A Review of the Regulations on Interchangeability of Generic Medicines and Comparability of Biosimilars in the Philippines

Paul Marvin T. Quizon*

*Corresponding author's email address: ptquizon@up.edu.ph

College of Pharmacy, University of the Philippines Manila

REVIEW ARTICLE

Abstract

Background: The access to quality, safe, effective, and affordable medicines, such as generics and biosimilars remains to be one of the strategies of the Philippine government to achieve its health agenda, as seen in various legislations and policies. In order to ensure the interchangeability of generic medicines and comparability of biosimilars with their respective reference products, regulations to assure these characteristics have been implemented by the national regulatory authority.

Objectives: This narrative review aimed to compare the current regulations on interchangeability of generic medicines and comparability of biosimilars in the Philippines with those of selected international regulatory agencies and organizations, and identify research opportunities that can address some of the challenges in complying with these regulations.

Methods: Local regulations related to interchangeability and comparability were obtained from the official website of the Philippine Food and Drug Administration. Similarly, international regulations and guidelines which were selected based on a set of inclusion criteria were reviewed and compared with the local regulations. The internet search was conducted from 01-15 September 2017 and no statistical calculations or techniques were involved in the thematic content analyses.

Results and Discussion: The current regulation to ensure the interchangeability of generic medicines in the Philippines is based on the ASEAN and WHO Guidelines, and recognizes both *in vivo* and *in vitro* methods to demonstrate therapeutic equivalence. For the *in vitro* method, drug substances classified as BCS Class 1 and 3 are the only ones eligible for the biowaiver approach. For biosimilars, the Philippines adopted the WHO Guidelines which recognize comparability exercises as the approach to ensure the similarity of biosimilars with their respective reference products.

Conclusions: The current regulations on the interchangeability of generic medicines and comparability of biosimilars in the Philippines are aligned with those of international guidelines particularly of the World Health Organization (WHO). Research opportunities to address some of the identified challenges include permeability testing methods, development of biowaiver monographs, and practice research on biosimilars interchangeability, safety, and nomenclature.

Keywords: *generics, biowaivers, biosimilars, interchangeability, comparability, regulations*

Introduction

The access to quality, safe, effective, and affordable medicines remains to be the direction of the Philippine government since the passing of the Generics Act of 1988 and the Cheaper Medicines Act of 2008 [1,2]. Under the "Affordability and Availability" pillar of the current Philippine Medicines Policy, "the adoption and use of generics shall be actively promoted in both the public and private sectors as the government commits to increase financing for medicines and deliver the best health outcomes to more patients" [3]. Furthermore, as declared in the Philippine Health Agenda for 2016 to 2022 by the Duterte Administration, the use of generics was one of the milestones during the last 30 years of Philippine Health Sector Reform [4]. Generic medicines, also referred to as multisource pharmaceutical products, are the off-patented versions of small, chemical innovator molecules

