A Survey of the Regulatory Requirements for the Waiver of *In Vivo* Bioequivalence Studies of Generic Products in Certain Dosage Forms by Participating Regulators and Organisations of the International Pharmaceutical Regulators Programme

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ABSTRACT -- The requirements to waive *in vivo* bioequivalence studies for immediate release solid oral dosage forms based on the Biopharmaceutics Classifications System (BCS) are well known, and biowaivers[a] for other types of oral dosage forms based on pre-defined criteria may also be acceptable. Similarly, biowaivers for dosage forms such as injectable products may also be allowed if certain criteria are met. The current paper summarises the biowaiver requirements for oral solutions and suspensions, soft gelatin capsules and injectable products (intravenous injections, subcutaneous and intramuscular injections, emulsions for injection and micellar solutions for injection) among the participants of the Bioequivalence Working Group for Generics (BEWGG) of the International Pharmaceutical Regulators Programme (IPRP). A review of the requirements indicated that there was a trend towards convergence when the dosage form became less complex; however, the most common approach used by each of the jurisdictions was a case-by-case approach given that most jurisdictions do not have well defined guidelines to support all possible scenarios. Even in the simplest case of intravenous solutions, the acceptability of qualitative changes in excipients differ between the IPRP members. Notwithstanding the differences, the dissemination of the information is a first step towards regulatory convergence regarding biowaivers for certain dosage forms and should be useful for pharmaceutical companies currently developing generic medicinal products for IPRP jurisdictions.

INTRODUCTION

Medicines regulatory authorities aim to address rising health care costs and promote access to medicines worldwide through review and approval of quality generic products that are interchangeable with the corresponding reference medicinal product.

[a] For the U.S. FDA, the term "biowaiver" refers to either the decision to waive an *in vivo* bioequivalence requirement under 21 CFR 320.22 or the decision to accept *in vitro* bioequivalence data in accordance with 21 CFR 320.24(a).

The International Generic Drug Regulators Programme (IGDRP) was created to promote collaboration and convergence among generic drug regulators in order to address the challenges posed by increasing workloads, globalisation and complexity of scientific issues. In 2018 the IGDRP merged with the International Pharmaceutical Regulators Forum (IPRF) to form the International Pharmaceutical Regulators Programme (IPRP), which allows its members to exchange information on issues of mutual interest, promote cooperation, maximise synergies and avoid duplication of effort, create a regulatory hub for pharmaceutical manufacturers of all medicinal products and enable linkages with other initiatives to simplify the numerous forms of international regulatory collaboration (1).

The Bioequivalence Working Group for Generics (BEWGG), in particular, aims to promote greater collaboration, regulatory convergence and potential mutual reliance on respective bioequivalence assessments in the longer term. This group is composed of the following 15 regulators/organisations: 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, EU), Health Canada (HC), the Health Sciences Authority (HSA, Singapore), Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA, Colombia), South African Health Products Regulatory Authority (SAHPRA), Medsafe (New Zealand), the Ministry of Food and Drug Safety (MFDS, Republic of Korea), the Pharmaceuticals and Medical Devices Agency (PMDA, Japan), Swissmedic (Switzerland), the Taiwan Food and Drug Administration (TFDA), Therapeutic Goods Administration (TGA, Australia) and the United States Food and Drug Administration (U.S. FDA), as well as one observer from the World Health Organization (WHO).

The requirements to waive *in vivo* bioequivalence studies for immediate release (IR) solid oral dosage forms based on the Biopharmaceutics Classification System (i.e., BCS biowaivers) in IPRP jurisdictions have been previously described (2) and are now harmonised by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (3). In addition, waivers of *in vivo* bioequivalence studies may be applied to additional strengths of IR solid oral dosage forms with respect to the strength for which *in vivo* bioequivalence has been shown (4). Furthermore, waivers of *in vivo* bioequivalence studies may also apply to certain dosage forms irrespective of the BCS waiver criteria. For example, *in vivo* bioequivalence studies may be waived for some orally administered and systemically-acting dosage forms (e.g., oral solutions, oral suspensions and soft gelatin capsules), non-oral systemically acting dosage forms (e.g., intravenous injections, subcutaneous and intramuscular injections, emulsions for injection and micellar solutions for injection) and locally-acting dosage forms (e.g., otic and ophthalmic solutions, cutaneous/topical products, vaginal pessaries, enemas, nasal and orally inhaled products for pulmonary action). In such cases, waivers of *in vivo* bioequivalence studies could be based on *in vitro* data alone.

