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Commentary

Global Harmonization of Comparator Products for Bioequivalence Studies

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Abstract. Comparator products should be the products that were shown to be safe and efficacious in pivotal clinical trials to ensure prescribability of generics. The use of a common comparator ensures switchability between generics. The selection of the comparator is a national responsibility and may be different between countries. This paper discusses the current recommendations on selection of comparators, the associated problems, and the possibility of harmonization. Most countries follow the World Health Organization (WHO) recommendations for selecting comparator products and require the comparator product to be obtained from their national markets to ensure switchability between the local comparator and their generics. These recommendations are only feasible in the few countries where the repetition of the bioequivalence study is economically feasible, but they are impracticable in all other countries. Furthermore, the exclusive use of the local comparator to ensure switchability is ethically and scientifically questionable. The innovator product from well-regulated markets should be the global comparator. This harmonization is feasible as the concept already applies in the WHO prequalification program. It is ineffectual to harmonize only the requirements for performing bioequivalence studies, if such a study has to be repeated for every single country simply because of the different comparator products.

KEY WORDS: bioequivalence study; comparator product; generic drug development; generic drug product; generic medicines; harmonization; interchangeability; reference product.

INTRODUCTION

An innovator product demonstrates efficacy and safety through preclinical and clinical development, whereas generic medicines, which are marketed after the expiry of the patent and other market exclusivity rights of the innovator product, only have to show equivalence to the innovator product. Accordingly, WHO recommends the approval of generic medicines by the national medicine regulatory authorities (NMRA) based on demonstration of interchangeability with the innovator product through bioequivalence studies (1), since bioequivalence is accepted as a surrogate for equivalent safety and efficacy.

Interchangeability implies that the generic medicine can be prescribed in place of the innovator product in a new/naïve patient under the same conditions (prescribability) (2, 3), and it can also be substituted in place of the innovator product in patients under chronic treatment (switchability) (4, 5). Additionally, demonstration of bioequivalence of all generics with the same innovator product is considered to be an indirect demonstration of switchability between the generics (2). Then, generic medicines become important in public health programs because they reduce the cost of medicines providing the same level of efficacy and safety as the innovator or comparator product.

Harmonization of bioequivalence requirements, though incomplete, has yielded significant benefits to both industry and regulators. Nonetheless, there is a need for complete harmonization (6) because it is ineffectual to harmonize only the requirements for performing bioequivalence studies if such a study has to be repeated for every single country simply because of the different local comparator products. Presently, each NMRA identifies the comparator to be used as reference in the bioequivalence studies of the generics for their market, as this is recognized as a national responsibility (7). Consequently, the choice of the appropriate comparator

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for a generic manufacturer intending to market in several countries may be confusing, because the selection criteria may be heterogeneous between jurisdictions, necessitating multiple studies to demonstrate bioequivalence to the different national comparators. This is further complicated when different innovator products or different formulations or dosage forms of the same innovator are available in different markets. Nonetheless, considering the globalization of the pharmaceutical industry, it could be considered unreasonable to perform several bioequivalence studies due to differences in the local comparator. Standardizing comparator products is not only of interest and benefit for development of generic products but also in clinical documentation of combination treatments and for use as comparator product in clinical phase III trials.

The aim of this paper is to comment on the current recommendations and practices on the selection of an appropriate comparator product, the problems associated with that selection, and the possibility of a global or regional harmonization to use a common comparator product.

WHO RECOMMENDATIONS TO NATIONAL REGULATORY AUTHORITIES ON SELECTION OF A COMPARATOR PRODUCT

The comparator product is defined by the WHO as a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The WHO provides recommendations to national regulatory authorities on how to select an appropriate comparator product (7). Briefly, in order of priority, the WHO recommended comparator product should be as follows: (i) an innovator product available on the local market, (ii) national market leader product for which a national marketing authorization has been granted, (iii) a WHO comparator product, (iv) an innovator product imported from an ICH country, and, lastly, (v) a product that has been granted approval in an ICH country. In some cases, where the innovator has never been available in that market and bioequivalence was never demonstrated, the national market leader may not have a direct link to the innovator product in terms of safety and efficacy if the market leader is not bioequivalent to the innovator product and exhibits clinically relevant bioavailability differences. The WHO recommends that only when there is no innovator in the local market should a foreign reference be accepted or local market leader (from a company different from the innovator company).

