Annex 8

Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products

1. Introduction

In recent years the need for the regulation and assurance of quality of medicines has continued to increase. Large numbers of multisource (generic) medicines are being produced by many different companies and in different countries; this may result in different products. On a global level there is thus a need to address not only the quality, safety and efficacy of multisource products that are exported and imported, but also their possible interchangeability.

In light of the various approaches in scientific and regulatory environments, the feasibility of developing a system of international comparator products was considered in the past. This initiative led to the recommendations published in 2002 entitled, *Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (*1*). Since the guidance was published, the World Health Organization (WHO) Model List of Essential Medicines (EML) has been revised several times and many of the products originally listed are no longer marketed and/or available as indicated in the list, which means that the list of international comparators recommended by the WHO Expert Committee on Preparations for Pharmaceutical Specifications needs updating.

In view of the complexity of the list of comparators it was decided to prepare two new, separate, guidance documents: one on the selection of comparator products, including the general guidance on how to select comparator products, and the second one comprising the international list of comparator products. The aim was to facilitate the updating and maintenance process.

2. Background

The *Guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products* (*2*) are designed to provide recommendations to national regulatory authorities and manufacturers on the requirements for approval of multisource (generic) pharmaceutical products in their respective countries. The guidance provides appropriate in vivo and in vitro requirements to assure interchangeability of the multisource product.

Multisource pharmaceutical products need to conform to the same appropriate standards of quality, efficacy and safety as those applicable to the innovator's product. In addition, reasonable assurance should be provided that the multisource product is therapeutically equivalent and interchangeable with the comparator product. For some classes of products including, for example, parenteral formulations of highly water-soluble compounds, interchangeability is adequately assured by implementation of good manufacturing practices (GMP) and provision of evidence of conformity with relevant pharmacopoeial specifications.

This guidance document provides an update of the previously published list (*1*) and the respective chapter on selection of comparator products (*3*, *4*). The information could also be used for medicine procurement purposes.

The historical development of comparator product criteria is summarized in Table A8.1.

Table A8.1
Historical development of comparator product criteria

Year	Development	Description
Pre-1996	International Conference of Drug Regulatory Authorities (ICDRA) (1991 and 1994) recommended development of global standards and requirements for interchangeability of multisource products; WHO initiated the process	No agreement on the criteria for selecting a list of international comparator products or any list of such products exists. The comparator product chosen is either the most widely used (leading) product on the market or the product that was first introduced in that market. For this reason, among others, significant differences could exist between the comparator products used in different countries
1996	The question of choice of reference product was raised	*Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 863), Annex 9, including Appendix 7 on "Choice of reference product"
2002	WHO issued the first list of *International comparator products for equivalence assessment of interchangeable multisource (generic) products*	*Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products* (WHO Technical Report Series, No. 902), Annex 11
2006	"In order of preference" principle in comparator product selection was clarified	*Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937), Annex 7

3. General principles

The comparator product is defined as a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice.

As a general principle, multisource products should comply with the same standards of quality, safety and efficacy as are applicable to the corresponding comparator product. In addition, quality attributes of a multisource product should be tested against the comparator product with which it should be interchangeable.

The selection of the comparator pharmaceutical product is usually made at the national or regional level by the national or regional regulatory authority.

The innovator product is usually the most logical comparator product because its quality, safety and efficacy should have been well assessed in pre- and post-marketing studies and, in addition, the data on its safety and efficacy are usually linked to a pharmaceutical product with defined specifications for quality and performance. However, these products may not always be easy to obtain or may no longer be available on the market. The comparator product chosen is therefore often the most widely used product (market leader) or the product that was first introduced in that market. For this reason, among others, significant differences may exist between the comparator products used in different countries.

In principle, a national regulatory authority has several options for selection of a comparator product. These are listed below in order of preference:

1. the innovator product for which quality, safety and efficacy has been established if this product has been granted a national marketing authorization (*nationally authorized innovator*);
2. national market leader product for which a national marketing authorization has been granted;
3. the WHO-recommended comparator product included in the International list of comparator products (*1*) or, if different and if it exists for the active pharmaceutical ingredient in question, the one suggested within the context of the Prequalification Team;
4. an innovator product approved by a stringent regulatory authority, i.e. a country associated to The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH);
5. a product that has been granted approval in an ICH-associated country;
6. in the case that no innovator or comparator product can be identified according to the above, the choice of the comparator

should be made carefully and should be comprehensively justified by the applicant. In this case, the most important selection criteria in order of preference are:

- prequalification by WHO,
- extensive documented use in clinical trials reported in peer-reviewed scientific journals,
- a long and unproblematic period of post-market surveillance.

Additionally, these comparators should conform to all appropriate compendial quality standards.

It is important to note that a product that has been approved based on comparison with a comparator product that has no national marketing authorization in the country which approved the multisource product, including the study for interchangeability, may or may not be interchangeable with currently marketed domestic products.

The choice of comparator product should be justified by the applicant. The country of origin of the comparator product should be reported together with the product's lot number and expiry date. Consultation with the relevant regulatory authority before purchase of the comparator product is strongly recommended.

Information specifically related to the selection of comparator products for use in studies to be conducted for submission to the WHO Prequalification Team – Medicines is available on the WHO website (www.who.int/prequal) and in the WHO comparator document (*1*).

References

1. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-sixth report. Geneva: World Health Organization; 2002: Annex 11 (WHO Technical Report Series, No. 902).
2. Guidelines on registration requirements to establish interchangeability for multisource (generic) pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2014: Annex 7 (WHO Technical Report Series, No. 992).
3. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 7 (WHO Technical Report Series, No. 937).
4. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Revision. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2014: Annex 7 (WHO Technical Report Series, No. 992).