For the purpose of this paper, *in vivo* bioequivalence investigations refer not only to pharmacokinetic studies, but also to therapeutic equivalence studies with pharmacodynamic or clinical endpoints, although in some jurisdictions the term “bioequivalence studies” refers only to pharmacokinetic studies.

The objective of this paper is to summarise the requirements to waive the *in vivo* demonstration of bioequivalence for the abovementioned oral and injectable dosage forms among the regulators and organisations that participate actively in the IPRP BEWGG. The waiver requirements for the remaining dosage forms will be summarised in separate papers. The sharing of this information is a first step towards regulatory convergence in this area.

MATERIALS AND METHODS

The IPRP BEWGG conducted a survey of the requirements to demonstrate bioequivalence in different types of immediate release oral and injectable dosage forms: oral solutions, oral suspensions, soft gelatin capsules, intravenous injections, subcutaneous and intramuscular injections, emulsions for injection, micellar solutions for injection and powders for reconstitution.

This information was obtained from the participating regulatory authorities and organisations in the BEWGG and is based on their respective regulatory guidance documents and policies (5-23).

RESULTS

Oral products

Oral solutions. *In vivo* bioequivalence studies for

oral solutions can be waived in all jurisdictions except Japan (Table 1), where waivers for aqueous solutions are not accepted and current Japanese guidelines do not contain information regarding waivers for oral solutions. In the case of oily solutions, the situation is more diverse. Based on current regulations, Taiwan and the USA would accept a waiver for oily oral solutions as they do not differentiate oily solutions from other solutions; however, waiver requirements for oily solutions are not described in current guidance documents from Argentina, Australia, Canada, Colombia, the European Union (EU), New Zealand, Mexico, Singapore, South Africa, Switzerland and the WHO. Regardless, these members have indicated that they would consider the acceptability of a waiver based on the physicochemical properties of the dosage form. For example, Argentina, Australia, Canada, the EU, New Zealand, South Africa and Switzerland would require that the type of oil used in the vehicle for the proposed generic be the same as that in the reference product. On the contrary, Brazil and the Republic of Korea would not accept waivers for oily solutions.

For other types of oral solutions, a waiver from conducting *in vivo* bioequivalence studies would be considered acceptable based on the qualitative and quantitative differences in the non-medicinal ingredients / excipients in the formulation of the test product when compared to the reference product. Qualitative differences in excipients are acceptable in principle if the excipients are not considered to be critical (i.e., known not to affect the bioavailability of the active ingredient(s)). For example, qualitative and quantitative modifications in preservatives, viscosity agents, pH buffers, colorants, flavors, some sweeteners) could be permitted whereas qualitative similarity and remarkably close quantitative similarity would be expected for excipients that enhance absorption (e.g., polysorbate 80). In 2016, the EU published an online questions and answers (Q&A) document clarifying that the similarity of excipients in oral solutions should be assessed according to the requirements for BCS-based biowaivers (24). Colombia (12), Mexico and the WHO (20) also provided similar recommendations. The principles used by Colombia, the EU, Mexico and the WHO are also applied in Australia, Canada, New Zealand and Switzerland, where non-critical excipients can be modified for oral solutions containing BCS class I drugs, but not for oral solutions containing BCS class II, III and IV drugs where the excipients must be qualitatively the same and quantitatively similar. For example, the substitution of a co-solvent for another co-solvent cannot be justified by *in vitro* data showing a similar solubilising capacity of the new formulation/excipient mixture; as a result, an *in vivo* bioequivalence study would be required. While recommended criteria are described in Health Canada guidance documents, any difference beyond the described criteria should be scientifically justified and the potential impact on the safety and efficacy of the drug product should be discussed (6). Similarly, in the USA, the different amount of any excipient should be within US FDA inactive ingredients database limits and the new amounts should not be associated with safety or efficacy concerns (25).

For excipients that are considered critical because they are known to potentially affect the bioavailability of active ingredients by altering the gastrointestinal transit, permeability or stability of the active ingredients, Australia, Brazil, Canada, Colombia, the EU, New Zealand, the Republic of Korea, South Africa, Singapore, Switzerland, Taiwan and the WHO do not allow qualitatively changes, but permit minor quantitative changes in the formulation of the generic product when compared to the reference product. In the case of the USA and Argentina, critical excipients can be changed qualitatively and quantitatively within certain justified limits (25). The list of critical excipients is not exhaustive but includes surfactants (e.g., SLS, castor oil ethoxylate, polysorbate 80), sweeteners (e.g., sorbitol and mannitol), excipients that affect transporters (e.g., PEG-400), co-solvents and complexing agents (e.g., cyclodextrins). Each jurisdiction may have different criteria on the types of excipients that are considered critical and the quantitative differences allowed. For example, there are no defined criteria, or it is considered case-by-case in Argentina, Australia, Brazil, Colombia, the EU, New Zealand, Republic of Korea, Singapore, Switzerland, Taiwan and the USA. A relative change of 10% with respect to the absolute amount in the reference is allowed in Canada, and a level 1 difference, as described in the US FDA SUPAC-IR guideline (26), is allowed by South Africa and the WHO.

