Requirements for Additional Strength Biowaivers for Modified Release Solid Oral Dosage Forms in International Pharmaceutical Regulators Programme Participating Regulators and Organisations: Differences and Commonalities

Matthias S. Roost[1], Henrike Potthast[2,3], Chantal Walther[1], Alfredo García-Arieta[4,5], Ivana Abalos[6], Eduardo Agostinho Freitas Fernandes[7], Gustavo Mendes Lima Santos[7], Zulema Rodríguez Martínez[8], Andrew Tam[9], Clare Rodrigues[10], Diego Alejandro Gutierrez Triana[11], Erwin Guzmán Aurela[11], Nayive Rodríguez Rodríguez[11], Sang Aeh Park[12], Jayoung Kim[12], Rami Kariv[13], Milly Divinsky[13], Ben Jones[14], Ryosuke Kuribayashi[15], Aya Myoenzono[15], Miho Kasuga[15], Joy van Oudtshoorn[16], Jo-Feng Chi[17], Wen-Yi Hung[17], Li-Feng Hsu[18], Christopher Crane[19], Tony Jarman[19], April C. Braddy[20]

[1]Swissmedic, Schweizerisches Heilmittelinstitut, Bern, Switzerland; [2]European Medicines Agency's (EMA) Pharmacokinetics Working Party; [3]Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Bonn, Germany; [4]WHO Prequalification of Medicines Programme; [5]Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Madrid, Spain; [6]Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), Ciudad Autónoma de Buenos Aires, Argentina; [7]Agência Nacional de Vigilância Sanitária (ANVISA), Brasília, Brazil; [8]Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), Ciudad de México, Mexico; [9]Health Canada, Ottawa, Ontario, Canada; [10]Health Sciences Authority (HSA), Health Products Regulation Group, Pre-Marketing Cluster, Therapeutic Products Branch, Singapore, Singapore; [11]Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA), Bogotá. Colombia; [12]Ministry of Food and Drug Safety (MFDS), Osong-eup Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea; [13]Ministry of Health (Israel), Pharmaceutical Division, Jerusalem; [14]New Zealand Medicines and Medical Devices Safety Authority (Medsafe), Ministry of Health, Thorndon, Wellington, New Zealand; [15]Pharmaceuticals and Medical Devices Agency (PMDA), Kasumigaseki, Chiyoda-ku, Tokyo, Japan; [16]South African Health Products Regulatory Authority (SAHPRA), Loftus Park, Arcadia, Pretoria, South Africa; [17]Taiwan Food and Drug Administration (TFDA), Nangang, Taipei, Taiwan, R.O.C.; [18]Center for Drug Evaluation (CDE), Taipei, Taiwan R.O.C.; [19]Therapeutic Goods Administration (TGA), Woden, Australia; [20]U.S. Department of Health and Human Services, Food and Drug Administration (USFDA), Center for Drug Evaluation and Research, Office of Generic Drugs, Silver Spring, Maryland, USA.

Corresponding author: Dr Matthias S. Roost, Swissmedic, Schweizerisches Heilmittelinstitut, Hallerstrasse 7, 3012 Bern, Switzerland; email: Matthias.Roost@swissmedic.ch

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ABSTRACT- This article describes an overview of waivers of *in vivo* bioequivalence studies for additional strengths in the context of the registration of modified release generic products and is a follow-up to the recent publication for the immediate release solid oral dosage forms. The current paper is based on a survey among the participating members of the Bioequivalence Working Group for Generics (BEWGG) of the International Pharmaceutical Regulators Program (IPRP) regarding this topic. Most jurisdictions consider the extrapolation of bioequivalence results obtained with one (most sensitive) strength of a product series as less straightforward for modified release products than for immediate release products. There is consensus that modified release products should demonstrate bioequivalence not only in the fasted state but also in the fed state, but differences exist regarding the necessity of additional multiple dose studies. Fundamental differences between jurisdictions are revealed regarding requirements on the quantitative composition of different strengths and the differentiation of single and multiple unit dosage forms. Differences in terms of *in vitro* dissolution requirements are obvious, though these are mostly related to possible additional comparative investigations rather than regarding the need for product-specific methods. As with the requirements for immediate release products, harmonization of the various regulations for modified release products is highly desirable to conduct the appropriate studies from a scientific point of view, thus ensuring therapeutic equivalence.

INTRODUCTION

Generic products contribute significantly to the access of medicines worldwide and have become a cornerstone in reducing growing healthcare costs. The Bioequivalence Working Group (BEWG) of the International Generic Drug Regulators Programme (IGDRP) was initiated to deal with the increasing pressure on international regulatory health authorities arising from rising review loads relating to generic drug applications. The IGDRP merged with the International Pharmaceutical Regulators Forum in January 2018 to form the International Pharmaceutical Regulators

Programme (IPRP), leading to the continuation of the work of the BEWG as the Bioequivalence Working Group for Generics (BEWGG) (1).

The IPRP BEWGG's twin objectives are to facilitate regulatory convergence and identify opportunities for harmonization in the area of bioequivalence, in addition to supporting bioequivalence assessments, especially in the scope of generic drug applications (2). It is currently composed of representatives from the following regulatory agencies: Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT, Argentina), Agência Nacional de Vigilância Sanitária (ANVISA, Brazil), Federal Commission for the Protection against Sanitary Risks (COFEPRIS, Mexico), European Commission/European Medicines Agency (EC/EMA), Health Canada (HC), Health Sciences Authority (HSA, Singapore), Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA, Colombia), Medsafe (New Zealand), Ministry of Food and Drug Safety (MFDS, Republic of Korea), Ministry of Health (Israel), Pharmaceuticals and Medical Devices Agency (PMDA, Japan), South African Health Products Regulatory Authority (SAHPRA), Swissmedic (Switzerland), Taiwan Food and Drug Administration (TFDA), Therapeutic Goods Administration (TGA, Australia), United States Food and Drug Administration (USFDA) as well as World Health Organization (WHO) as an observer.

