outside Level 1 allowable deviations as shown in Table 1. Further, the total absolute value of excipient changes (% w/w) is outside the total difference allowed for Level 1 deviations as shown in Table 1.

Factors to consider for Drug B: The amount of drug substance in each of the strengths is no more than 5% of the total core weight of the strength so, the principles applicable to high-potency drugs can be applied (see Section 2.2.2). As such, the amount of drug substance in the strengths can vary. However, the excipient deviations as discussed above for Drug A need to be considered.

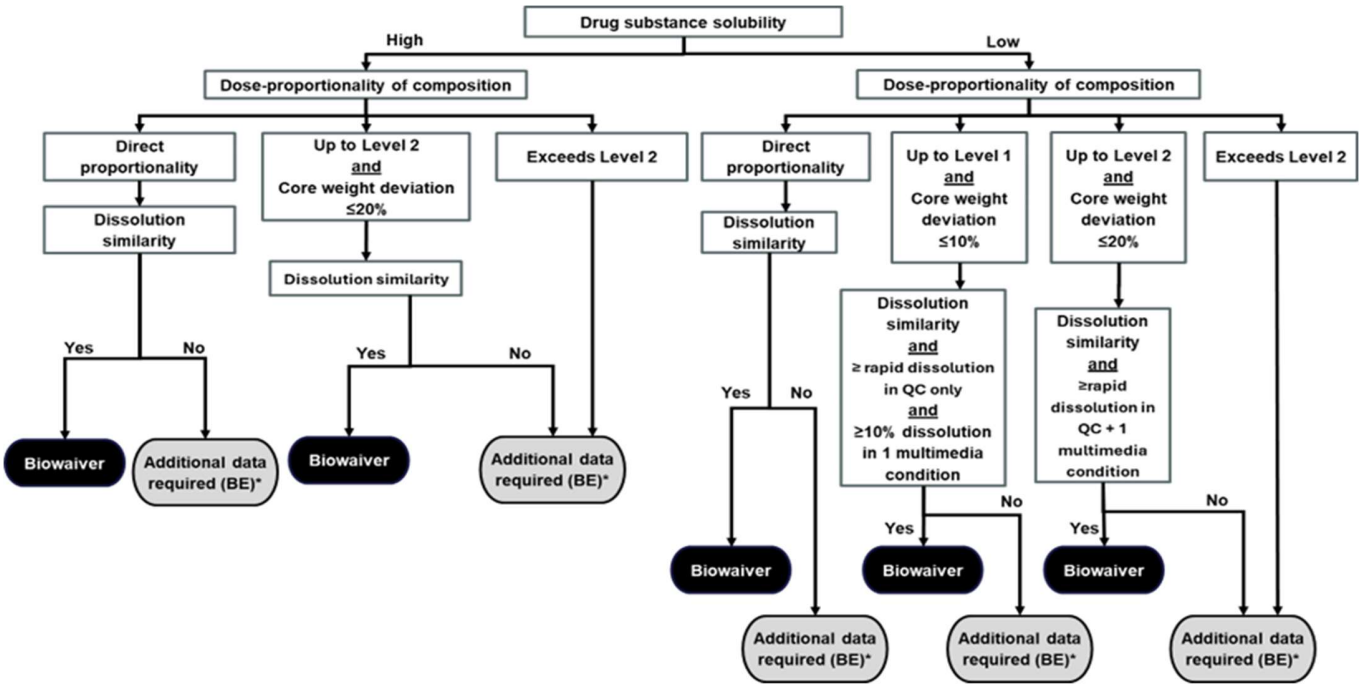
Considering the above factors, biowaivers for the lower strengths are not possible based on a BE study conducted with the highest strength (40mg/20mg). However, since the differences in the formulations of the strengths are bracketed by the highest (40mg/20mg) and lowest (40mg/5mg) strengths, waiver for the intermediate strengths (40 mg/10 mg and 40 mg/15 mg) may be possible based on BE studies conducted with each of the lowest and highest strengths.

With respect to dissolution, as discussed in Section 3.2, if the biobatch strengths show similar dissolution, then the intermediate strengths should show similar dissolution against either of these biobatch strengths. Alternatively, if the biobatch strengths have different dissolution between themselves, the intermediate strengths mean dissolution profiles should fall within the dissolution boundaries of these two biobatch strengths.

ANNEX II: DECISION TREE TO DETERMINE THE POSSIBILITY OF AN ADDITIONAL STRENGTH BIOWAIVER FOR NON-HIGH-RISK DRUG PRODUCTS

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

Figure 2: Decision tree to determine the possibility of a biowaiver for non-high-risk products*



*Footnotes:

Additional data needed (BE) - A biowaiver is not supported by the dose-proportionality and/or comparative dissolution data. The additional strength should be supported with a BE study(ies). In some situations, a bracketing approach may be applicable (see Section 3.2). Alternatively, an IVIVC or other modelling approach 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 version assuming direct proportionality (see Annex I).

Direct proportionality - each strength contains the same ingredients in the same proportion (see Section 2.2).

Dissolution similarity – See Section 2.4.

Level 1 or Level 2 – See Table 1, Annex I.