

A Survey of the Criteria Used for the Selection of Alternative Comparator Products by Participating Regulators and Organizations of the International Pharmaceutical Regulators Programme

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ABSTRACT -- The safety and efficacy of a generic product are partly based on demonstrating bioequivalence to the innovator product; however, when the innovator product is no longer available as a comparator product, a survey conducted within the Bioequivalence Working Group for Generics (BEWGG) of the International Pharmaceutical Regulators Programme (IPRP) indicated that the criteria for selecting an alternative comparator product varies. For most members of the BEWGG, an existing marketed generic that was approved based on a comparison with the locally registered innovator product can be used, contingent on criteria that ranges from allowing any generic to be used, to allowing only specific criteria-defined generics to be used. Notwithstanding the acceptability of a generic as an alternative comparator, it is not always the preferred comparator for several jurisdictions. Some jurisdictions require the use of a locally sourced alternative innovator comparator (*e.g.*, the same medicinal ingredient manufactured by a different company) or a foreign innovator comparator. Unlike the other members of the BEWGG, the European Union (EU) has no such options available, rather mechanisms are in place to allow manufacturers to develop a new comparator. The criteria described herein regarding the use of an alternative comparator product can also be applied to scenarios where a specific strength of a series of strengths or an innovative fixed dose combination are discontinued. The results of the survey demonstrate that while criteria for selecting alternative comparator products are not harmonized among the BEWGG participants, the common concern for all jurisdictions is to select a comparator product that meets the safety and efficacy standards of the original innovator product.

INTRODUCTION

The safety and efficacy of an innovator product are generally established based on data consisting of numerous nonclinical studies, clinical trials, and quality data, whereas the safety and efficacy of a generic product are partly established by demonstrating bioequivalence with the innovator product. The data supporting the approval of the innovator product are extrapolated to the generic product when bioequivalence and pharmaceutical equivalence are demonstrated.

In the current pharmaceutical landscape, new drugs and improved versions of existing drugs are continually in development and sometimes by the same company. As a result, multiple drugs and drug products can be available to treat the same disease state. For some companies, it is not always in their financial interest to market multiple versions of a drug product, especially if a generic product of one of the versions exists. Consequently, some innovator companies may withdraw their products from the market as part of a business strategy decision.

The availability of generic products plays an

increasingly important role in helping to address rising health care costs and promoting access to medicines worldwide given that they are generally less expensive versions that are interchangeable¹ (1) with an existing innovator product. In the situation where the innovator product is no longer available, regulatory authorities have criteria for selecting alternative comparator products for bioequivalence studies to allow for the approval of generic products. In most cases, the criteria differ between jurisdictions but perhaps more importantly, the differences between the criteria are not necessarily well known by the pharmaceutical industry and regulatory communities. As a result, the sharing of information among the regulatory agencies could be used to facilitate possible convergence of criteria, which would benefit pharmaceutical companies developing generic medicinal products for all the jurisdictions.

The International Generic Drug Regulators Programme (IGDRP) was created to promote collaboration and convergence among generic drug regulators, and address the challenges posed by increasing workloads, globalisation, and complexity of scientific issues such as selecting an alternative comparator product. In 2018, the IGDRP merged with the International Pharmaceutical Regulators Forum (IPRF) to form the International Pharmaceutical Regulators Programme (IPRP) (2). The work that was begun by the Bioequivalence Working Group (BEWG) of IGDRP continues as part of the IPRP. The Bioequivalence Working Group for Generics (BEWGG) of IPRP aims to promote greater collaboration, regulatory convergence, and potential mutual reliance on respective bioequivalence assessments in the longer term (2). The group is composed of the following regulatory agencies: ANMAT, Argentina; ANVISA, Brazil; COFEPRIS, Mexico; EC, Europe; Health Canada, Canada; HSA, Singapore; INVIMA, Colombia; Medsafe, New Zealand; MFDS, Republic of Korea; CPED, Israel; MHLW/PMDA, Japan; SAHPRA, South Africa; Swissmedic, Switzerland; TFDA, Chinese Taipei; TGA, Australia; FDA, United States; and the WHO - Observer. As part of the ongoing work, the BEWGG previously published the results of surveys of participating members regarding the Biopharmaceutics Classification System (BCS)-based biowaiver requirements (3), biowaivers for

oral and injectable dosage forms (4), biowaiver requirements for additional strengths of immediate release (5) and modified release solid oral dosage forms (6), and acceptability of foreign comparators (7).

The requirements regarding the acceptability and conditions related to the use of foreign comparator products in bioequivalence studies for oral dosage forms were previously published (7) but did not describe situations where an alternative comparator product had to be selected when the local comparator product was unavailable. The objective of the current review paper is to describe the criteria used by regulatory agencies that participate in the BEWGG when selecting an alternative comparator product for a previously accepted comparator product that was withdrawn from the market and is no longer available. The complexities of selecting an alternative comparator are also described when one or more strengths in a series of approved strengths of a single medicinal ingredient comparator or when a fixed-dose combination product have been discontinued from the market.

MATERIALS AND METHODS

The BEWGG conducted a survey on the criteria employed to define an alternative comparator product when the medicinal product selected previously as a comparator product is no longer available to the generic manufacturer for use in a bioequivalence study. The information was obtained from the participating regulatory authorities and organizations in the BEWGG and is based on their respective regulations, guidance documents and policies (1, 6-31). For the purpose of the survey, the comparator product could have been withdrawn from an approved listing/register and market or just from the market. In either case, the comparator product is not available for use to demonstrate bioequivalence with a proposed generic. Furthermore, the survey was limited to the selection of comparator products for solid oral dosage forms, but for some participating members, the criteria may also apply to other dosage forms for establishing equivalence.