Waivers of *in vivo* bioequivalence (BE) studies [1], i.e. biowaivers, have been a topic of interest of the IPRP BEWGG since its formation under IGDRP. Biowaivers can generally be considered in three cases: biowaivers based on the characteristics of the dosage form, biowaivers based on the Biopharmaceutics Classification System (BCS) and biowaivers for additional strengths ('additional strength biowaivers') with respect to the strength in which *in vivo* BE has been demonstrated. The IPRP BEWGG has previously described the BCS-based biowaiver criteria used by the IPRP BEWGG's participating regulators and organisations in 2018 (3). Their requirements for additional strength biowaivers specific to immediate release solid oral dosage forms with systemic action were presented in a further publication in 2019 (4). Recently, the biowaiver requirements for oral and injectable dosage forms were published (5).

Modified release dosage forms are formulations where the rate and/or site of release of the drug substance(s) are different from that of the immediate release dosage form when administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing methods. Given that the requirements to waive BE studies for modified release solid oral dosage forms may differ compared to those for immediate release solid oral dosage forms, the objective of this paper is to summarize the requirements of additional strength biowaivers of modified release solid oral dosage forms.

MATERIAL AND METHODS

The IPRP BEWGG conducted a survey to provide an overview of the requirements to waive BE studies for additional strengths of modified release solid oral dosage forms of the participating regulatory authorities and organizations based on their regulatory guidance documents and policies (6-27).

In this survey, 'modified release dosage forms' refer to the following solid oral dosage forms:

- Prolonged (termed 'extended' in Brazil, Japan, Republic of Korea, Taiwan and the USA) release dosage forms are modified release dosage forms showing a sustained release compared to that of an immediate release dosage form administered by the same route. They are sometimes called continuous, controlled, or sustained release dosage forms.
- Delayed release (e.g. gastro-resistant) dosage forms are modified release dosage forms where the release of the drug substance is delayed for a certain period after administration. The subsequent release is similar to that of an immediate release dosage form.
- Multiphasic release dosage forms have multiple release phases after administration, which may correspond to a combination of delayed and prolonged release profiles.
- Additionally, the respective dosage forms can be classified as a) single unit dosage forms which consist of only one unit, e.g. osmotic

[1] In addition to waiver of an *in vivo* BE requirement as described under USFDA's 21 CFR 320.22, there are certain circumstances in which BE can be evaluated using *in vitro* approaches under 21 CFR 320.24(b)(6). The scientific principles described in this paper regarding waiver of an *in vivo* requirement also apply to consideration of *in vitro* data under that regulation. In such circumstances, an *in vivo* data requirement is not waived, but rather, USFDA has determined that *in vitro* data is the most accurate, sensitive, and reproducible for a product, as required under 21 CFR 320.24(a). Nonetheless, for ease of the reader, in this paper we will refer to either the decision to waive an *in vivo* BE requirement under 21 CFR 320.22 or the decision to accept *in vitro* BE data in accordance with 21 CFR 320.24(a) as a "biowaiver".

tablets, matrix tablets, or coated tablets, or b) multiple unit dosage forms comprising a plurality of units, such as pellets or beads each containing release-controlling excipients in e.g., a gelatine capsule or compressed in a tablet.

Other formulations such as depot injections and transdermal drug delivery systems are outside the scope of this paper.

RESULTS

As for immediate release products, demonstrated *in vivo* BE with the most sensitive strength(s) within a product series is the prerequisite for granting biowaivers for additional strengths of modified release products. Identifying the most sensitive strength(s) to be used *in vivo* is basically dependent on the pharmacokinetics of the drug in the modified release dosage form. The waiver thus depends on the degree of similarity of the manufacturing process, the qualitative and quantitative composition of the different strengths of the test drug product and the *in vitro* dissolution behaviour of the different strengths of the test drug product (4). Additional factors that may affect bioavailability and the requirements for obtaining a waiver specific to modified release dosage forms include the release mechanism, product shape and whether it constitutes a multiple unit or single unit dosage form. Hence, identifying the most sensitive strength(s) for investigating *in vivo* BE may in certain cases be challenging.

BE Studies for Prolonged and Delayed Release Products

The release mechanism of a modified release product is the most important factor that determines the pharmacokinetic profile and bioavailability of the drug as well as the design and number of BE studies required by the BEWGG participants (Table 1). For most jurisdictions, the characteristics of the modified release formulation (i.e. prolonged or delayed) determine whether a fed study is required or recommended in addition to a fasted study to rule out the possibility of dose dumping in the presence of food. For prolonged release products, all participants require or recommend single dose fasted and fed studies. Additionally, a multiple dose study is required for Australia, Colombia, the European Union (EU), New Zealand, Singapore, Switzerland and WHO, unless the ratio of area under the curve in the posology interval to area under the curve to infinity ($AUC_{0-\tau}/AUC_{0-\infty}$) is more than 90% in the single dose study conducted with the highest strength, signifying a low risk of plasma drug accumulation upon repeated dosing (12). If the multiple dose study is waived, the shape of the pharmacokinetic profiles for the single dose studies are compared by means of partial AUCs with cut-offs based on the shape of the pharmacokinetic profile of the comparator (reference) product. However, this requirement is not defined in the WHO guideline (23). In Israel, the multiple dose study is optional (13), however, Israeli guidelines are currently under revision.

Additional BE demonstration at steady state is not required for delayed release products in any jurisdiction given that the formulations only postpone the onset of release resulting in certain lag times in dissolution and absorption. Once released, absorption and elimination of the drug are similar to those of an immediate release formulation. Hence, only single dose fasted and fed studies are required or recommended except in Republic of Korea, where the demonstration of BE in the fed state is currently not required. Interestingly, Brazil requires only one study for delayed release products, i.e. either fasted or fed, if the comparator product is to be taken only in the fasted or only in the fed state, respectively.