that need to demonstrate therapeutic equivalence to ensure interchangeability in clinical practice [5,6]. Therapeutic equivalence means that a generic medicine is a pharmaceutical equivalent or alternative to a reference product, and has demonstrated bioequivalence to it using *in vivo* or *in vitro* methods, whichever is applicable. Interchangeability is essential when switching or substitution occurs from an innovator product to a generic medicine, or from one generic to another generic. Biosimilars or Similar Biotherapeutic Products (SBPs), on the other hand, are biological products which are similar in terms of quality, safety, and efficacy to already licensed reference biotherapeutic or biological products (RBPs). However, biosimilars should not be treated as "generics" of their RBPs since the concept of therapeutic equivalence is not applicable to these products [7]. Unlike the smaller, chemical molecules of generic medicines, biosimilars are composed of large, complex molecules, such as proteins, which are more difficult to characterize due to inherent variabilities. Furthermore, since biosimilars are produced in living organisms through sophisticated biotechnology processes, such as, recombinant DNA technology, exact replication of their RBPs is not possible. Therapeutic equivalence is, therefore, not sufficient for biosimilars to demonstrate that these differences do not affect safety and efficacy [8]. Thus, biosimilars must prove a similarity to innovator biological products through comparability studies which involve the head-to-head comparison of a biosimilar with its reference product to rule out any significant differences between them in terms of structure and function [7]. In order to ensure that generic medicines and biosimilars are interchangeable or comparable, respectively with their corresponding reference products, regulations have been issued and are currently implemented by the Philippine Food and Drug Administration (FDA). The latest regulation on the interchangeability of generic medicines is FDA Circular No. 2016-019 issued on 25 October 2016 [9]. For biosimilars, the current Philippine regulation is outlined in the Department of Health (DOH) Administrative Order (AO) No. 2014-0016 issued on 11 April 2014 [7]. In this context, this review paper aimed to compare the current regulations on interchangeability of generic medicines and comparability of biosimilars in the Philippines with those of selected international regulatory agencies and organizations; and identify research opportunities that can address some of the challenges in complying with these regulations. The outcomes of this narrative review can serve as the starting points for future research studies that will impact local policies, regulations, and practice.

Methodology

Local regulations related to interchangeability and comparability were obtained from the official website of the Philippine Food and Drug Administration (PFDA). International regulations and guidelines were reviewed and identified parameters were compared to the local regulations. The said regulations and guidelines were selected based on a set of inclusion criteria. The United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) were selected since both are reference regulatory agencies recognized by the PFDA. Furthermore, these agencies were pioneers in the said regulations. The guidelines from the Association of Southeast Asian Nations (ASEAN) and World Health Organization (WHO) were included due to the ongoing regional harmonization and recommendations for minimum requirements, respectively. The internet search was conducted from 01-15 September 2017 and no statistical calculations or techniques were involved in the thematic content analyses.

Results And Discussion

Interchangeability of Generic Medicines

The comparison of selected regulatory parameters on the interchangeability of generic medicines is summarized in Tables 1 and 2. There is general convergence for bioequivalence and biowaiver requirements since similarities were mostly observed among the regulations reviewed. The only differences noted include the US FDA conditions for therapeutic equivalence; the list of products requiring *in vivo* equivalence studies; and the ASEAN biowaiver eligibility and permeability requirements [5-6, 9-13]. The current interchangeability regulation of the Philippines is aligned with that of the ASEAN and the WHO for bioequivalence and biowaivers, respectively. The Philippine FDA has outlined the scope, requirements, and conditions in complying with the guidelines. It has also published the list of comparator products to be used in the conduct of equivalence studies. The latest version of the list was issued on 08 August 2017 [14]. The requirement for *in vivo* equivalence testing (eg. bioequivalence studies) has been introduced in the Philippines since 1989 but it was only in 2013, that the concept of "biowaivers" was recognized [5]. FDA Circular No.2016-019 allows for the use of biowaivers for pharmaceutical products containing Class 1 and Class 3 drug substances under the