Terminology

For some members, the terms comparator product

¹ The FDA, United States uses the term “substitutability” or “therapeutic equivalent” for generic drug products. Under 21 CFR 314.3(b), therapeutic equivalents are defined as approved drug products that are pharmaceutical equivalents for which bioequivalence has been

demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

and reference products can have different meanings. For example, in Switzerland, a reference product is a medicinal product that is the locally marketed reference, whereas the comparator product is the medicinal product to which the medicinal product pending authorisation (*e.g.*, generic) is compared in the bioequivalence study (27). If the comparator product is the locally marketed product, then it is equivalent to the reference product. For most applications to Swissmedic, Switzerland, the comparator product is a foreign reference product purchased from a European Union (EU) member state. For the purposes of the survey, the terms are considered the same and may be used interchangeably regardless of the source of the product.

In the US, the *Reference Standard* (RS) is primarily the locally marketed innovator product (*Reference Listed Drug* (RLD)). If the RLD is withdrawn from the market, then an appropriate locally marketed alternative product will be selected as a RS. In addition, the newly selected reference standard will remain as such even if the original RS returns to the market.

RESULTS

General Aspects

The approval of an innovator product is generally based on the assessment of its quality, nonclinical and clinical development programs, and in some cases publicly available literature to establish its safety and efficacy. The innovator product is always considered the first option as a comparator product for a bioequivalence study.

The following BEWGG members list specific comparators to be used for bioequivalence studies: Brazil (*List of reference medicines* (32)), Colombia (*Anexo Técnico 2, Resolución número 1124 de 2016* (33)), Mexico (*Listado actualizado de medicamentos de referencia, 2021/01* (34)), the Republic of Korea (*K-Orange Book* (35)), Chinese Taipei (*Lists of local BA/BE/Dissolution studies of approved generic products* (36 and 37)), the US (*The Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* (38)) and the WHO-Observer (*List of International Comparator products (September 2016)* (39)). Only innovator comparators are listed in the Colombian lists. The WHO-Observer lists the international comparator products for the medicines on the Essential Medicine List (39) and the WHO Prequalification of Medicines Programme (WHO PQT/MED) identifies the comparator

products in the therapeutic areas of interest (Hepatitis B and C (40), HIV/AIDS (41), infections of newborns and young infants and childhood pneumonia (42), Influenza (43), Malaria (44), Neglected Tropical Diseases (45), Reproductive Health (46), COVID-19 (47) and Tuberculosis (48)) for the program and where the comparator products should be purchased.

Reasons for the withdrawal of the innovator product from the market can be the result of the following: safety or efficacy reasons, business reasons or other reasons within the respective jurisdictions. In most cases, if an innovator product is withdrawn for safety or lack of efficacy of the medicinal ingredient, any existing generic versions of the comparator product should also be withdrawn. Furthermore, the development and registration of any future generic versions of the innovator product will be discontinued. For example, under FDA, United States regulations (21 CFR 314.161) (29), the determination of whether an RLD was voluntarily withdrawn from the market for safety and efficacy reasons is published in the Federal Register and can occur at any time. The determination of whether the withdrawal was for safety or effectiveness reasons is made before the FDA, United States can approve a generic that references the RLD. In order to expedite the availability of generic drugs, the FDA, United States has decided that it may approve a generic for which the FDA, United States has made a final determination that the RLD was not withdrawn from sale for safety or effectiveness reasons even if that determination has not yet been published in the Federal Register.

Notwithstanding the safety and efficacy withdrawals, if a comparator product is withdrawn as part of business strategy reasons, it is generally still possible to develop generics by using an alternative comparator product in all jurisdictions.

For all participants, if a bioequivalence study was conducted before the withdrawal of the comparator product, the study can be submitted as part of an application to obtain marketing authorization for a generic product; however, if the comparator product is withdrawn from the market and is no longer available for purchase, several participating members have defined criteria to facilitate the selection of an alternative comparator product (8, 12, 16-18, 21, 22, 24, 26, 31). Furthermore, in most jurisdictions, a generic drug manufacturer also has the option to develop a new comparator product through the conduct of clinical trials and/or the use of third-party data (*i.e.* develop a

new drug product for the same medicinal ingredient) (Table 1).

Selection of Alternative Comparator Product

The following options are available among BEWGG participants for selecting an alternative comparator product (Table 1):

- a. Select a locally registered comparator product
 - i. generic product
 - ii. alternate innovator product
- b. Select a foreign comparator product
- c. Register a product that becomes the new comparator

a. Select a locally registered product

There are two types of locally registered comparator products that can be used for bioequivalence studies: i) generic products that have been shown to be bioequivalent to the locally registered innovator product; and ii) alternate locally registered innovator product(s) with nonclinical and clinical trial data, and/or scientific literature (*i.e.*, third-party data).

i. Generic product

Except for the EU, Israel, and Mexico, all remaining BEWGG members allow the use of an existing marketed generic product that was approved based on a comparison with the locally registered innovator product. The acceptability for using a marketed generic as an alternative comparator is currently assessed on a case-by-case basis in Mexico.