Single and Multiple Unit Formulations

The distinction between single unit and multiple unit dosage forms has been introduced by some jurisdictions to minimise the risk of falsely concluding BE in the case of extrapolation within a modified release product series. Different requirements are applied to these two types of products because in the case of multiple unit formulations, different strengths are generated by simply changing the quantity of the units, e.g. pellets or beads, whereas different strengths of a single unit (monolithic) dosage form may have substantially different sizes and/or shapes. Consequently, the risk of bio-inequivalence within a series of strengths of a multiple unit formulation is considered lower compared to that for single unit formulations, and this influences the biowaiver criteria.

While Australia, the EU, New Zealand, Singapore, South Africa and Switzerland included this concept in their regulatory guidelines, Argentina, Brazil, Canada, Colombia, Israel, Japan, Mexico, Republic of Korea, Taiwan, the USA and WHO do not draw this distinction (Table 2). Consequently, this second group generally requires single dose fasted and fed studies only with the highest or most sensitive strength, if all the strengths have the same release mechanism and the conditions regarding composition and *in vitro* dissolution is met, whereas in the first group those

Table 1. BE Studies for Modified Release Products (Y: yes; N: no)

	Argentina	Australia	Brazil	Canada	Colombia	European Union	Israel	Japan	Mexico	New Zealand	Republic of Korea	Singapore	South Africa	Switzerland	Taiwan	USA[5]	WHO
Prolonged Release																	
Single dose fasted	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Single dose fed	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Multiple dose	N	Y[1]	N	N	Y[4]	Y[1]	Y[3]	N	N	Y[1]	N	Y[1]	N	Y[1]	N	N	Y[4]
Delayed Release																	
Single dose fasted	Y	Y	Y[2]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Single dose fed	Y	Y	Y[2]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y

[1]Can be waived in case of low extent of accumulation, but partial AUCs would be requested in the single dose study to assess the shape of the concentration-time curve. [2]Can be waived depending on the method of administration. [3]Optional. [4]Multiple dose studies may be considered for extended-release dosage forms with a tendency to accumulate. [5]These are "recommendations", but applicants can use alternative approaches if the alternative approach complies with applicable statutes and regulations.

Table 2. Distinction between Single and Multiple Unit Formulations (Y: yes; N: no)

	Argentina	Australia	Brazil	Canada	Colombia	European Union	Israel	Japan	Mexico	New Zealand	Republic of Korea	Singapore	South Africa	Switzerland	Taiwan	USA	WHO
Single vs. Multiple Unit Formulations	N	Y	N	N	N	Y	N	N	N	Y	N	Y	Y	Y	N	N	N

requirements apply only to multiple unit dosage forms with delayed release or prolonged release without significant accumulation. In the case of significant accumulation, multiple dose studies are also required, except in South Africa. In the case of single unit dosage forms, the first group requires additional BE studies as described below.

Nevertheless, the USA has issued several product-specific guidances for generic drug development in which there are deviations from the general recommendations (28). For example, fasted studies with the highest and the lowest strengths and a fed study with the lowest strength alone are recommended for the prolonged release formulation of nisoldipine due to the lack of proportionality between strengths of the comparator product, and for safety reasons (29). In contrast, for quetiapine fumarate prolonged release tablets, fasted and fed studies are recommended for an intermediate strength in the proposed product range due to safety concerns (30). The EU also provides product-specific BE guidelines (31) and paliperidone prolonged release tablet is an EU example where unique recommendations are made due to product-specific considerations, including safety and tolerability in healthy subjects. In this example, single dose fasted studies should be investigated at the highest and lowest strengths, while the single dose fed study may involve a lower strength if the release mechanism is the same as the reference. This guideline further stipulates the multiple dose fasted study to be conducted with an intermediate strength (32).

For single unit prolonged and delayed release products, the following strengths must be investigated in Australia, the EU, New Zealand, Singapore, South Africa and Switzerland:

- If the comparator product is recommended to be administered under fasted conditions or irrespective of food, BE must be demonstrated for all strengths following a single dose in fasted state. However, there is the potential to use a bracketing approach with the lowest and highest strengths as these strengths represent the “extremes” of the product series. The single dose fed study should be conducted at the highest or most sensitive strength and the multiple dose fasted study (prolonged release products only) should be performed with the highest strength (unless accumulation is low). For the additional strengths, biowaivers of the single dose fed study and the multiple dose fasted study may be considered based on the general waiver criteria outlined for immediate release products if the difference strengths have the same shape (4).
- Similarly, if the comparator product is recommended to be administered under fed

conditions, BE must be demonstrated for all strengths (or with a bracketing approach) in a single dose fed study. A single dose fasted study should be conducted at the highest or most sensitive strength and the multiple dose fed study (prolonged release products only) should be conducted at the highest strength (unless accumulation is low). For the additional strengths, biowaivers of the single dose fasted study and multiple dose fed study may be considered based on the general waiver criteria for immediate release products if the difference strengths have the same shape (4).

In some cases, the highest strength (even as a single dose) cannot be investigated in healthy subjects for ethical and/or tolerability reasons. It is then generally acceptable to investigate BE in healthy subjects at a lower dose. For those jurisdictions that require demonstration of BE at steady state, and where the highest strength cannot be administered to healthy subjects, BE should be demonstrated at steady state (i.e. in a multiple dose study) with the highest strength in patients who require such high doses by means of direct switching (i.e. using an active wash-out instead of a passive wash-out). This approach provides data on the highest strength at least at steady state in patients, and data on the highest tolerable strength in healthy volunteers after a single dose.

In Australia, Brazil, Canada, Colombia, the EU, Japan, New Zealand, Singapore, South Africa, Switzerland, Taiwan and the USA, the administration of supra-therapeutic doses may be accepted in cases of low sensitivity of the bioanalytical method. This may also be accepted by WHO, but it would have to be clearly demonstrated that there are no methods with greater sensitivity.

Pharmacokinetics Aspects

Narrow Therapeutic Index/Range (NTI/NTR)

As for immediate release products, possible biowaivers for additional strengths of modified release products are not affected due to the NTI status of the drug substance and may be considered in all jurisdictions (4). However, in Japan, a BE study is required for a level C change (difference) between strengths involving NTI drugs in both delayed release products and prolonged release products (14) (see Table 3 and Table 4).