In the case of powders for reconstitution of oral solutions, the same requirements apply because the product is an oral solution at the time of administration. Japan has not described this possibility in the guidelines, and a waiver is not acceptable in principle. In Canada and the USA, the requirements for a waiver for powders for oral solution are not specifically described in their respective guidelines but a waiver may be possible based on physicochemical properties of the formulation.

Oral suspensions. South Africa will consider waivers for oral suspensions for systemic action if they have the same qualitative composition and comparable physicochemical properties for parameters such as crystallographic structure, particle size distribution and *in vitro* dissolution profiles. Australia and Singapore have no specific guidance but will consider an application based on the test and reference products having identical quantitative formulations and the physicochemical equivalence of justified parameters (e.g., polymorphic form, particle size distribution, viscosity, pH and dissolution profiles across the pH range 1.2 to 6.8). In all other jurisdictions *in vivo* bioequivalence studies are required.

In the case of locally acting suspensions, waivers can be accepted in Brazil and Singapore, and considered on a case-by-case basis in Argentina, Australia, Canada, Colombia, and the EU (27), New Zealand, the Republic of Korea, Switzerland and Taiwan if the drug substance is not systemically absorbed. In addition, in the USA, specific examples where a waiver is accepted are sevelamer (28-30), colesevelam (31,32) and cholestyramine (33). It should be noted that the above recommendations for the USA may be based primarily on the locally acting nature of the drug and not specifically the dosage form. For South Africa and the WHO, the requirements for waivers for locally acting suspensions are not described in the current guideline (20), but existing guidelines from Stringent Regulatory Authorities may be considered. Presently, Japan and Mexico do not accept waivers for locally acting suspensions.

In the case of powders for reconstitution of oral suspensions the same requirements apply because the product is an oral suspension at the time of administration.

Soft Gelatin Capsules. With the exception of Brazil, Canada, Japan and the Republic of Korea, a waiver from conducting *in vivo* bioequivalence studies could be acceptable in the remaining jurisdictions. Although soft gelatin capsules are solid oral dosage forms and the possibility of a waiver is not included in the guidance of these jurisdictions, it may be possible to consider a biowaiver if the drug substance is in solution inside the capsule and the gelatin coating is fast-dissolving (e.g., products containing Omega-3-acid ethyl esters). For example, a waiver from conducting *in vivo* bioequivalence studies could be accepted for products containing omega-3-acid ethyl esters in the USA (34); however, in most cases *in vivo* studies are required to demonstrate bioequivalence (e.g., products containing progesterone (35)). Similar to the biowaiver requirements for aqueous and oily oral solutions, the acceptability of a biowaiver for a soft gelatin capsule would be considered acceptable for Australia, the EU (36), New Zealand, Singapore and Switzerland if the fill liquid is qualitatively the same and quantitatively similar to that of the comparator product. Argentina, Colombia, Mexico, South Africa, Taiwan and the WHO Prequalification Programme (WHO PQT-m) would consider a biowaiver if the excipients of the test product are qualitatively and quantitatively identical to the reference product).

Injectable products

Intravenous injections. *In vivo* bioequivalence studies for simple intravenous solutions for injection or infusion may be waived in all jurisdictions (Table 2). For Canada, the formulations of the generic product and the reference product should be qualitatively the same and quantitatively essentially the same (excipient variation between products is within ±10% unless data is available to support a wider variation) (7). Any differences beyond the criteria should be scientifically justified. Only preservatives, buffers, antioxidants can be different in the Republic of Korea and the USA, while isotonic agents can also be changed in Australia, Canada, Colombia, the EU, Japan, New Zealand, Singapore, South Africa, Switzerland, Taiwan and WHO. Furthermore, Australia no longer approves new sterile single use injection products with preservatives that have no other function given that there is no use for the preservative; as a result, Australia will allow waivers for single use injections for a generic without a preservative even though a reference may contain a preservative. In the EU and Switzerland, change in the type of cyclodextrin has been accepted based on *in vitro* data for voriconazole because it was justified that it does not affect the *in vivo* release of the drug substance. In Canada, change in the type of cyclodextrin was supported by *in vitro* data as well as a clinical justification. Excipients that may affect disposition and/or safety (e.g., surfactants like Cremophor) should not differ in Australia, Colombia, the EU, New Zealand, Singapore, Switzerland and WHO while Argentina, Canada and Japan would assess the acceptability of the waiver on a case-by-case basis. In South Africa and Taiwan, the criteria have not been defined for changes to the mentioned excipients. For Brazil, any excipient can be changed as long as the new excipients are well established for intravenous administration and used in suitable concentrations, but any differences in preservatives, buffers and thickening agents need to be justified.