Argentina, Canada, Chinese Taipei, Colombia and Switzerland would allow the use of any locally approved and marketed generic as a comparator and the WHO PQT/MED would allow the use of an existing marketed generic product as an alternative reference product if it has been approved to be used as a comparator product by a Stringent Regulatory Authority (SRA) (*e.g.*, isoniazid 100 mg and 300 mg tablets manufactured by Sandoz, US) (49).

For several BEWGG members, the selection of a generic as an alternative comparator is dependent on varying factors. New Zealand, the Republic of Korea and the US designate the generic with the largest market share as the new comparator (24, 30, 50). In New Zealand, the Pharmaceutical Management Agency (PHARMAC), a government agency, decides which medicines and pharmaceutical products are subsidized for use in the community and public hospitals. In the case of generics, companies tender for a sole supply contract of a particular medicine (usually for three years) (50). As a result, the generic that was awarded the right to be the sole

subsidized brand is selected as the new comparator. In the Republic of Korea, a one-time review of the medical insurance claims, as reported by the Health Insurance and Assessment (HIRA) of the Ministry of Health and Welfare is conducted and the MFDS, Republic of Korea selects the product with the highest claim quantity of medical expense of health insurance from January 1 to December 31 of the previous year. In the US, if the innovator (RLD) is currently marketed it will be designated as the RS; however, if the RLD is withdrawn from the market and generics exist, then a generic will be designated as the new comparator (*i.e.*, RS). For example, the RLD for isoniazid is no longer available on the US market; as a result, the ISONIAZID 100 mg tablets from Barr Laboratories Incorporated was designated as the RS for isoniazid 100 mg tablets. The selection of the RS is generally based on the product's market share as well as other factors (*e.g.*, whether the new RS would prevent shortage of a particular drug product or a category of drug products). The *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* is updated monthly but generally, once a comparator is selected, it will remain the comparator until it has been withdrawn or there are factors which dictate that it should be revised (*e.g.*, safety concerns). Interestingly, if there is no RLD and a RS has not been assigned, the FDA, United States can then be requested to select a specific RS, provided a justification is submitted.

In Australia, Japan, Singapore and South Africa, the acceptability of a specific generic comparator is decided on a case-by-case basis, but a justification should be submitted by an applicant and include information regarding market leader status (10, 25, 26).

Brazil is the only BEWGG member that considers the degree of similarity between the reference and its multiple generics when selecting the alternative comparator. The criteria used to select a generic as an alternative comparator are based on the following parameters obtained from each bioequivalence study comparing the approved generic to the original comparator product: (i) the 90% confidence interval; (ii) the mean of $AUC_{test}/AUC_{reference}$; (iii) the mean of $C_{max, test}/C_{max, reference}$; and (iv) the overlapping of partial pharmacokinetics curve. The generic that exhibits the most similarity with respect to the four parameters would be designated as the new comparator (12). The comparators for all medicinal ingredients in their respective strengths or concentrations and dosage forms are published in a

positive list (*List of Reference Medicines* (32)) that is updated as required. Only one comparator is listed per dosage form, strength, and medicinal ingredient. For example, amoxicillin oral suspension is available in several strengths in Brazil but there are different comparator products for each strength: AMOXIL 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL oral suspension by GlaxoSmithKline and NOVOCILIN 400 mg/ 5mL oral suspension by Aché.

Notwithstanding the acceptability of a generic as a comparator, it is not the preferred comparator for several jurisdictions. In Argentina, Colombia, New Zealand and South Africa, the use of a generic comparator is acceptable only when an innovator sourced from a foreign market cannot be used based on defined criteria or is unavailable (8, 16, 17, 22, 26).

ii. Alternate Innovator Product

It is possible to have several innovator products for the same medicinal ingredient; therefore, if one of the innovator products is withdrawn from the market, a generic manufacturer could continue to develop a generic product by choosing one of the other available innovator products to demonstrate bioequivalence.

There are cases where multiple innovator products may share the same nonclinical and clinical data as a result of co-development between two or more manufacturers, or a manufacturer licensing the product from another manufacturer. For example, mupirocin ointment is marketed in France as Mupiderm by Almirall, S.A. through a licensing agreement with Laboratoire GlaxoSmithKline, which used to market the ointment as Bactroban. Brazil, Chinese Taipei, and Mexico accept the use of comparator products in the order that they were approved, even if they were co-developed. In other instances, there could be different innovator products that were approved based on completely different nonclinical, clinical studies and/or scientific literature. In either case, the use of either innovator product would be considered acceptable as a comparator product by all BEWGG members with the exception of Brazil, Chinese Taipei and Mexico. For example, ribavirin is marketed in the EU by Roche Products Limited and Merck Sharp & Dohme Limited and either product would be considered acceptable as a comparator product by EU member states. Caution should be exercised when selecting a comparator where multiple innovator products exist for a specific medicinal ingredient since the formulation and pharmacokinetics may differ

between the innovator products. As a result, demonstrating bioequivalence against one innovator does not necessarily equate to bioequivalence against the other innovator.

b. Select a foreign reference product

The criteria regarding the acceptability of the use of a foreign reference product in Australia, Canada, Chinese Taipei, New Zealand, Singapore, South Africa, Switzerland, and the WHO-Observer was previously described (7) and have since been updated for Australia (11). In general, most countries would prefer the use of a locally-registered innovator product; however, in Australia, Israel, New Zealand, Singapore, South Africa and Switzerland, applicants frequently use a foreign comparator product for bioequivalence studies when country-specific requirements such as qualitative and quantitative comparison data (*e.g.*, excipient comparison and reverse engineering data) and physicochemical comparison data (*e.g.*, dissolution data and physicochemical properties) between the locally sourced reference and the foreign comparator can be met (7, 11). Consequently, with the exception of Argentina, Colombia, Israel, Mexico, New Zealand and South Africa, the use of a foreign reference comparator would not normally be permitted if the locally sourced innovator is removed from the market since it would not be possible to generate comparative data between the locally sourced innovator and the foreign reference.