Pharmacokinetic linearity

All regulators/agencies take linearity of the pharmacokinetics into account in order to specify the appropriate strength/s (most sensitive) to be used in the BE study. The criteria for linearity applied to immediate release products by the different members of the IPRP BEWGG were previously described (4).

In the case of prolonged release products, dose-proportional pharmacokinetics is expected and/or observed more frequently than for immediate release products because saturation of the first pass metabolism is reduced due to the slower rate of absorption. Similarly, the slow release rate also diminishes non-linearity arising from either low solubility or saturation of uptake transporters. Consequently, the requirement of linear pharmacokinetics is less relevant for prolonged release products. However, EMA's guideline particularly highlights the formulation impact with regard to linearity by stating that the pharmacokinetic linearity of the originator modified release product should be considered rather than that of the drug substance, because the solubility of the drug substance generally plays a minor role since the formulation itself determines the biopharmaceutic characteristics (12).

Manufacturing and Formulation Criteria

The manufacturing and formulation criteria refer mainly to specific formulation characteristics of a modified release product series and recommendations regarding *in vitro* dissolution.

Manufacturing

In all jurisdictions apart from Canada, the manufacturing process should be the same for all strengths including the strength investigated in the BE study. While the requirements for Canada and Mexico have not been specified in their respective guidance, a case-by-case risk assessment is conducted by Canada and Mexico if there are differences.

Without further BE data to support differences, the manufacturing site is required to be same for all strengths in Argentina, Brazil, Canada, Colombia, Mexico, New Zealand, Republic of Korea, Singapore and Taiwan. Australia, the EU, Israel, Japan, Switzerland, the USA and WHO do not address this issue in their respective guidelines, but Australia, the EU, Mexico and Switzerland allow different manufacturing sites within the range of strengths if the same manufacturing process is applied. The same can be deduced from the WHO guideline based on the requirements for immediate release products (23). South Africa additionally requires equivalence to be demonstrated between the different sites.

Release Mechanism

In all jurisdictions, the same release mechanism is required for all strengths of both prolonged and delayed release products; however, Canada would

conduct a risk assessment if there was a change in the ratio of excipients that would the affect release.

Qualitative Composition

Changes in flavours, colours and non-functional coatings may be accepted by all IPRP BEWGG members.

Quantitative Composition

All participating regulators/agencies except Argentina, Mexico and WHO have a general reference for modified release product requirements described in the same BE guidelines that apply to immediate release products, and as described in the previous publication (4). However, Brazil accepts differences in the quantitative composition (weight/weight) of a maximum of 5% of release-controlling excipients across the range of strengths in the case of NTI drugs. In contrast, Argentina and WHO provide a specific section for dose-proportionality for prolonged and delayed release formulations in their guidelines (23, 27).

The quantitative proportionality of delayed release products needs particular consideration in terms of the gastro-resistant coating. Accordingly, Argentina, Australia, Canada, Colombia, the EU, New Zealand, Singapore, South Africa, Switzerland and WHO require similarity (proportionality) of the coating with respect to the surface area rather than to core weight, i.e. the coating layer should be the same in mg/cm² surface area. The same applies for prolonged release products with release controlling excipients in the coating layer. Brazil, Israel, Japan, Mexico, Republic of Korea and Taiwan do not have requirements regarding the surface area of coating. USA does not have requirements, but in general, core weight is taken into account and surface area may also be factored into the evaluation.

Shape

The size and shape of a tablet may affect transit of the product through the pylorus and should be considered during formulation development. Furthermore, the shape at the edges may have an impact on the resistance to dissolution and consequently on the absorption of the drug substance.

In multiple unit formulations, the single pellets or beads are relatively small and are expected to have uniform shape. In these cases, the shape of the finished product (tablet or capsule) is not considered to have a significant bearing on the pharmacokinetic profile as the pellets or beads rapidly disperse in the stomach after oral dosing.

In the case of single unit formulations, there are generally two approaches concerning whether shape should be allowed to differ within the product series. Australia, Canada, the EU, Mexico, New Zealand, Singapore and Switzerland expect all strengths to have the same shape, otherwise different shapes may affect the selection of the most sensitive strength to be investigated *in vivo*. Mexico assesses differences in shape case-by-case. Different shapes for prolonged release and delayed release products may be accepted in Australia, Canada, the EU, New Zealand, Singapore and Switzerland if BE studies on the two 'extremes' are conducted. On the other hand, Argentina, Brazil, Colombia, Israel, South Africa, Republic of Korea, Taiwan, the USA and WHO allow differences in shape within the product series. In addition, the USA has specifically addressed the issue of the shape in a Guidance for Industry for comparative evaluation of test to comparator (33). Among other aspects, the document stipulates that the shape of the tablet requires particular attention for biowaivers within a modified release product series as the resistance to dissolution in acidic pH is lower at the coating edges/borders and different shapes may affect angles, and consequently resistance towards acidic conditions.

In Japan, the same size and shape for all strengths of prolonged release products is required, whereas the shape may differ for delayed release products. Additionally, a BE study is required for a diameter change of enteric-coated multiple units from less than 4 mm to more than 4 mm or *vice versa*, as this is considered a level E change in Japan (see Table 3 and Table 4).

Bracketing

If the regular proportionality-based waiver criteria are not met, Australia, Canada, Colombia, the EU, New Zealand, Singapore, South Africa, Switzerland and WHO (although not specified for modified release products in the WHO guideline) accept a bracketing approach, which is considered to cover deviations from proportional composition and/or non-similar dissolution profiles, or when shape differences and consequent differences in release rate are evident. However, release-controlling excipients, mechanisms and coatings are expected to be the same. Accordingly, conducting *in vivo* BE studies with the disparate strengths, e.g. highest and lowest or other "extremes", should cover remaining differences within the product series. This implies that the single dose studies in fasted and fed states and the multiple dose study, if needed, should be conducted at the extremes of the brackets. The bracketing approach is either not specified in the guidelines or not accepted in other jurisdictions.