Table 1. Comparison of Biowaiver Requirements for Certain Oral Dosage Forms Among IPRP BEWGG Participants

	Argentina	Australia	Brazil	Canada	Colombia	European Union	Japan	Mexico	New Zealand	Singapore	South Africa	Rep. of Korea	Switzerland	Taiwan	US	WHO
Oral solutions																
Aqueous Solutions																
Consider waivers	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N[a]**	**Y[a]**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Oily Solutions																
Consider waivers	**C[a]**	**-**	**-**	**-**	**-**	**-**	**N**	**Y[a]**	**-**	**Y**	**-**	**N**	**-**	**Y**	**-**	**-**
May consider waivers with the same oil vehicle	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**N**	**Y[a]**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**
May consider waivers with different oil vehicle	**N**	**N**	**N**	**N**	**-**	**N**	**N**	**N[a]**	**N**	**Y**	**N**	**N**	**C**	**Y**	**C**	**N**
Similarity in Excipient Composition																
Consider qualitative changes in excipients that are known not to affect BA, e.g., preservatives, etc.	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N/A**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Consider qualitative changes in other non-critical excipients for BCS class II, III and IV drugs	**Y**	**N**	**N**	**N**	**N**	**N**	**N/A**	**Y[a]**	**N**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**N**
Can critical excipients be changed quantitatively?	**C**	**C**	**C**	**Y[b]**	**C**	**C**	**N/A**	**C**	**C**	**C**	**Y[b]**	**N**	**C**	**C**	**Y[b]**	**Y[b]**
Oral suspensions																
Consider waivers for systemically acting products	**N**	**Y[c]**	**N**	**N**	**N**	**N**	**N**	**N[a]**	**N**	**Y[c]**	**Y**	**N**	**N**	**N**	**N**	**N**
Consider waivers for locally acting products	**C**	**C**	**Y**	**C**	**C**	**C**	**N**	**N[a]**	**C**	**Y**	**C**	**C**	**C**	**C**	**C[e]**	**C**
Soft Gelatin Capsules																
May consider waivers	**Y[c,d]**	**Y[a]**	**N**	**N**	**Y[d]**	**Y[a]**	**N**	**Y[c]**	**Y[a]**	**Y[a]**	**Y[d]**	**N**	**Y[a]**	**Y[d]**	**N**	**Y[d]**

[a] Not defined in the guidelines, [b] Within the predefined limits in the corresponding guidelines, [c] Not defined, but acceptable if identical quantitative formulations and the physicochemical equivalence of justified parameters, [d] A justification for a waiver could be considered, [e] Additional *in vitro* comparisons or *in vivo* data may be required in certain cases (see product-specific guidance). Y: Yes; N: No; C: case-by-case, -: Not defined, N/A: Not applicable.

In Canada and Brazil, a physicochemical comparison is always required even when excipient composition is the same. In some jurisdictions (e.g., Australia, the EU, New Zealand, the Republic of Korea, Switzerland, the USA), a physicochemical comparison is required in cases of differences in excipient composition, whereas in other jurisdictions (Argentina, Colombia, Japan, Mexico, Singapore, South Africa, Taiwan and WHO), compliance with pharmacopoeial requirements for intravenous solutions is considered sufficient without any comparison with the comparator product. For example, in Australia, the pH, osmolality, viscosity and buffer capacity are compared if the excipient composition is qualitatively or quantitatively modified. In the USA, the applicant will be advised to submit additional data (e.g., physicochemical data) to support the differences.

In the case of powders for reconstitution of intravenous solutions, the same requirements apply because the product is an intravenous solution at the time of administration. In the USA, this topic is not covered in the guidelines, but the same principles apply.