In Argentina, Colombia and Mexico, the acceptance of a foreign comparator from another jurisdiction is allowed only if the locally sourced innovator comparator is no longer available (8, 16, 17). In such cases, a detailed decision tree is described for selecting an alternative comparator for Argentina and Colombia (8, 17). In Argentina, if the locally sourced innovator product is not available, a comparator product identified in the WHO Technical Report No. 902 from 2002 or later (31), or an innovator product marketed in and purchased from an ICH member country identified in Annex 1 (*e.g.*, the EU, Japan and the US) could be used in a bioequivalence study (8, 9). Similarly, for Colombia, an innovator marketed in a reference country (*i.e.*, Australia, Canada, the EU, Japan, Switzerland, and the US) could be imported for use in a bioequivalent study. In Mexico, an innovator product marketed in Australia, Brazil, Canada, the European Union, Japan, Switzerland, and the US could be used as a comparator. If the innovator product is not available in any of the reference countries, then an alternative

foreign innovator product (*i.e.*, a different innovator product containing the same medicinal ingredient) could be used in Argentina and Colombia if it was approved based on clinical trial safety and efficacy data and has been designated as a comparator by a foreign reference agency. For the three members, if neither foreign comparator is available, a locally sourced generic could then be used as an alternative comparator in a bioequivalence study.

Israel, New Zealand, and South Africa have similar guidelines for selecting a foreign reference comparator if the local-registered innovator product is no longer available. In Israel, an innovator marketed in a reference country (Australia, Canada, the EU, Iceland, Japan, New Zealand, Switzerland, and the US) could be used as a comparator product in a bioequivalence study if pharmaceutical bridging data based on a qualitative comparison of the excipients between the withdrawn innovator product and the foreign reference comparator is provided (19). Qualitative information regarding the formulation for the innovator product is indicated on the labelling and is available even after the innovator is no longer available. In New Zealand, a reference product from Australia can be used if essential similarity is demonstrated through evidence that the same innovator product was marketed in both New Zealand and Australia (*i.e.*, innovator was harmonized for the New Zealand and Australian market) (22). An alternative foreign reference product (*e.g.*, from the EU) may also be used based on essential similarity testing conducted against the Australian innovator if evidence can be provided to confirm that the same innovator product was marketed in both New Zealand and Australia (22). In South Africa, the use of a foreign comparator from a country that SAHPRA, South Africa aligns itself with or a comparator selected from the *WHO International comparator products for equivalent assessment of interchangeable multisource (generic) products* QAS/05.143 could be used (26).

Brazil does not normally accept the use of a foreign comparator; however, if the local-registered innovator product is no longer available, the acceptance of a foreign comparator product as an alternative comparator product would be considered on a case-by-case basis. For example, the use of a foreign comparator would be acceptable in Brazil if evidence is available demonstrating that the foreign comparator is identical to the Brazilian reference product with respect to chemistry and manufacturing and if the unavailability of the Brazilian reference

product is only for a defined period of time (*e.g.*, reduced market supply) (13).

For EU member states, any suitable reference available within the EU jurisdiction is considered acceptable even when the product is marketed in only one member state. However, non-EU reference products are not considered acceptable for generic applications (18). Similarly, Japan, the Republic of Korea and the US would not accept a foreign reference product as a comparator in a bioequivalence study for generic applications (30).

c. Register a product that becomes the new comparator

For some jurisdictions, if an innovator product was withdrawn from the market, it is possible to develop a new product for a medicinal ingredient without duplicating safety and efficacy studies. For example, an option exists under the EU regulatory framework where a well-established use application (Article 10a, also known as a bibliographic application) is allowable if the medicinal ingredient of the product has been used for at least 10 years in the EU, and the safety and efficacy are well documented in the scientific literature (*i.e.*, third-party data). It is preferred that supportive data be provided to demonstrate that the evidence available in the literature is applicable to the proposed product (*e.g.*, by showing similar exposure with the product described in the literature, which might be available in another country outside the EU) (51).

Similarly, the 505(b)(2) New Drug Application (NDA) within the US regulatory framework also allows for drug manufacturers to gain approval of a drug product through the comparison with a comparator that has the same active ingredient, dosage form, route of administration and strength as the RLD without necessarily demonstrating bioequivalence (52). For the approval of a 505(b)(2) NDA, the demonstration of safety and effectiveness of the drug product are required, with some information based on studies not conducted by or for the applicant (including literature) for which the applicant has not obtained a right of reference or use (52).