Biopharmaceutics Classification System (BCS) [5,9]. This is similar to the US FDA, EMA, and WHO. A "biowaiver" is defined by the WHO as a regulatory approval process wherein a generic product registration is approved based on evidence of equivalence to an innovator or reference product using *in vitro* methods [6]. This process provides a more affordable alternative to *in vivo* or bioequivalence studies. However, biowaivers are allowed only for certain drug classes under certain eligibility criteria as specified by the WHO. This is a challenge for an applicant since the BCS Class of the drug substance must be proven either by conducting validated laboratory tests to demonstrate the required solubility and permeability, or by providing sound, peer-reviewed literature to support biowaiver eligibility [5]. The challenge in the first approach is the availability of permeability testing resources in the country. Unlike solubility determination, permeability testing may be conducted using absolute bioavailability or mass balance study, *in vivo* intestinal perfusion in humans, *in vivo* or in situ intestinal perfusion using animal models, or *in vitro* permeation across a monolayer of cultured epithelial cells such as Caco-2 [6]. All of these require more sophisticated study designs, techniques and instruments. It is, therefore, recommended that studies on permeability testing be conducted locally. For the literature search approach, the challenge was the availability of reliable data that may be used in substantiating biowaiver applications. This was partially addressed by the International Pharmaceutical Federation (FIP) through its publications of the biowaiver monographs, which were literature reviews of publicly available data gathered and organized by experts to provide scientific and unbiased recommendations on biowaiver eligibility [15]. To be eligible for BCS-based biowaivers, the following must all be considered: the solubility and permeability of the active pharmaceutical ingredient (API); the similarity of the dissolution profiles; the excipients used in the formulation; and the risks of an incorrect biowaiver decision in terms of the therapeutic index of and clinical indications of the API [6]. As of 14 September 2017, the FIP has already published 48 biowaiver monographs in the Journal of Pharmaceutical Sciences which can be downloaded for free from the FIP website. However, the publicly available monographs are not sufficient to cover all of the essential medicines in the market and those which are widely used in clinical practice. This is now an opportunity for pharmaceutical researchers in the country to collaborate with experts from the FIP in writing more biowaiver monographs that can be made accessible to generic drug applicants.

Comparability of Biosimilars

Selected biosimilar parameters were compared and the results are summarized in Table 3. It can be seen from the table that there is convergence among the regulations since similarities were noted in the parameters compared [7-8, 16-17]. The current Philippine regulation on biosimilars adopted the WHO Guidelines on Evaluation of Similar Biotherapeutic Products which covers all biological drug applications except vaccines, plasma-derived products and their recombinant analogues since a separate regulatory guidance for these products is recommended by the WHO [6]. In this regulation, biosimilars must demonstrate that minor differences with the RBPs will not affect product safety and efficacy. This is also aligned with that of the US FDA and EMA. As previously mentioned, the therapeutic equivalence approach in establishing interchangeability of generics is not applicable to biosimilars. Thus, following the WHO guidelines, a biosimilar must prove its similarity to the RBP through comparability exercises which are designed to demonstrate that a biosimilar has high similarity in terms of physical, chemical and biological properties with the RBP. There may be minor differences but these must be proven to have no clinically meaningful impact on safety or efficacy [8]. This heavy emphasis on comparative studies is based on the assumption that demonstrating high similarity will be the basis for reducing the non-clinical and clinical data requirements for biosimilars [7,8]. Comparability exercises involve a step-wise approach in which the data from the initial comparative quality studies will be used to determine the type and extent of comparative non-clinical, and then the subsequent comparative clinical studies to be performed [8]. As per the WHO recommendation, if significant differences are found in the comparability studies, the product will not likely qualify as a biosimilar and must not be referred to as such [7].

If a biological product is found to be "biosimilar" through comparative exercises, it does not follow that it is already interchangeable with the RBP. In the United States (US), interchangeability for biosimilars is achieved when, "the biological product is biosimilar to the reference product, and it can be expected to produce the same clinical result as the reference product in any given patient" [18]. This means that additional data may be required by the regulatory authority to determine interchangeability. This poses a challenge to practitioners, such as prescribers in switching therapy for their patients to a biosimilar. Thus, there is a need to educate health professionals and the general public regarding biosimilars interchangeabilty. The Philippine FDA may also