The WHO recommends that a generic product should not be used as a comparator as long as an innovator pharmaceutical product is available (7), because this could lead progressively to less similarity between the systemic exposure that has shown to be safe and efficacious by the innovator (or the systemic exposure of other existing generics) and that of any future generic product that is approved by comparisons to the generic selected as the new comparator. This is called "biocreep." For example, bioequivalence data for efavirenz, a poorly soluble drug with low intra-subject variability, shows generic products with higher or lower bioavailability, but bioequivalent to the reference (Atripla®) (8), *e.g.*, 90% confidence interval for HA527 is 89.38–98.5% (lower bioavailability), while that of HA562 is 101.5–118.5% (higher bioavailability). If Atripla® is no longer available in a national market and one of these generics (*e.g.*, the market leader) is selected as new reference in bioequivalence studies for approval of new generics, say HA527 (as reference), then new generics with lower bioavailability compared to HA527 have systematic decreasing bioavailability compared to the innovator, Atripla®, and will not be bioequivalent when compared with Atripla® or the existing generics like HA562. If the future generics were not bioequivalent to the systemic exposure that was shown to be safe and efficacious, the prescribability of the new generics would be compromised, and if the future generics were not equivalent to the existing generics that showed to be bioequivalent to the innovator, their switchability would be compromised.

In principle, a comparator product should have or maintain a direct link with the product that was shown to be safe and efficacious in phase III clinical trials to ensure prescribability and switchability in clinical practice. Consequently, the requirements for comparator products for the WHO Prequalification Team-Medicines (WHO PQT-m) (www.who.int/prequal) define that the sources or markets/countries from which the comparator product should be obtained are those that have robust pre- and post-market regulatory systems and, in addition, the availability of extensive documented safety and efficacy data from post-marketing surveillance, *i.e.*, stringent regulatory authorities. It is generally accepted that countries that are founding members of the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) fulfill these requirements.

A PATH TO HARMONIZATION OF REQUIREMENTS FOR COMPARATOR PRODUCT SELECTION

Ideally, globally accepted comparator products would decrease the number of *in vivo* bioequivalence studies and reduce the cost of generic drug development. Therefore, the logical first harmonization step should be the acceptability of foreign or international comparator products. Moreover, there is little knowledge gained by repeating exactly the same design for each individual country where the generic company desires to market its product.

Harmonization of the comparator would allow for more in-depth knowledge about a generic-comparator relationship, by asking for additional types of studies if necessary, *e.g.*, fasting and fed studies, with different strengths (9), or in patients under real conditions of use (10) without increases in costs because generic companies have to do many studies as the situation stands now. So, better generics would result from this harmonization because they could demonstrate bioequivalence to the comparator under more diverse conditions in those areas where bioequivalence problems might be identified in the future.

Countries with large pharmaceutical market sizes may be able to enforce the requirement for local comparators in bioequivalence studies that have to be submitted for the approval of generic medicines. The USA, Europe Union (EU), and Japan account for more than two-thirds of the over US$ 1 trillion global pharmaceutical market (11). Therefore,

from a business point of view, repetition of bioequivalence studies with a local reference product may be justified in these cases. At most, this will mean a limited number of bioequivalence studies using the US, European, and Japanese comparator products. On the contrary, for low- and middle-income countries (LMICs) with relatively small market sizes enforcing procurement of the comparator product from their local markets may be impractical because the cost of a specific bioequivalence study for each of those countries would be profitable for very few companies only. That would reduce the access to medicines by reducing the number of generics and by increasing their cost. For instance, sub-Saharan Africa has 47 countries and accounts for less than 0.6% of the global pharmaceutical market (12). Then, each country insisting on bioequivalence studies with the local comparator products from their national markets, or even with a national market leader, is illogical. Furthermore, it is unreasonable to expect a manufacturer to perform these repetitive bioequivalence studies for each country in which they intend to market their products. The countries that require the exclusive use of the local comparator argue that this is necessary to ensure the switchability of the generics with the innovator in their market, under the suspicion that the foreign comparator may exhibit a different bioavailability to that of the local comparator. In order to address this problem, we identify some possible scenarios or cases.

Case 1. The easiest case is where a global pharmaceutical company develops an innovator product that is marketed around the world, mainly for the biggest markets of the USA and the EU. Ideally, this pharmaceutical company should identify the markets where the product is most similar to the "clinical batches" shown to be safe and efficacious in the pivotal phase III trials (*e.g.*, the same or most similar formula, specifications, manufacturing site, and process). Theoretically, this company should identify all markets as similar, because even if the product is manufactured in different sites with minor differences, the product should be similar in order to extrapolate the phase III trial conclusions to all local markets. If not, this implies that in the other markets, the product is not as similar as it should be, since in all those markets it has been approved based on the same clinical development.

From the regulatory authority point of view, the NMRA that requires the exclusive use of a local comparator is acknowledging that their local comparator perhaps has a different efficacy or safety profile than the one marketed in the USA or the EU. Consequently, the future generics will be switchable with the local comparator that is possibly not prescribable with the same benefit-risk relationship as the comparator in the USA or the EU. Moreover, if the rationale for the exclusive use of a local comparator is to ensure switchability, the variations that may exist between the foreign and local comparator product could be of the same magnitude as the post-approval variations made by the innovator on the formulation, specifications, manufacturing site, or process of the comparator. However, when the innovator makes such post-approval variations, the approved generics are neither withdrawn from the market nor required to re-demonstrate equivalence with this changed comparator product. Therefore, switchability does not seem to be the real cause of using exclusively a local comparator, but perhaps it is more related to national protectionism.