Australia, Canada, and Switzerland also have similar application processes (Literature-Based Submission (LBS) in Australia (53), Submission Relying on Third-Party Data (SRTD) in Canada (54) and Article 14 para. 1 letter a^{bis} TPA (medicinal products whose active substances are used in a medicinal product that has been authorized in an EU

Table 1. Comparison of alternative comparator product selection among IPRP BEWGG participants when innovator product is no longer available marketed locally. (Y: Yes or Acceptable; N: No or Not acceptable; C: case-by-case)

	Argentina	Australia	Brazil	Canada	Chinese Taipei	Colombia	European Union	Israel	Japan	Mexico	New Zealand	Singapore	South Africa	Republic of Korea	Switzerland	US	WHO-Observer
Has a positive list of acceptable comparators	N	N	Y	N	N	Y	N	N	N	Y	N	N	N	Y	N	Y	Y
Other locally registered product bioequivalent to innovator product (<i>i.e.</i> , generic product)	Y	Y	Y	Y	Y	Y	Y ^a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
with nonclinical and clinical trial safety and efficacy data	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
with nonclinical and clinical literature-based data	C	Y	N	Y	N	C	Y	C	N	N	C	C	C	N	Y	Y ^b	N
Foreign reference product	Y	Y	Y ^c	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	N	Y ^d

^aProducts registered in any EU member state; ^bSee 505(b)(2) NDA (52); ^cForeign reference product must be the same as the Brazilian reference product; ^dForeign/international reference products.

or European Free Trade Association (EFTA) country for at least 10 years) in Switzerland (55)) that allow for the use of third-party data. While not explicitly described in Argentina, Colombia, Israel, New Zealand, Singapore and South Africa guidance documents, a literature-based application may also be submitted on a case-by-case basis. The caveat for the described application processes is that the approved product would not be considered as a generic product but rather as a new alternative innovator comparator. Conversely, Brazil, Chinese Taipei, Japan, Mexico, the Republic of Korea, and the WHO PQT/MED would not allow the use of a product that was approved based on literature as an alternative innovator comparator product, while the US will permit the use of the product on a case-by-case basis.

Different strength of innovator/comparator product

In general, a bioequivalence study should be performed on the same strength of the proposed generic product and the comparator product. For approval of any strength within or outside the approved strength range, the main variables considered by participating agencies are the therapeutic dose range, pharmacokinetic linearity, and type of dosage form (*e.g.*, immediate-release vs. modified-release).

Although rare, there are situations where one strength from a series of approved strengths of the innovator product is discontinued from the market

(*e.g.*, 1 mg strength discontinued from currently marketed 1 mg, 2.5 mg, and 5 mg strengths). Assuming that the strength was not discontinued for safety and efficacy reasons, all jurisdictions would accept the conduct of a bioequivalence study using a different strength (*e.g.*, 5 mg) of both generic product and the comparator product, and a waiver from conducting bioequivalence studies on the other strengths based on proportionality. Similarly, if the 5 mg strength was withdrawn, a bioequivalence study conducted against the 1 mg strength or the 2.5 mg strength, and a waiver from conducting a bioequivalence study for the 5 mg strength could be granted in Argentina, Australia, Brazil, Canada, Chinese Taipei, Israel, Japan, Mexico, New Zealand, the Republic of Korea, Singapore, South Africa, Switzerland and the US), provided that the waiver requirements for each jurisdiction are met (*e.g.* linear pharmacokinetics). In Colombia, the EU and WHO PQT/MED, a waiver from conducting a study with the 5 mg strength of the generic product would only be considered acceptable if the drug substance is highly soluble according to the BCS or if the 5 mg dose is not tolerable by healthy volunteers. As a result, a study comparing 1 x 5 mg of the generic product to 2 x 2.5 mg of the comparator product is recommended.

Using the same example of when the 5 mg strength was discontinued but the active substance is poorly soluble according to the BCS, several jurisdictions would also accept a bioequivalence study with the same dose but difference strengths

(e.g. 1 x 5 mg strength of the generic product is compared to 2 x 2.5 mg strength of the comparator product) given that a waiver from conducting a study with the 5 mg strength based on proportionality to the 2.5 mg strength may not meet comparative dissolution profile requirements. In addition to the EU and the WHO PQT/MED, Australia, Brazil, Chinese Taipei, Colombia, Israel, Mexico, New Zealand, the Republic of Korea, Singapore, South Africa, Switzerland and the US would accept the use of different strengths to reach the same dose while Argentina, Canada, Japan would not prefer or allow such a comparison since the bioequivalence study should be conducted with the same dosage form containing the same amount of the medicinal ingredient. Interestingly, if generic versions of the 1 mg, 2.5 mg and 5 mg strengths were approved prior to the withdrawal of the innovator 5 mg strength, the generic 5 mg strength would not be considered as an alternative comparator in Australia, Canada, Chinese Taipei, Colombia, Japan, Singapore, and the WHO PQT/MED given that the innovator 1 mg and 2.5 mg strengths are still available. As a result, a study comparing the 1 x 2.5 mg proposed generic to the currently marketed 2.5 mg innovator product would be required to limit the amount of “formulation creep” (i.e., differences in the formulation and/or manufacturing) between the innovator and subsequent generic products.

In cases where drugs exhibit non-linear pharmacokinetics in the range of 1 mg to 5 mg, the acceptability of waiving studies for the 1 mg or 5 mg strengths in the preceding examples will depend on the requirements for additional strength biowaivers of the IPRP member (5, 6). For example, for immediate-release drug products that exhibit non-linear pharmacokinetics due to limited solubility of the medicinal ingredient and resulting in less than proportional increases in AUC with increasing dose, bioequivalence studies conducted on at least the lowest strength (or a strength in the linear pharmacokinetic range) and the highest strength would be required by most jurisdictions; therefore, in the situation where the 5 mg innovator strength was withdrawn, Canada would not allow approval of the 5 mg strength, while Australia, Brazil, the EU, Israel, Mexico, Chinese Taipei, Colombia, New Zealand, the Republic of Korea, Singapore, South Africa, Switzerland the US and the WHO PQT/MED would accept a comparison between 1 x 5 mg strength of the proposed generic and 2 x 2.5 mg strength of the innovator as emphasis is placed upon detecting product performance differences at a dose level

where the non-linear pharmacokinetics occur. Argentina and Japan would assess the suitability of dose and strength on a case-by-case basis.