Table 1. *Comparison of selected bioequivalence regulations and guidelines*

Parameters	PFDA	US FDA	EMA	ASEAN	WHO
Conditions for therapeutic equivalence	Pharmaceutical Equivalence/Alternatives + Bioequivalence	Pharmaceutical Equivalence + Bioequivalence	Pharmaceutical Equivalence/Alternatives + Bioequivalence	Pharmaceutical Equivalence/Alternatives + Bioequivalence	Pharmaceutical Equivalence/Alternatives + Bioequivalence
Products requiring in vivo equivalence (bioequivalence) studies	1. BCS Class 2 and 4 oral immediate-release pharmaceutical products with systemic action 2. Modified-release pharmaceutical products designed to act systemically 3. Pharmaceutical products containing drug/s with narrow therapeutic index 4. Fixed-dose combination products with systemic action where at least one of the drug substance requires an in vivo study	An in vivo study is generally recommended for all solid oral dosage forms approved after 1962 and for bioproblem drug products approved before 1962.	In applications for generic medicinal products according to Directive 2001/83/EC, Article 10(1), the concept of bioequivalence is fundamental. Other types of applications may also require demonstration of bioequivalence, including variations, fixed combinations, extensions and hybrid applications.	1. Non-oral immediate-release dosage forms with systemic action 2. Modified-release and transdermal dosage forms 3. Fixed-dose combination products 4. Locally applied products with systemic action	1. Oral, immediate-release pharmaceutical products with systemic action, except for those eligible for BCS-based biowaivers 2. Non-oral, non-parenteral pharmaceutical products designed to act systemically (eg. transdermal patches, suppositories, nicotine chewing gum, testosterone gel, skin-inserted contraceptives) 3. Modified-release pharmaceutical products designed to act systemically, except in certain conditions. 4. Fixed-dose combination products with systemic action where at least one of the APIs requires an in vivo study 5. Non-solution pharmaceutical products, which are for non-systemic use (eg. for oral, nasal, ocular, dermal, rectal or vaginal application) and are intended to act without systemic absorption
Bioequivalence testing methodology	Based on ASEAN and WHO Guidelines	In descending order of preference, these include pharmacokinetic, pharmacodynamic, clinical, and in vitro studies	The number of studies and study design depend on the physico-chemical characteristics of the substance, its pharmacokinetic properties and proportionality in composition, and should be justified accordingly. In particular it may be necessary to address the linearity of pharmacokinetics, the need for studies both in fed and fasting state, the need for enantioselective analysis and the possibility of waiver for additional strengths.	Pharmacokinetic studies, human studies with clinical or pharmacodynamic end points, studies using animal model or in vitro studies as long as appropriately justified and/or validated	Comparative pharmacokinetic studies in humans, in which the API and/or its metabolite(s) are measured as a function of time in an accessible biological fluid such as blood, plasma, serum or urine to obtain pharmacokinetic measures such as AUC and Cmax that reflect the systemic exposure ; comparative pharmacodynamics studies in humans; comparative clinical trials; comparative in vitro tests

Legend: PFDA Philippine Food and Drug Administration; US FDA United States Food and Drug Administration; EMA European Medicines Agency; ASEAN Association of Southeast Asian Nations; WHO World Health Organization; BCS Biopharmaceutics Classification System; API Active Pharmaceutical Ingredient