Intramuscular and subcutaneous solutions for injections. Argentina, Australia, Brazil, Canada, Colombia, the European Union, Mexico, New Zealand, the Republic of Korea, Singapore, South Africa, Switzerland, Taiwan, the USA and WHO accept waivers for subcutaneous and intramuscular solutions; however, in the USA *in vivo* PD studies may be required for certain products to demonstrate similar activities (e.g., dalteparin (37), enoxaparin (38)). *In vivo* studies would also be considered in the other jurisdictions for low molecular-weight heparins since they are classified as biosimilars (39). Waiver requirements are not described in current Japanese guidelines but rather waivers are assessed on a case-by-case basis.

In Australia, Brazil, Canada, Colombia, the EU, New Zealand, Singapore, the Republic of Korea, South Africa, Switzerland, the USA and WHO, a waiver is possible for oily solutions only if the same oily vehicle is used. Waiver requirements are not described in current Argentinian and Taiwanese guidelines.

As stated for intravenous injections, qualitative and quantitative differences in buffer agents, antioxidants and preservatives are acceptable in principle for all jurisdictions if the differences are scientifically justified. Argentina, Australia, Brazil, Colombia, the EU, New Zealand, Singapore, South Africa, Switzerland, Taiwan and the WHO would also accept differences in isotonic agents. Excipients such as those affecting viscosity, surfactants and complexing agents should not be changed in Australia, Canada, Colombia, the European Union, New Zealand, Singapore, the Republic of Korea, South Africa, Switzerland, Taiwan, the USA and the WHO. In contrast, Brazil and Argentina assess changes on a case-by-case basis.

In Canada and Brazil, a physicochemical comparison is always required even when excipient compositions are the same. In other jurisdictions a physicochemical comparison is required in case of differences in excipient composition (e.g., Australia, the EU, New Zealand, the Republic of Korea, South Africa, Switzerland and the USA). For example, in Australia the pH, osmolality, viscosity and buffer capacity are compared. On the contrary, compliance with pharmacopoeial requirements for intramuscular or subcutaneous solutions is considered sufficient without any comparison with the comparator product in Argentina, Colombia, Mexico, Singapore, Taiwan and WHO.

In the case of powders for reconstitution of subcutaneous or intramuscular solutions the same requirements apply because the product is a solution at the time of administration. Japan has not described this possibility in the guidelines and waivers are assessed case-by-case. In the USA this topic is not covered in the guidelines, but the same principles apply.

Intramuscular and subcutaneous suspensions for injections. For intramuscular and subcutaneous suspensions for injection, a waiver of the *in vivo* bioequivalence study is not acceptable in principle in any of the jurisdictions. However, in rare instances, a waiver of in vivo bioequivalence study may be acceptable, e.g., azacitidine, as specified in the product-specific guidances from the U.S. FDA (40) and Brazil (41). *In vivo* bioequivalence studies have also been waived for azacitidine powder for suspension for injection products by Australia, Canada, the EU and Switzerland as exceptional cases since azacitidine is not completely soluble at room temperature (25ºC), but rather is soluble at 37ºC. As a result, given that azacitidine dissolves soon after administration due to its drug particle size and solubility properties, it can be considered that it is released as an injectable solution if all *in vitro* tests are shown to be similar for the test and the reference products.

Emulsions for intravenous injection. In Australia, Canada, the EU, New Zealand, Singapore, South Africa, the Republic of Korea, Switzerland and the USA, a waiver of *in vivo* bioequivalence studies is possible for emulsions for intravenous injection

(e.g., aprepitant (42), clevidipine (43) and propofol (44)), whereas a waiver is not possible in Brazil, Japan and Taiwan. In Australia, Canada, New Zealand, Singapore and South Africa the excipient composition should be qualitatively the same and quantitatively very similar while minor differences (e.g., antioxidants) have been accepted in the EU, the qualitative Republic of Korea and Switzerland. The waiver is based on physicochemical comparability of droplet size distribution of the dispersed lipid phase, viscosity / rheological properties, pH, osmolarity, specific gravity, surface properties such as zeta potential, etc.

Waiver requirements for this type of products are not currently described in guidance documents from Argentina, Canada, Colombia and the WHO.

Micellar solutions for intravenous injection. The waiver requirements described here relate to products that are administered as micellar injections (typically formed spontaneously on dilution of a concentrate with a bulk aqueous infusion solution) and are not intended to provide a modified release of drug *in vivo*.