For the same example of an approved series of innovator strengths (i.e., 1 mg, 2.5 mg, and 5 mg strengths), if a generic manufacturer wanted to market an additional 10 mg strength, all members would only consider the approval of the 10 mg strength if it was within the approved therapeutic dosing range. Of note, all members would consider the approval of the 10 mg as a generic product except for Australia and the EU since the innovator was not available as a 10 mg strength. The approval of the 10 mg strength would be submitted as a Major Variation (Additional Strength) Application in Australia and as a hybrid application in the EU (51). For example, if the labelling (e.g., Summary of Product Characteristics (SmPC)) of the innovator product includes the possibility of administering a 10 mg dose with two units of a 5 mg strength, then the approval of the 10 mg strength could be justified. A bioequivalence study could be conducted that involves a comparison between 1 x 5 mg strength of both the proposed generic and innovator, and a waiver from conducting a study with the 10 mg strength could be granted if the pharmacokinetics are linear within the 1 mg to 10 mg dose range and the 10 mg strength is proportionally formulated to the 5 mg strength. Formulation proportionality between the 5 mg and 10 mg strengths is not required in Japan but the differences in the strengths should meet the requirements described in the guideline for waivers of bioequivalence studies (56). If the medicinal ingredient exhibits low solubility (3), Australia, Brazil, Chinese Taipei, Colombia, the EU, Israel, Mexico, New Zealand, the Republic of Korea, Singapore, South Africa, Switzerland, the US and the WHO PQT/MED would allow or require the comparison between 1 x 10 mg strength of the proposed product and 2 x 5 mg strength of the comparator product, while Argentina, Canada and Japan would not prefer or allow such a comparison. Notwithstanding Canada's preference for a comparison of the 5 mg strengths of the proposed generic and the innovator comparator and granting a waiver from conducting a study with the 10 mg strength, if dissolution cannot support the proportionality of the 10 mg strength due to low solubility, Canada would then allow a comparison between the 1 x 10 mg generic strength and 2 x 5 mg of the innovator comparator strength.

If the 10 mg dose is not within the approved therapeutic dosing range of the innovator product, all

members would require clinical and other relevant data to support the approval of the 10 mg strength and would not consider the 10 mg strength as a generic product.

Several members would also allow for a dose-normalization approach (assuming dose-proportional pharmacokinetics) where there is a difference in strengths between the generic product and the comparator that does not allow for the administration of the same dose. For example, the recommended WHO PQT/MED comparator products for pyrazinamide are available as a 500 mg strength (48); however, the WHO PQT/MED requests that generic manufacturer also develop a 250 mg strength and a 400 mg strength of the proposed generic (49). If the pharmacokinetics of the medicinal ingredient are linear within the therapeutic dose range, all participants except Argentina, Canada, Colombia, Israel, Japan, Republic of Korea, and the US would accept dose-normalized pharmacokinetic parameters for assessing bioequivalence. Singapore would consider the acceptability of dose-normalization on a case-by-case basis (Table 2).

Fixed-dose combination (FDC)

When the FDC innovator product is no longer registered locally, Australia, Chinese Taipei, Colombia, Israel, New Zealand, South Africa, the US, and the WHO PQT/MED would accept individual single-component products as comparator products (*e.g.*, proposed FDC generic product *versus* the co-administration of acceptable single-component comparator products) if it is known that the innovator FDC was bioequivalent to those individual comparator products (Table 3). In addition, the approval of the FDC can also occur if the single components are indicated to be administered concomitantly. The situation occurs frequently for the WHO PQT/MED since many of the expression of interest (EoI) therapeutic areas include fixed combination products for which an FDC comparator product does not exist (57). As a result, the approval of the FDC products is based on a comparison with the WHO PQT/MED recommended single-component comparator products (41).

While Argentina, Brazil, Canada, the EU, Japan, Mexico, the Republic of Korea, Singapore, and Switzerland would not accept the use of single-component comparators for the approval of an FDC generic, with the exception of Switzerland, they would allow the use of single-component comparators for approval as a non-generic drug

product (*i.e.*, new drug product/alternative innovator comparator). Colombia and Switzerland would decide on case-by-case basis if single comparators could be used for the approval as a non-generic FDC. Notwithstanding the manner by which the proposed FDC is approved, most jurisdictions would consider it as a comparator product (Table 3).

DISCUSSION

The results of the survey demonstrate that while criteria for selecting alternative comparator products are not harmonized among the BEWGG participants, the common concern for all jurisdictions is to select a comparator product that meets the safety and efficacy standards of the original innovator product. As a result, most jurisdictions have policy and guidance documents (8-10, 12, 15-19, 21-23, 25-28, 30, 31, 52) based on regulations (1, 14, 18, 20, 23, 29, 33) that enable risk-based assessments for selecting an alternative reference/comparator product that is either a locally-sourced generic or a foreign innovator comparator. In the EU, no such options are available but rather mechanisms are in place to allow manufacturers to develop a new comparator.

As described previously (7), the criteria for allowing the use of foreign comparator products appear to correlate with the market size of the jurisdictions, purchasing power of the population and the availability of local manufacturers. Similar factors also appear to play a role in determining whether a locally sourced generic or a foreign product should be used as an alternative comparator when the local innovator comparator is no longer available.