Table 2. *Comparison of selected biowaiver regulations and guidelines*

Parameters	PFDA	US FDA	EMA	ASEAN	WHO
BCS Class eligible for biowaiver	1, 3	1, 3	1, 3	Not specified	1, 3
Solubility requirements	Based on WHO	A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1-6.8. The volume estimate of 250 mL is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.	The drug substance is considered highly soluble if the highest single dose administered as immediate release formulation is completely dissolved in 250 mL of buffers within the range of pH 1-6.8 at 37±1°C. This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range.	An active substance is considered highly water soluble if the amount contained in the highest dose strength of an immediate release product is dissolved in 250 mL of each of three buffers within the range of pH 1-8 at 37°C (preferably at or about pH 1.0, 4.6, 6.8)	An API is considered highly soluble when the highest single therapeutic dose as determined by the relevant regulatory authority, typically defined by the labelling for the innovator product, is soluble in 250 mL or less of aqueous media over the pH range of 1.2-6.8. The pH-solubility profile of the API should be determined at 37±1°C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended.
Permeability requirements	Based on WHO	A drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 85% or more of an administered dose based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or in comparison to an intravenous reference dose.	High permeability is considered to be established where measured extent of absorption is ≥ 85% as supported by data from absolute bioavailability or mass balance studies.	Linear and complete absorption indicates high permeability.	An API is considered highly permeable when the extent of absorption in humans is 85% or more based on a mass balance determination or in comparison with an intravenous comparator dose.
Dissolution profile comparison	Based on WHO	An IR drug product is considered rapidly dissolving when 85% or more of the labeled amount of the drug substance dissolves within 30 minutes, using USP Apparatus I at 100 rpm (or Apparatus II at 50 rpm or at 75 rpm when appropriately justified) in a volume of 500 mL or less in each of the following media: 0.1 N HCl or 100 Simulated Gastric Fluid USP without enzymes; pH 4.5 buffer; and a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes. An IR product is considered very rapidly dissolving when 85% or more of the labeled amount of the drug substance dissolves within 15 minutes using the above-mentioned conditions.	Drug products are considered “very rapidly” dissolving when more than 85% of the labeled amount is dissolved within 15 minutes. In such cases, the similarity of dissolution profiles may be accepted without any mathematical calculation. In cases where it takes more than 15 minutes but not more than 30 minutes to achieve at least 85% dissolution, f2-testing or other suitable tests should be used to demonstrate profile similarity.	In vitro data should demonstrate the similarity of dissolution profile between the test product and the reference product in each of three buffers within the range of pH 1-8 at 37°C (preferably at or about pH 1.0, 4.6, 6.8). However, in cases where more than 85% of the active substance are dissolved within 15 minutes, the similarity of dissolution profiles may be accepted as demonstrated.	Studies should be performed in at least three media covering the physiological range, including pH 1.2 HCl, pH 4.5 buffer and pH 6.8 buffer. If both the test and reference (comparator) products show more than 85% dissolution in 15 minutes, the profiles are considered similar and no calculations are required.

Table 2. *Comparison of selected biowaiver regulations and guidelines (continuation)*

Parameters	PFDA	US FDA	EMA	ASEAN	WHO
		Two dissolution profiles are considered similar when the f2 value is ≥50. Note that when both test and reference products dissolve 85% or more of the label amount of the drug in 15 minutes using all three dissolution media recommended above, the profile comparison with an f2 test is unnecessary.			
Evaluation of excipients	Based on WHO	A list of excipients used, the amount used, and their intended functions should be provided. Excipients used in the test product should have been used previously in FDA-approved IR solid oral dosage forms. In addition, it is important to provide quantitative comparison of excipients between the test and reference products, for BCS Class 3 drug products.	In the case of Class 1 drugs, it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product. If a biowaiver is applied for a Class 3 drug substance excipients have to be qualitatively the same and quantitatively very similar in order to exclude different effects on membrane transporters.	The excipients included in the composition of the medicinal product are well established and no interaction with the pharmacokinetics of the active substance is expected. In case of atypically large amounts of known excipients or new excipients being used, additional documentation has to be submitted.	For product containing Class 1 APIs, it is recommended that the excipients employed be present in the comparator product or be present in other products which contain the same API as the multisource product and which have marketing authorizations in ICH-associated countries. For products containing Class 3 APIs, all excipients in the product formulation should be qualitatively the same and quantitatively similar to that of the comparator product, as defined by the WHO quality limits on allowable quantitative changes in excipients for a variation.
Risk assessment	Based on WHO	Biowaivers are not applicable for drug substances that have narrow therapeutic ranges.	Generally, the risks of an inappropriate biowaiver decision should be more critically reviewed (e.g. site-specific absorption, risk for transport protein interactions at the absorption site, excipient composition and therapeutic risks) for products containing Class 3 than for Class 1 drug substances.	Consider the risk of therapeutic failure or adverse drug reactions and the risk of bioinequivalence.	Only when there is an acceptable risk-benefit balance in terms of public health and risk to the individual patient should bioequivalence testing be waived and the in vitro methods applied as a test of product equivalence.