The USA does not distinguish injectable micelles as dosage form; therefore, these products are designated as injections or injectable solutions. In Australia, Canada, Colombia, the EU, New Zealand, Singapore, South Africa, the Republic of Korea, Switzerland and the WHO, a biowaiver is possible for micellar solutions for injection (e.g., docetaxel micellar solutions), whereas in Argentina and Brazil, the waiver requirements are not addressed in current guidelines and applications are assessed case-by-case. In those jurisdictions where a biowaiver is acceptable, the excipient composition should be qualitatively the same and quantitatively very similar, although minor qualitative differences in buffer agents, antioxidant and preservatives are accepted. In addition, Australia, Colombia, the EU, New Zealand, Singapore, South Africa, Switzerland and the WHO could accept qualitative changes in the co-solvents if they are not considered critical (e.g., alcohol and PEG). The waiver is based on physicochemical comparability of critical micellar concentration (CMC), micelle size distribution, solubilisation capacity (free and bound amounts) and pH, osmolarity and viscosity.

In Japan and Taiwan waivers are not acceptable. When demonstrating *in vivo* bioequivalence, the excipient composition of the test product can be different from that of the reference for Taiwan but should be qualitatively and quantitatively the same for Japan except for buffer agents, antioxidants and preservatives.

DISCUSSION

The survey illustrates that the criteria employed to waive the requirement to conduct *in vivo* bioequivalence studies for certain types of oral and parenteral dosage forms are diverse among the members of the IPRP BEWGG. The survey results showed that as a dosage form increases in complexity, so does the risk associated with accepting biowaivers, especially in the presence of differences in composition between the generic and comparator products. This helps to explain the observation that convergence in accepting biowaivers and regulatory requirements becomes less common as a dosage form becomes more complex in composition.

In even the simplest case of an intravenous solution where an *in vivo* bioequivalence study can be waived in all jurisdictions, the allowable differences in excipient composition between a generic and reference are not harmonised. In the most prescriptive case, the non-medicinal ingredients in the formulations between the generic product and the reference product should be qualitatively the same and quantitatively essentially the same (within ± 10% absolute amount in the reference); however, differences beyond the defined criteria can be scientifically justified. In contrast, changes in preservatives, buffers, antioxidants and isotonic agents are allowed in most of the remaining jurisdictions. In the USA, the absolute amount in reference is within ± 5%. In the most flexible case, even surfactants can be changed if they are well established for the route of administration and present in usually acceptable amounts. This change in surfactants might modify the safety profile, since not all surfactants exhibit the same tolerability profile (45).

A waiver for oral solutions has been accepted in most jurisdictions based on the fact that the drug is already dissolved and available, and it is only necessary to ensure that excipients do not affect solubility/precipitation, stability, transit time and permeability of the drug in the gastrointestinal tract. Hopefully, the present survey and scientific discussion might facilitate the development of recommendations in countries where there is no guidance (Japan) or where oily solutions cannot be waived despite having the same or similar qualitative and quantitative composition as the comparator product (Brazil and the Republic of Korea). Regarding excipients, the most prescriptive jurisdictions only accept changes in non-critical excipients of oral solutions containing BCS class I drugs, but they do not allow those changes for BCS class II, III and IV drugs. This is

Table 2. Comparison of Biowaiver Requirements for Certain Parenteral Dosage Forms Among IPRP BEWGG Participants

	Argentina	Australia	Brazil	Canada	Colombia	European Union	Japan	Mexico	New Zealand	Singapore	South Africa	Rep. of Korea	Switzerland	Taiwan	US	WHO
Intravenous solutions																
Accept waivers	**Y**	**Y**	**Y**	**Y[a]**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Accept changes in preservatives, buffer agents, antioxidants	**Y**	**Y[e]**	**Y**	**Y[c]**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Accept changes in isotonic agent	**Y**	**Y**	**Y**	**Y[c]**	**Y**	**Y**	**Y**	**C**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**Y**
Accept changes in surfactants	**C**	**N**	**Y**	**Y[c]**	**N**	**N**	**C**	**C**	**N**	**N**	**N**	**N**	**N**	**-**	**N**	**N**
Requires *in vitro* comparison with the comparator even if excipients are the same	**N**	**N**	**Y**	**Y**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**
Requires *in vitro* comparison with the comparator if differences in excipients	**N**	**Y**	**Y**	**Y**	N	**Y**	**N**	**N**	**Y**	**N**	**Y**	**Y**	**Y**	**N**	**Y**	**N**
Intramuscular and subcutaneous solutions for injection																
Accept waivers for aqueous solutions	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N[c]**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Accept waivers for oily solutions with the same oil vehicle	**-**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**-**	**Y**	**Y**	**Y**	**Y**	**Y**	**-**	**Y[d]**	**Y**
Accept waivers for oily solutions with a different oily vehicle	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**-**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**
Accept changes in preservatives, buffer agents, antioxidants	**Y**	**Y[e]**	**Y**	**Y[c]**	**Y**	**Y**	**N/A**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Accept changes in isotonic agent	**Y**	**Y**	**Y**	**Y[c]**	**Y**	**Y**	**N/A**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**Y**
Accept changes in all type of excipients (e.g. surfactants)	**Y[c]**	**N**	**Y**	**Y[c]**	**N**	**N**	**N/A**	**Y**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**