Table 3. Levels of Formulation Change for Modified Release Products in Japan

Function of excipient and component	Difference in excipient content compared to BE study strength (% *w/w*) B	C	D	E
Part: Core				
Disintegrating agents				
Starch	≦3.0	≦6.0	≦9.0	>9.0
Others	≦1.0	≦2.0	≦3.0	>3.0
Binders	≦0.50	≦1.0	≦1.5	>1.5
Lubricants, polishers				
Stearate salts	≦0.25	≦0.50	≦0.75	>0.75
Others	≦1.0	≦2.0	≦3.0	>3.0
Fluidizing agents				
Talc	≦1.0	≦2.0	≦3.0	>3.0
Others	≦0.10	≦0.20	≦0.30	>0.30
Diluting agents	≦5.0	≦10	≦15	>15
Others (preservatives, sweeteners, stabilizers, etc.)[1]	≦1.0	≦2.0	≦3.0	>3.0
Sum of absolute values of difference of content (%) of changed components	≦5.0	≦10	≦15	>15
Part: Film coating[2]				
Sum of absolute values of difference of content (%) of changed components in film coating layer[1]	≦5.0	≦10	≦15	>15
Rate of change (%) of film coating weight/cm^2 of surface area of core[2]	≦10	≦20	≦30	>30
Part: Sugar coating				
Sum of absolute values of difference of content (%) of changed components in sugar coating layer	≦5.0	≦10	≦15	>15
Rate of change (%) of sugar coating weight/cm^2 of surface area of core[3]	≦10	≦20	≦30	>30

[1]Levels of change for excipients categorized as "Others" are determined by separate calculations of the differences in content (%) regarding the respective use. Components for which the composition is described as "trace use" can be ignored. [2]Most coatings are included (waterproof coating, undercoating, enteric coating, and controlled release coating) except sugar coating. [3]The shape of the formulation influences the calculation of the surface area of the core. When it is not possible to calculate the surface area of the shape, the shape of the core is assumed a sphere, and the specific gravity of the core does not change with the formulation.

Table 4. Levels of Formulation Changes and Required Tests for Modified Release Products in Japan

Level	Enteric-coated / prolonged release	Therapeutic range	Poorly soluble[1] / soluble	Data required
B	Enteric-coated[2] / prolonged release			Multiple dissolution test conditions
C	Enteric-coated[2]	Non-narrow	Soluble	Multiple dissolution test conditions
			Poorly soluble	Human bioequivalence study
		Narrow	Soluble	Human bioequivalence study
			Poorly soluble	Human bioequivalence study
	Prolonged release	Non-narrow		Multiple dissolution test conditions
		Narrow		Human bioequivalence study
D				Human bioequivalence study
E				Human bioequivalence study

[1]A poorly soluble drug is a drug product for which, when the test is performed at 50 rpm, the average dissolution rate of the comparator product does not reach 85% within the designated test time in any of the multi-dissolution media not containing surfactants. [2]If the change of the diameter of the units having substantial enteric function is from less than 4 mm to 4 mm or more, or *vice versa*, the formulation change of the level is E.

Regulations for Level of Formulation Change in Japan

In Japan, the biowaiver requirements for additional strengths depend in part on the level of formulation change (difference) between the strengths (Table 3). Although the concept is the same as for immediate release products, i.e., that a small formulation change should not significantly alter bioavailability (4), there are some differences in the requirements for modified release products (Table 4).

As for immediate release products, the levels of change should be determined by calculating the differences in content of each excipient based on the "function of the excipient and component" as illustrated in Table 3. It is important to note that the

overall level of change, i.e. B, C, D or E, in case of differences between strengths in multiple excipients is the highest level assigned to the individual differences and the sum of the absolute differences (see Table 3). For example, if there are differences between strengths in the content (%) of a disintegrating agent (e.g. 5% difference in starch) and a diluting agent (e.g. 1% difference), the levels of formulation change for the disintegrating agent (5%), the diluting agent (1%) and the sum of the absolute differences of these components (6%) are level C, level B and level C, respectively, according to Table 3. Since C is classified as higher level of change than B, the overall level of change is C.

in Vitro Dissolution Aspects

Comparative *in vitro* dissolution data according to pharmacopoeial standards are required in all jurisdictions for a biowaiver for additional strengths to be considered. The requirements include the products to be compared, the dissolution media and apparatus to be used and the comparison of dissolution profiles.

Products to be Compared

Comparison of the non-study strengths with the test product biobatches used in the *in vivo* study/studies are expected in all jurisdictions. The USA requires additional comparisons with the comparator product.

Dissolution Media and Apparatus

For prolonged release formulations, product-specific discriminative dissolution methods are expected to be developed that can be used for all strengths for which a biowaiver is needed. This method should ideally be able to indicate deviations in the biopharmaceutic performance not only for the purpose of batch release but also between strengths. Generally, the product-specific method is also considered essential for supporting additional strength biowaivers in most jurisdictions, since the dissolution of modified release products may be rather limited with simple aqueous multimedia testing (pH 1.2, 4.5 and 6.8). Of note, the latter has been implemented to be used without surfactants as a kind of worst-case scenario, though initially installed in the framework of BCS-based biowaivers.