Brazil, Japan, the Republic of Korea, and the US benefit from having larger populations and the presence of local innovator product manufacturers, which allow for them to require the use of locally sourced generics as alternative comparators. The advantage for using locally sourced generics as an alternative comparator is that the safety, efficacy, chemistry and manufacturing, and pharmacovigilance (post-market) data are well known by the regulatory agency. Furthermore, the use of a local generic would help limit the amount of “formulation creep” between the innovator and subsequent generic products and maintain the level of “interchangeability” between the generics. While it can be argued that it is better off to use a foreign comparator product from the same innovator company, the foreign comparator product may be

Table 2. Comparison of Requirements Regarding the Use of Different Strength as Comparator Products Among IPRP BEWG Participants (Y: Yes; N: No; ND: Not Defined)

	Argentina	Australia	Brazil	Canada	Chinese Taipei	Colombia	European Union	Israel	Japan	Mexico	New Zealand	Singapore	South Africa	Republic of Korea	Switzerland	US	WHO-Observer
Accept the use of different strengths to reach the same dose	N	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Accept the approach of dose-normalized PK parameters (under linear PK situation)	N	Y	Y	N	Y	N	Y	N	N	Y	Y	Y	Y	N	Y	N	Y

Table 3. Comparison of Requirements Regarding the Fixed-dose Combination (FDC) Among IPRP BEWG Participants (Y: Yes; N: No; ND: Not Defined, C: Case by Case)

	Argentina	Australia	Brazil	Canada	Chinese Taipei	Colombia	European Union	Israel	Japan	Mexico	New Zealand	Singapore	South Africa	Republic of Korea	Switzerland	US	WHO-Observer
Accept individual single-component product as comparator products for generics	N	Y	N	N	Y	Y	N	Y	N	Y	Y	N	Y	N	N	Y	Y
Accept individual single-component product as comparator products for non-generics	Y	Y	Y	Y	Y	C	Y	Y	Y	Y	Y	Y	Y	Y	C	Y	Y
- FDC considered as alternative comparator product	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	C	C	Y

different than the locally sourced innovator product with respect to chemistry and manufacturing, resulting in differences in product performance. Information regarding the foreign comparator product is not readily accessible across member jurisdictions.

Brazil, the Republic of Korea, and the US have publicly available positive lists, but the criteria used to select a comparator product differ. Brazil is unique with respect to the selection of a generic as an alternative comparator since the selection is based on the pharmacokinetic similarity of the generic to the reference to which it was compared in a bioequivalence study (12). Interestingly, Brazil has recently modified their regulations to allow for the use of a foreign innovator comparator on the conditions that there is evidence that the foreign innovator comparator is identical to the Brazilian reference product and the Brazilian reference product is only unavailable for a limited amount of time (13). For the Republic of Korea and the US, the selection

of a generic as a comparator (RS in the US) is generally based on the product's market share. Japan would consider the acceptability of a specific generic as a comparator on a case-by-case basis.

Australia and Canada do not have populations comparable to Brazil, the Republic of Korea, and the US, yet both require the use of a locally sourced generic as an alternative comparator given that the use of a foreign reference product would not be permitted due to the requirement of providing comparative pharmaceutical bridging data between a foreign reference product and the locally sourced innovator product. It has been reported by the International Generic and Biosimilar Medicines Association that both countries have relatively high market penetration of generic medicines when compared to the rest of the world (58). As a result, current regulations permit Australia and Canada to require the use of a local generic to maintain the level of "interchangeability" within their relatively large generic markets.

Australia considers as part of a justification, the use of a generic with the largest market share. In Canada, it was previous practice to designate the generic with the largest market share as the comparator based on IMS Health (now IQVIA) data; however, the criterion was removed since market sales for a generic fluctuated from year to year. Furthermore, it should not be assumed that the formulation and manufacturing of any product is static over time. To use a local generic as a comparator, evidence must be provided to support that the approval of the proposed comparator (generic) was based on the demonstration of bioequivalence to the innovator product. In most cases the labelling for the generic (*e.g.*, Canadian Product Monograph) contains information regarding the bioequivalence study that was used to approve the generic. Nevertheless, most generic manufacturers tend to use the local generic that has significant market share in Canada. Neither of the countries have lists specifying specific comparator products to be used for bioequivalence studies; therefore, if a generic manufacturer is unsure of what generic product to use for a study, consultation with the appropriate agency is recommended.

For the remaining countries with smaller populations, there is a commonality such that reference products from the larger countries with recognized regulatory authorities (*e.g.*, Australia, Canada, the EU, and the US) or those listed on the WHO positive lists are used. Emphasis is then placed more on the fact that the foreign reference products provide adequate safety and efficacy while not necessarily being interchangeable with currently marketed local generics (*i.e.*, foreign reference product may not be bioequivalent to discontinued local reference product). However, given that the smaller countries more often than not, accept the use of foreign comparator even when the locally sourced reference product is available, the preferred use of a foreign comparator is consistent with this practice. Argentina, Chinese Taipei, Colombia, New Zealand, Singapore, and South Africa prefer the use of a foreign innovator comparator but if the foreign innovator comparator is not available, any generic could be used in Argentina and Singapore (if suitably justified), the established decision tree would be used for Argentina and Colombia and the market leader generic would be recommended in New Zealand and South Africa. Switzerland has no preference for use of either locally sourced generic or foreign innovator but in most cases, a foreign innovator comparator is almost always used if it meets pre-defined criteria.