Table 2. continues…

	Argentina	Australia	Brazil	Canada	Colombia	European Union	Japan	Mexico	New Zealand	Singapore	South Africa	Rep. of Korea	Switzerland	Taiwan	US	WHO
Requires *in vitro* comparison with the comparator even if excipients are the same	**N**	**N**	**Y**	**Y**	**N**	**N**	**N/A**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**
Requires *in vitro* comparison with the comparator if differences in excipients	**N**	**Y**	**Y**	**Y**	**N**	**Y**	**N/A**	**N**	**Y**	**N**	**Y**	Y	Y	N	**Y**	**N**
Intramuscular and subcutaneous suspensions for injection																
Accept waivers	**-**	**N**	**N**	**N[c]**	**N**	**N**	**N**	**N[c]**	**N**	**N**	**N**	**N**	**N**	**N**	**Y[d]**	**N**
Emulsions for injection																
Accept waivers	**-**	**Y**	**N**	**Y[c]**	**-**	**Y**	**N**	**N[c]**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y[d]**	**-**
Qualitative differences allowed for e.g. antioxidant and preservatives	**-**	**N**	**N/A**	**Y[c]**	**-**	**Y**	**N/A**	**-**	**N**	**N**	**Y**	**Y**	**Y**	**N/A**	**N[d]**	**-**
Micellar solutions for injection																
Accept waivers	**N[c]**	**Y**	**Y[c]**	**Y[c]**	**Y**	**Y**	**N**	**N[c]**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y[d]**	**Y**
Only if the micelle dissemble on dilution	**N/A**	**Y**	**-**	**Y[c]**	**Y**	**Y**	**N/A**	**-**	**Y**	**Y**	**Y**	**N/A**	**Y**	**N/A**	**N[d]**	**Y**
Qualitative differences allowed for buffer agents, antioxidant and preservatives	**N/A**	**Y[e]**	**Y[c]**	**Y[c]**	**Y**	**Y**	**N/A**	**-**	**Y**	**Y**	**Y**	**Y**	**Y**	**N/A**	**N[d]**	**Y**
Qualitative differences allowed for co-solvents	**N/A**	**Y**	**Y[c]**	**N**	**Y**	**Y**	**N/A**	**-**	**Y**	**N**	**Y**	**N**	**Y**	**N/A**	**N[d]**	**Y**
Qualitative differences allowed for surfactants	**N/A**	**N**	**Y[c]**	**N**	**N**	**N**	**N/A**	**-**	**N**	**N**	**N**	**N**	**N**	**N/A**	**N/A**	**N**
Comparison based on pharmacopoeial tests only	**N/A**	**N**	**Y**	**N**	**N**	**N**	**N**	**-**	**N**	**N**	**N**	**Y**	**N**	**N/A**	**N/A**	**N**

[a]Within the predefined limits in the corresponding guidelines, [b]A justification for a waiver could be considered, [c]Not defined in the guidelines, but assessed case by-case, [d]Additional *in vitro* comparisons or *in vivo* data may be required in certain cases (see relevant product-specific guidance), [e]Australia does not register new single use injection products that contain preservatives with no other functions; therefore, a difference is mandatory if the reference product contains a preservative with no other function.

(Y: Yes; N: No; C: case-by-case, -: Not defined, N/A: Not applicable)

consistent with the BCS biowaivers for class III drugs where excipients should be very similar (3). For non-class I drugs, the excipients must be qualitatively the same and quantitatively similar. However, in Canada, preservatives, colorants and flavors may vary. Additionally, in Australia, Colombia, the European Union, Switzerland and the WHO, other non-functional excipients may also vary (e.g., viscosity agents, pH buffers and some sweeteners). In the rest of the countries, a more flexible approach is taken towards the changes in other functional excipients, like co-solvents, as long as the amount is considered 'normal' for an oral solution.