Some jurisdictions (Australia, the EU, New Zealand, Singapore, South Africa and Switzerland) require multimedia testing as an additional comparative step, similar to immediate release products, i.e. in simple aqueous solutions without any surfactants, which could lead to relatively low dissolution results due to the complexity of formulations (Table 5). In Taiwan, dissolution testing should be conducted using at least three pH buffers that mimic fluids in the gastrointestinal tract. If the products cannot be completely dissolved in the tested buffer, additional dissolution data with surfactant is required. In Australia, justification to waive multimedia testing may be accepted in certain cases, e.g. with compressed microspheres. In the case of Argentina, Colombia and WHO, three buffers without surfactants in the physiological range from pH 1.2 to 7.5 and the QC medium should be used. However, for multiple unit formulations and for osmotic pumps, the QC medium is considered sufficient for Colombia, South Africa and WHO. In Mexico, only the QC medium is required. For prolonged release products, Japan and Republic of Korea require dissolution in three pH buffers using 50 rpm in the paddle apparatus (pH 1.2, (3.0-5.0) and (6.8-7.5) in Japan; pH 1.2, (4.0 or 4.5), 6.8 and water in Republic of Korea). In addition, Japan mandates water and pH 6.8 to 7.5 with polysorbate 80 (1.0% w/v) using 50 rpm in the paddle apparatus. Furthermore, different conditions of agitation (100 rpm and 200 rpm) and other dissolution apparatuses, i.e. basket or basket-rack assembly are required (34). Basket-rack assembly is an apparatus for the disintegration test, but in this situation, it is used to evaluate the equivalency of dissolution behaviour between different strengths. On the other hand, Republic of Korea requires a basket method at 100 rpm at pH 6.8. When the dissolution of pH 6.8 at 50 rpm does not reach ≥85% within the testing time specified, surfactants such as polysorbate 80 or sodium lauryl sulfate can be added or the QC method could be applied. There are some differences between the two countries and the differences are summarized below (Table 6). Singapore considers this topic to be product-specific and refers to the comparator product dissolution testing method. The USA has a database outlining the dissolution method for drug products (35), along with certain product-specific guidelines. In addition, the USA requires *in vitro* dissolution data with the comparator employing the QC method, along with multi-media dissolution.

For delayed release dosage forms, Australia, the EU, New Zealand, and Switzerland require *in vitro* dissolution for 2 hours at pH 1.2 followed by 45 minutes at pH 6.8 plus 2 hours at pH 4.5, followed again by 45 minutes at pH 6.8. WHO describes the first conditions as an example of a QC method (23). Canada generally requires testing for a minimum of 1 hour at pH 1.2 followed by additional testing at an alkaline pH where the delayed release polymer is soluble, until complete dissolution or a plateau is achieved; however, the

Table 5. Dissolution Media for Comparative Dissolution Studies for Additional Strength Biowaivers for Each Participating Member Jurisdiction (Y: yes; N: no)

	Argentina	Australia	Brazil	Canada	Colombia	European Union	Israel	Japan	Mexico	New Zealand	Republic of Korea	Singapore	South Africa	Switzerland	Taiwan	USA	WHO
Prolonged release dosage forms																	
QC Medium	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Multimedia	Y	Y	N	Y	Y[1]	Y	Y	Y	N	Y	Y	Y	Y[1]	Y	Y	Y	Y[1]
Delayed release dosage forms																	
QC Medium	Y	Y	Y	Y	Y[2]	Y	Y	N[3]	Y	Y	N[3]	Y	Y	Y	Y	Y	Y
Acidic Pre-treatment	Y	Y	N	Y	N	Y	Y	N[3]	N	Y	N[3]	Y	Y	Y	Y	Y	Y
45 min at pH 4.5	N	Y	N	N[2]	N	Y	N	N[3]	N[2]	Y	N[3]	N	N	Y	N	N[4]	N
2 h at pH 4.5	N	Y	N	N[2]	N	Y	N	N[3]	N[2]	Y	N[3]	N	N	Y	N	N[4]	N
45 min at pH 6.8	Y[2]	Y	N	N	N	Y	Y	N[3]	N[2]	Y	N[3]	Y	Y	Y	Y	N[4]	Y

[1]Only for single unit formulations, not required for osmotic pumps or multiple unit formulations. [2]Duration not defined. [3]Multimedia testing (pH 1.2, 6.0 and 6.8) are required (see text above for details). [4]Duration may exceed the specified time of 45 minutes.

Table 6. The Differences of Dissolution Test between Japan and Republic of Korea for Prolonged Release Products

	Japan	Republic of Korea
50 rpm in the paddle apparatus	pH 1.2	pH 1.2
	pH 3.0 to 5.0[1]	pH 4.0 or 4.5
	pH 6.8 to 7.5[1]	pH 6.8
	water	water
	pH 6.8 to 7.5[1] with surfactant	pH 6.8 with surfactant[2]
	—	QC Method[2]
100 rpm in the paddle apparatus	pH 6.8 to 7.5[1]	—
200 rpm in the paddle apparatus	pH 6.8 to 7.5[1]	—
100 rpm in the basket method[3]	pH 6.8 to 7.5[1]	pH 6.8
200 rpm in the basket method[3]	pH 6.8 to 7.5[1]	—
30 strokes/min in the basket-rack assembly[3]	pH 6.8 to 7.5[1] with and without disk	—

[1] In the test solutions where the average dissolution of comparator product reaches 80% within 24 hours, the test solution where the dissolution is the slowest should be selected. When the average dissolution of the comparator product does not reach 80% within 24 hours in any of the test fluids, the test solution where the dissolution is fastest should be selected. [2] When dissolution at pH 6.8 and 50 rpm does not reach ≥85% within the testing time specified, surfactant can be added, or QC method could be applied. [3] Select either basket method or basket-rack assembly in Japan.

time profile may be altered depending on the *in vitro* behaviour of the comparator product. Singapore and Taiwan require 2 hours at pH 1.2 followed by 45 minutes in pH 6.8, but further testing in other media is not required. Argentina and Israel require 2 hours at pH 1.2 followed by dissolution at pH 6.8 (duration not defined). In Mexico, only the QC medium is required. In Japan and Republic of Korea, the delayed release products need to be investigated with multimedia testing (pH 1.2, 6.0 and 6.8 at paddle speed of 50 rpm). If the dissolution at pH 6.0 does not achieve ≥85% within the time (30 minutes in Japan, the testing time specified in Republic of Korea), an additional test at pH 6.0 using 100 rpm in the paddle apparatus shall be performed. In Japan, additional pH 6.0 at paddle speed of 50 rpm with low ion strength is required. The testing time is 2 hours at pH 1.2 and 6 hours in other test fluids. The test can be stopped at the time when the average dissolution of comparator product reaches 85%.