The rationale for use of a foreign reference product is likely due to the assumption that the reference products marketed in the larger countries or founding International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) countries are the same as those marketed in the smaller countries (7). The same rationale holds true for the use of recommended reference products indicated on the WHO positive lists (40-48).

Mexico appears to adopt a hybrid approach of both the small and large countries where a positive list of local innovator comparators is available and the use of a foreign comparator from a select group of countries is also allowed if the local innovator comparator is no longer available. If neither option is available, the acceptability for using a generic would be assessed on a case-by-case basis.

The EU is unique when compared to the other BEWGG participants such that it consists of multiple countries, but legislation require that all member States accept the comparator product from the market of any other member state with respect to the approval of generic medicines. Drugs that are approved according to Articles 8.3, 10a, 10b and 10c of Directive 2001/83/EC (59) are considered as complete dossiers that can be used as comparators for the development of generic medicines. For example, the reference product for omeprazole gastro-resistant capsules was withdrawn from several member states due to the market introduction of a new reference dosage form (MUPS, multiple unit pellet system) of omeprazole. To gain approval of a generic omeprazole gastro-resistant capsule when the locally sourced reference was withdrawn, generic companies had two options: 1) submit an application with a BE study with the national/local reference product conducted before its withdrawal; or 2) conduct a bioequivalence study against a reference gastro-resistant capsule from any EU member state where it is still marketed. In either case, the point of emphasis is that the reference from any other EU member state is acceptable for use in a bioequivalence study. Reference products obtained from outside of the EU are not considered acceptable for the development of a generic. The potential risk regarding the use of a comparator from any member state was previously described (7) and ultimately leads to questions regarding the “interchangeability” of generics at the state level but does not preclude the approval of a generic product.

If the EU reference product is withdrawn from all member states, then the generic manufacturer may develop a new reference product via one of the

following pathways (e.g. Articles 8.3, 10a, 10b and 10c). For a generic manufacturer, the simplest route to develop a complete dossier would be to file an Article 10a (well-established use or bibliographic) application. Australia, Canada, New Zealand, Singapore, Switzerland, and the US have similar application processes that allow for the use of third-party data. In all cases, the approved product would not be considered as a generic since bioequivalence was not demonstrated to an acceptable reference product.

As noted, how the approval of different strengths and FDC products varies across the jurisdictions with no apparent correlation; however, what appears to be more interesting is whether the approved product can be classified as a generic. The importance of labelling an approved product as generic or “not generic” may not be relevant on a regulatory approval basis but rather regarding the potential reimbursement and “interchangeability” of a generic. Generally, for business and financial reasons, generic manufacturers would rather gain approval of a product as a generic that is interchangeable with an innovator product rather than be approved as a new reference product. In most cases, when a patient goes to a pharmacy to fill a prescription, the pharmacist can supply the brand-name (innovator) or generic drug product listed on formularies (or drug plan product lists) as interchangeable for the prescribed medicine. The cost of the drugs may be paid for or subsidized by government or private drug plans with the remaining costs paid by the consumer.

In summary, the concern should not be whether it is more appropriate to use a locally sourced generic or a foreign comparator as an alternative comparator but rather what alternative comparator is best suited for the intended use of the generic. The term “interchangeability”¹ (1) has been mentioned and generally implies bioequivalence between drug products; however, interchangeability includes two components: the “switchability” in patients already under treatment and the “prescribability” for newly diagnosed patients or acute treatments (60).

If a jurisdiction has high availability of currently marketed generic products, then it may be more appropriate to use a locally sourced generic as the alternative comparator to ensure acceptable “interchangeability”. Such is the case with countries like Australia, Brazil, Canada, Japan, the Republic of Korea, and the US. However, if generics are limited or unavailable for a specific market, then perhaps the sourcing of a foreign reference as an alternative

comparator is appropriate given that the foreign sourced reference is expected to be more similar to the withdrawn innovator than currently approved generic products. For applicants submitting to the WHO PQT/MED, in most cases, the availability of generics in the applicable country may be lacking. As a result, the use of recommended reference products is obviously a necessity and ensures that the proposed generic will meet acceptable safety and efficacy standards (i.e., “prescribability”).

The situation for the EU contrasts with the concept of high market penetration of generics given that the use of a generic as an alternative comparator is not permitted. Given that the EU requires all member states to accept the comparator product from the market of any other member state without evidence confirming that they are the same or even similar, the “switchability” cannot be ensured and only “prescribability” is of interest for granting marketing authorisation. The prevention of using a generic as an alternative comparator may be a mechanism to ensure no additional formulation creep is introduced in the generic market and member states are responsible for the substitution policies.

CONCLUSION

The criteria for selecting an alternative comparator product among the BEWGG participants vary and appear to be dependent on generic availability and the intended use of the generics (i.e., substitution in previously treated patients or simply prescription). There appears to be a trend where jurisdictions with larger populations and/or a relatively substantial generic market prefer the use of locally sourced generics as the alternative comparator to ensure “interchangeability” within the existing generic market. Conversely, those jurisdictions with smaller populations and/or a smaller generic market would prefer the use of a foreign comparator that resembles the withdrawn innovator. In each case, it appears that the risk-based practices ensure a similar safety and efficacy profile for subsequent generics (“prescribability”) and “switchability” between existing generics. Notwithstanding the complexities of each jurisdiction, the pharmaceutical industry should find the information from this review interesting and helpful for the selection of comparator products for the conduct of bioequivalence studies among the BEWGG members.

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