Legend: PFDA Philippine Food and Drug Administration; US FDA United States Food and Drug Administration; EMA European Medicines Agency; ASEAN Association of Southeast Asian Nations; WHO World Health Organization; BCS Biopharmaceutics Classification System; BE Bioequivalence; API Active Pharmaceutical Ingredient; GI Gastrointestinal; IR Immediate-Release; USP United States Pharmacopeia; HCl Hydrochloric; f2 Similarity Factor

develop a listing, similar to the "Purple Book" of the US FDA, which provides information on whether a biological product has been determined to be biosimilar to, and interchangeable with, a reference product [18]. It is also recommended that practice-based researches on the utilization of biosimilars must be conducted to identify the prescribing and dispensing issues related to biosimilars. The last challenge with biosimilars regulation is on labeling and nomenclature. Since biosimilars are not the exact copies of their reference products, a biosimilar may not have the same labeling and nomenclature as its RBP. This is because not all approved indications of the RBP may be approved for the biosimilar and that the comparative clinical studies of the biosimilar may use design parameters that differ from those used to support the approval of the reference product [18]. Opportunities for research related to these challenges include the conduct of extrapolation studies and pharmacovigilance studies to address some of the issues on labeling, and for the Philippine FDA to develop a nomenclature system that can differentiate a biosimilar from its reference product.

Table 3. *Comparison of selected biosimilar regulations and guidelines*

Parameters	PFDA	US FDA	EMA	WHO
Terminology	Similar Biotherapeutic Product	Biosimilar	Biosimilar	Similar Biotherapeutic Product
Definition	A biotherapeutic product which is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product.	A biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.	A biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established.	A biotherapeutic product which is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product.
Submission Requirements	A full quality dossier for both drug substance and drug product is required. Evidence of similarity shall be the basis for a reduced clinical and non-clinical data. The list of documentary requirements for the initial registration of a Similar Biotherapeutic Product is provided under a separate Annex. Additional clinical and non-clinical data, if deemed appropriate and necessary by the applicant company, should also be submitted.	FDA recommends that sponsors use a stepwise approach to develop the evidence needed to demonstrate biosimilarity which can include a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness. FDA intends to consider the totality of the evidence provided by a sponsor when the Agency evaluates the sponsor's demonstration of biosimilarity, consistent with a longstanding Agency approach to evaluating scientific evidence.	A stepwise approach is normally recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation. The extent and nature of the non-clinical in vivo studies and clinical studies to be performed depend on the level of evidence obtained in the previous step(s) including the robustness of the physicochemical, biological and non-clinical in vitro data. If the biosimilar comparability exercise indicates that there are relevant differences between the intended biosimilar and the reference medicinal product making it unlikely that biosimilarity will eventually be established, a stand-alone development to support a full Marketing Authorisation Application should be considered instead.	The basis for licensing a product as a Similar Biotherapeutic Product (SBP) depends on its demonstrated similarity to a suitable Reference Biotherapeutic Product (RBP) in quality, non-clinical, and clinical parameters. The decision to license a product as a SBP should be based on evaluation of the whole data package for each of these parameters. If relevant differences are found in the quality, non-clinical, or clinical studies, the product will not likely quality as a SBP and a more extensive non-clinical and clinical data set will likely be required to support its application for licensure. Such products should not qualify as a SBP. If comparability exercises and/or studies with the RBP are not performed throughout the development process, the final product should not be referred to as a SBP.

Legend: PFDA Philippine Food and Drug Administration; US FDA United States Food and Drug Administration; EMA European Medicines Agency; WHO World Health Organization

Conclusions

The current regulations on interchangeability of generic medicines and comparability of biosimilars in the Philippines are aligned with international guidelines particularly that of the World Health Organization (WHO). Research opportunities to address some of the identified challenges include permeability testing methods, development of biowaiver monographs, and practice research on biosimilars interchangeability, safety and nomenclature.

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