Comparison of Dissolution Profiles

Generally, one common essential requirement for a biowaiver is that the f_2 criterion (≥50) is met, which confirms dissolution profile similarity based on 12 units each of both the test and comparator products. When f_2 calculation is not applicable, Argentina, Brazil, Canada, Israel, Mexico and Taiwan allow other justified comparison tools to be used. If similarity is not demonstrated, without proper justification, an additional BE study may be requested on the appropriate strength by all jurisdictions.

Japan and Republic of Korea require two criteria to be met, i.e. the equivalence of the average (mean) dissolution rate and individual dissolution variability. For evaluation of the average dissolution rate, Japan and Republic of Korea accept two methods: either comparison of the average dissolution rate between the strengths at some appropriate time points or the f_2 calculation (14, 18). The following are examples regarding

evaluation of the average dissolution rate of delayed release products in these jurisdictions. Here, the reference strength refers to the generic drug product strength for which bioequivalence with the innovator product has been demonstrated, and the test strength is a different (non-study) strength with respect to the reference strength. When the average dissolution rate of the reference strength reaches 85% or more within 15 minutes, should similarly reach 85% or more within 15 minutes or be within that of the reference strength ±10% at 15 minutes to be accepted (Figure 1a). When the rate of dissolution reaches 85% between 15 and 30 minutes, the average dissolution rate of the test strength should be within that of the reference strength ±10% at two time points corresponding to when the average dissolution rates of the reference strength are around 60% and 85%, or the f2 value should be at least 50. In this case, the testing time points for f2 value are 15, 30, and 45 minutes according to the guideline, but f_2 calculation is also required with three testing time points before 30 minutes (e.g. 10, 20 and 30 minutes) in the generic development in Japan. On the other hand, when the average dissolution rate of the reference strength reaches 85% or more after 30 minutes and a pre-specified time point, the average dissolution rate of the test strength should be within that of the reference strength ±10% at two time points corresponding to when the average dissolution rates of the reference strength are around 40% and 85%, or the f_2 value should be at least 50. In this case, the testing time points for f_2 value are specified at Ta/4, 2Ta/4, 3Ta/4 and Ta, where Ta is the point at which the average dissolution of the reference strength reaches approximately 85% (Figure 1b). Regarding the individual dissolution variability, the individual dissolution rate at the last point where the average dissolution of the test product is compared to that of the comparator product must meet the criteria. For example, when the average dissolution rate of comparator products reaches 85% in the delayed release products, the vessel number of test products with the dissolution rate exceeding 15% and 25% compared to the average dissolution rate of the test products should be “1 or less” and 0, respectively.

DISCUSSION

This review revealed that the requirements to waive additional strengths for modified release products include and exceed those of immediate release products. Formulation aspects of modified release products are more complex than those of immediate release products and hence require closer scrutiny by regulators when authorizing biowaivers, especially since modified release formulation characteristics influence the pharmacokinetic profile to a greater extent (e.g. delaying and/or prolonging the release and subsequent absorption). Consequently, a more careful review is required to minimise the possibility of bio-inequivalence between strengths in a product series. While this seems obvious and careful considerations have been adopted, there are a variety of perspectives and proposals as to how to ensure BE for a product series while avoiding redundant and/or unnecessary *in vivo* studies.

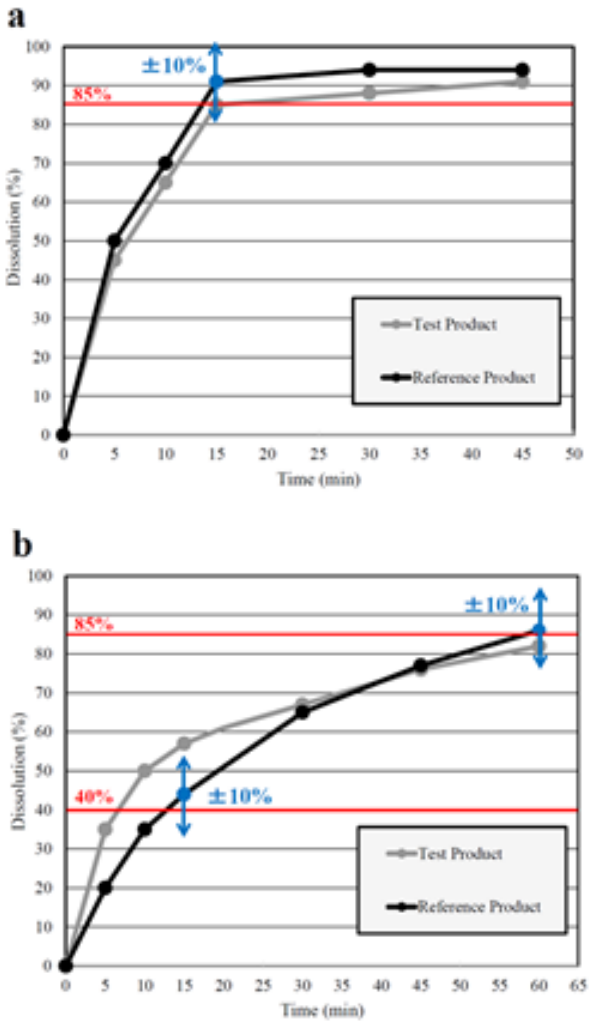

Figure 1. Examples for Evaluating Average Dissolution Rate in Japan and Republic of Korea. (a) When the average dissolution rate of reference strength reaches 85% or more within 15 minutes. (b) When the average dissolution rate of the reference strength reaches 85% or more between 30 minutes and the testing time specified. This case meets the f2 criteria but fails the average dissolution rate criteria.