In vivo bioequivalence studies for soft gelatin capsules may be waived in some countries based on the same principle used for waivers for oily oral solutions, i.e., once the capsule shell dissolves, the capsule contents are released similar to an oily oral solution and the assumption is that the composition of the capsule shell will not affect bioavailability. However, caution should be exercised when using *in vitro* tests to predict *in vivo* behaviour. For example, a change in the composition of the capsule shell without changing the composition of the oily solution for dutasteride capsules has been shown to affect C_{max} (46).

For intramuscular and subcutaneous aqueous and oily solutions for injection, almost all the jurisdictions will accept biowaivers when specified criteria are met. For example, waivers for oily solutions may be granted if the same oil vehicle is used. Japan does not have any guidance regarding the acceptability of a waiver for intramuscular and subcutaneous aqueous solutions for injection and Argentina, Japan and Taiwan lack guidance regarding waivers for oily solutions for injection. The possibility of convergence for both dosage forms may be possible when guidance documents are developed from these countries.

In contrast to oral solutions, *in vivo* bioequivalence studies for oral suspensions are not routinely waived with the exception of South Africa, where studies are waived based on *in vitro* parameters, and Argentina, Australia and Singapore, where the acceptability of a waiver is considered on a case-by-case basis. As a result, a review of the existing evidence addressing *in vitro* parameters that are predictive of bioequivalence seems to be necessary to facilitate regulatory convergence. It is interesting to note that some jurisdictions do not waive *in vivo* bioequivalence studies for systemically acting oral suspensions but may allow waivers for locally acting suspensions due to the fact that therapeutic equivalence studies using clinical, or pharmacodynamics endpoints are generally not that discriminatory when detecting potential formulation differences between different products. Furthermore, none of the jurisdictions allow waivers for intramuscular or subcutaneous suspensions for injection, except in the case of azacitidine due to its particular solubility properties.

When the formulation of a product becomes more complex, there is less commonality in the waiver requirements among the participating members. In the case of micellar solutions for intravenous injection, as illustrated by the case of docetaxel, some jurisdictions would not accept a waiver; however, other jurisdictions would allow a waiver based on *in vitro* data noting that the requirements for excipient similarity vary between members. Interestingly, some jurisdictions would accept qualitative differences in co-solvents, even though different storage conditions may be required to avoid precipitation. In contrast, other jurisdictions do not accept differences in excipients except for buffers, antioxidants and preservatives in order to ensure a higher degree of similarity under all conditions of use.

The requirements are even more diverse for other complex formulations such as emulsions for intravenous injections (e.g., propofol). Some jurisdictions do not accept a waiver, while others would. For those that do accept a waiver the requirements for excipient similarity vary because few jurisdictions have previously accepted qualitative differences in antioxidants. Others do not provide any guidance with respect to waivers for emulsions for intravenous injections. It is noteworthy that Brazil accepts changes in all excipients including surfactants of intravenous solutions or micellar solutions if the replacement excipients are justified and well established for that dosage form and route of administration, and used in acceptable concentrations, but does not accept waivers for emulsions even with the same qualitative and quantitative composition.

This survey shows that the criteria employed to waive *in vivo* bioequivalence studies for certain oral and parenteral dosages are diverse amongst the participating members of IPRP BEWGG. It also illustrates that case-by-case assessment is frequent due to the complexity of some dosage forms. Therefore, scientific evidence that justifies the national requirements should be shared in order to facilitate convergence in the future as a first step towards harmonisation and to avoid the uncertainty

of case-by-case assessments for pharmaceutical companies.

CONCLUSION

A waiver from *in vivo* demonstration of bioequivalence may be applied to several orally administered and systemically acting dosage forms like oral solutions, oral suspensions and soft gelatin capsules, and some systemically-acting parenteral dosage forms like intravenous injections, subcutaneous and intramuscular injections, emulsions for injection and micellar solutions for injection. The requirements for biowaivers for the more complex dosage forms (e.g., suspensions, micellar injection) tend to be more variable among the participating members; however, as the dosage forms become less complex (e.g., oral solutions, IV injections), the requirements for biowaivers become more similar as there are less risk factors to consider that may influence the safety and efficacy of the product. The sharing of this information is a first step towards regulatory convergence in this area since, for some dosage forms, large differences between members of the BEWGG of the IPRP have been identified. The next steps should involve identifying areas that could be harmonised based on sound scientific justifications. Convergence in this area would be useful for pharmaceutical companies developing generic medicinal products for more than one of these jurisdictions.

CONFLICT OF INTEREST

This manuscript represents the personal opinions of the authors and does not necessarily represent the views or policy of their corresponding regulatory agencies.

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