Case 2. In cases where the local comparator is a national market leader because the innovator product has never been available in that national market and bioequivalence with the innovator was never demonstrated or required at the time of approval, it is arbitrary to require the other generics to have a bioavailability similar to that of a product approved based on bibliographical references. On the contrary, the local market leader should have been demonstrated to be bioequivalent to the foreign reference product that has shown safety and efficacy. If this was not required at the time of approval, it should be required as soon as possible. Consequently, the local market leader would be approved as a generic of the foreign innovator and this should be the strategy to be followed in those countries where the innovator is not marketed.

Even in those cases where the innovator is only available in a country without a stringent regulatory system, this foreign comparator seems to be the best and only option to link with the efficacy and safety phase III trials.

Case 3. In cases where the local comparator is a national market leader because the innovator product was withdrawn after the approval of the first generics and the regulatory authority selected one of the local generics as the new comparator, we must take into account that the foreign innovator from a well-regulated country is more related to biobatches that demonstrated efficacy and safety, *i.e.*, prescribability, than any local generic. From a switchability point of view, both the local generic and the foreign innovator can be considered as bioequivalent versions of the initial local innovator, under the assumption that the local comparator and the foreign innovator are maintained bioequivalent over the years. This seems more likely in well-regulated markets; therefore, the foreign comparator seems to be the best option in most countries.

Case 4. The last and most difficult case is where the innovator is no longer available at all or it cannot be identified because it is a very old drug. In that case, a product marketed in the country of a stringent regulatory authority should be selected to better ensure the prescribability of future generics. The rationale for selecting the comparator from these countries is based on availability of post-marketing surveillance. Ideally, the same comparator should be selected all over the world.

Designating a global comparator product as the standard to which all generics must be shown to be bioequivalent would avoid variations among generic medicines all over the world and especially for countries with small markets that receive different generic applications compared with diverse comparator products. Nonetheless, though a global comparator product could be set, it will not be uncommon that more than one comparator product may be accepted; for instance, when two innovator products have been approved based on clinical safety and efficacy data (*e.g.*, transdermal patches of estradiol or nitroglycerine), or the innovator product is no longer marketed and a different comparator product has to

be selected. In those cases, where it is possible to have generic products in the market that have been compared with different comparator products, it is important for the regulatory authorities to provide such information to health care professionals to aid in prescribing and dispensing.

The EU is the example that demonstrates that the foreign comparator can be accepted if it belongs to the same company as the local comparator, even if it differs in manufacturing site, process, qualitative and quantitative composition, or even dissolution profiles. In the EU, the generic products of any drug and dosage form can be compared to the reference product from any of the member states and it has to be accepted in all other member states. Once in the market, these products are switched irrespective of the origin of the comparator that was used as reference in the bioequivalence study.

The WHO PQT-m publishes on their website a list of recommended comparator products, like the US FDA in the Orange Book (13, 14), and the specific markets from which these products should be obtained for bioequivalence studies intended for submission to the prequalification program (15). Unlike national authorities, the comparators selected by WHO PQT-m must be viable choices for the global market, especially in LMICs (16). Therefore in some cases, particularly old molecules, more than one comparator product is listed for a given drug product, *e.g.*, first-line anti-tuberculosis medicines (17). Consequently, the WHO PQT-m ensures prescribability and leaves switchability to national authorities (18). Experiences from WHO PQT-m provide insights in terms of how to identify and obtain an acceptable comparator product in a global context. It is worth mentioning that prequalified products are supplied to many markets and accepted by some national regulatory authorities without requiring further studies, whether dissolution studies or otherwise, with a local comparator product.

Finally, regulatory authorities could compare the respective comparator products to ensure their similarity as if they were a variation of each other or to confirm that they are two different products that deserve to be distinguished and not interchanged. That information should be made publicly available so regulatory authorities can accept the foreign comparator products from the identified primary markets. The qualitative and quantitative composition, the manufacturing site, and process as well as the specifications should be compared to ensure that the comparator products from the different markets are sufficiently similar.

CONCLUSION

The WHO recommendation to national regulatory authorities on the selection of comparator products is only feasible in a few countries or regions in which this makes economic sense, but impracticable in all other countries, particularly in LMICs. It is scientifically questionable to require the exclusive use of the local comparator to ensure switchability and unethical to require multiple repetitions of the same bioequivalence study with similar local comparators. Global harmonization of comparator products for bioequivalence studies is not only feasible, but the concept already applies to some extent, if one considers the EU and the WHO PQT-m approach on selection of comparator products for prequalification of generic products for the target disease areas.

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