The most important commonality observed in this survey was that all jurisdictions require both single dose fasted and single dose fed studies for prolonged release products. There was also a high

degree of convergence in the case of delayed release products – all regulators/agencies require single dose fasted and single dose fed studies except Republic of Korea, which does not require a fed study, and Brazil, which requires both studies only if the product can be taken irrespective of meals, but requires only one of them if the product is to be taken only in the fasted or only in the fed state according to the information described in the package insert. On the other hand, the most important differences between the participants were observed regarding the need for multiple dose studies with prolonged release products (with or without consideration for the extent of accumulation after a dosing interval). Half of the regulators/agencies do not require multiple dose studies. Among the other half, all agree to waive the multiple dose studies if the extent of drug accumulation is likely to be low, but most of these jurisdictions require partial AUCs to compare the shape of the concentration-time profiles in the single dose studies, since $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and C_{max} are not considered sufficient to ensure a similar shape of the curve. The EU has defined accumulation as $AUC_{(0\text{-}\tau)}$ after the first dose covering less than 90% of mean $AUC_{(0\text{-}\infty)}$ (13) and this definition has been adopted by several other regulators (Australia, Colombia, New Zealand, Singapore, South Africa, Switzerland and WHO). However, the 90% threshold has been questioned for being arbitrary and too strict (36).

Overall, the general waiver criteria regarding PK linearity, manufacturing and composition were similar to those for immediate release products as outlined in the previous publication (4). In addition, there are other aspects specific for modified release formulations such as shape, the discrimination between single and multiple unit formulations and the use of different dissolution media that are in part handled differently by the various jurisdictions.

The shape of the tablet may differ within a larger series of strengths simply due to technology reasons and may require additional considerations in terms of BE since it may have an impact on *in vivo* performance. It was also interesting to observe that nearly a third of the jurisdictions define different requirements for single unit and multiple unit formulations, while the rest take a more general approach by focussing on the release mechanism and compositional features of the product series. Nevertheless, it is recognized that if BE has been established with the most sensitive strength of a multiple unit formulation, varying the quantity of identical pellets or beads to obtain different strengths would be unlikely to result in bio-inequivalence with regard to the additional strengths. In contrast, additional strength biowaivers are generally handled less flexibly with single unit formulations in most jurisdictions.

In terms of comparative *in vitro* dissolution experiments between the reference strength and the test strengths, more importance is placed on developing experimental conditions which are tailored for the particular modified release product and hopefully proven to be discriminative (QC test). However, some jurisdictions additionally require multimedia testing without any surfactants, as usually employed for biowaivers of strengths for immediate release products. Using such simple aqueous media may result in rather low drug release from the more complex modified release products, and the interpretation of the results might be considered difficult or almost meaningless in some cases. Nevertheless, additional investigations may raise a red flag in case of possible differences between the strengths in a product series undetected in QC tests alone. Of note, some jurisdictions allow multimedia testing with the addition of surfactants. While adding surfactant to otherwise simple aqueous solutions would certainly improve dissolution, this may cast doubts on the outcome of such experiments unless additional validation experiments have been performed demonstrating discriminative abilities of such media. Otherwise, interpretation of those *in vitro* dissolution results may be considered highly questionable.

Some jurisdictions consider that evidence of BE cannot be extrapolated to the additional strengths of single unit formulations based on the similarity of the dissolution profiles, unless *in vitro-in vivo* correlations (IVIVC) have been established. This is because there have been cases when similarity in dissolution profiles between different strengths did not ensure BE for all strengths in the same products series, e.g. bupropion (37) and valproic acid (38). Of note, the USA does not currently accept IVIVC data as a basis of approval for generics; however, it can potentially be used as supportive evidence. As IVIVC are rarely submitted in support of generic product applications and *in vivo* testing of all strengths is not desirable, a bracketing approach has been proposed in these jurisdictions for either one of the single dose studies (fasted or fed according to the method of administration of the comparator product), if the biowaiver requirements are fulfilled. Bracketing may also be considered for all types of required studies if not all the biowaiver requirements are fulfilled, and if the extremes of the differences can be identified in the product series. However, the bracketing approach may be limited, e.g. in case of safety concerns with the

highest strength. In such a case, Australia, Canada, Singapore, Switzerland, Taiwan, the USA and WHO either accept a BE study using the highest strength in patients or a study with a tolerable lower strength in healthy subjects, on the proviso that a justification for the proposed approach is included. However, the USA would question the acceptability of the data, if a surfactant is added without justification.

Japan has relatively complex requirements regarding the quantitative composition of different strengths, but the levels of formulation change (difference) are similar to those for immediate release formulations. However, the requirements for modified release products regarding *in vitro* dissolution conditions and BE studies differ depending on the level of formulation change. Accordingly, an additional strength biowaiver is only possible up to Level C for enteric-coated and prolonged release products but up to Level D for immediate release products.

Overall, the harmonization for modified release products is somewhat more challenging compared to immediate release products. Nevertheless, harmonization of the various regulations concerning the submission of applications for modified release products is highly desirable in order to avoid unnecessary studies from a scientific point of view and facilitate greater access of these medicines to patients.

CONCLUSION

Most jurisdictions consider the extrapolation of BE results obtained with one (most sensitive) strength of a product series not as straightforward for modified release products as for immediate release products. Therefore, the number of studies required to demonstrate BE also differs between jurisdictions, in particular with regard to the requirement for a multiple dose study and the need to minimally demonstrate BE with the extremes of the product series (bracketing approach) in one of the single dose studies. However, there is a general consensus that modified release products should demonstrate BE not only in the fasted but also the fed state. Although harmonization seems realistic for certain aspects, there are fundamental differences between jurisdictions. As for immediate release products, the requirements regarding the quantitative composition of different strengths vary significantly. Furthermore, the design difference between single and multiple unit dosage forms in some jurisdictions presents another challenge. Interestingly, differences in terms of *in vitro* dissolution requirements are mostly related to possible additional comparative investigations rather than product-specific (QC) methods.

As with the requirements for immediate release products, companies preparing generic product dossiers in different countries should understand these differences in order to comply with the strictest requirements, in particular where a multiple dose study is required. Finally, we conclude that the requirements for additional strength biowaivers for modified release solid oral dosage forms would be a good choice as a topic for future harmonisation in the International Council for Harmonisation (ICH).

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