Annex IV: Selection of a Comparator Product to be used in Establishing Interchangeability

I Introduction

This annex is intended to provide applicants with guidance with respect to selecting an appropriate comparator product to be used to prove therapeutic equivalence (i.e. interchangeability) of their product to an existing medicinal product(s) in the context of the EAC Medicines Registration Harmonization programme.

II Comparator Product

A product with which a generic product is intended to be interchangeable in clinical practice.

III Guidance on Selection of a Comparator Product

General principles for the selection of comparator products are described in the EAC guidelines on therapeutic equivalence requirements, First Edition, 2014.

The innovator pharmaceutical product, which was first authorized for marketing, is the most logical comparator product to establish interchangeability, because its quality, safety and efficacy has been fully assessed and documented in pre-marketing studies and post-marketing monitoring schemes.

A generic pharmaceutical product should not be used as a comparator as long as an innovator pharmaceutical product is available, because this could lead to progressively less reliable similarity of future multisource products and potentially to a lack of interchangeability with the innovator.

Comparator products should be purchased from a well regulated market with stringent regulatory authority, i.e. from countries participating in the International Conference on Harmonization (ICH)[1]

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In the context of the EAC Medicines Regulatory Harmonization programme, the applicant has the following options which are listed in order of preference:-

1. To choose an innovator product;

2. To choose a product which is approved and has been on the market in any of the SRA countries. The definition of an SRA is rephrased as follows. A regulatory authority that is: a)a member of ICH prior to 23 October 2015, namely: the US Food and Drug Administration, the European Commission and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency; orb)an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; orc)a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement prior to 23 October 2015, namely: Australia, Iceland, Liechtenstein and Norway

3. To choose the WHO recommended comparator product (as presented in the list of international comparator pharmaceutical products);

In case no recommended comparator product is identified; or in case the EAC recommended comparator product cannot be located in a well regulated market with stringent regulatory authority as noted above, the applicant should consult EAC Partner States' National Medicines Regulatory Authorities (NMRAs) regarding the choice of comparator before starting any studies.

IV Origin of the Comparator Product

Comparator products should be purchased from a well regulated market with stringent regulatory authority, i.e. from countries participating in the International Conference on Harmonization (ICH)[1]. Within the submitted dossier, the country of origin of the comparator product should be reported together with lot number and expiry date, as well as results of pharmaceutical analysis to prove pharmaceutical equivalence.

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Further in order to prove the origin of the comparator product the applicant must present all of the following documents:-

1. Copy of the comparator product labelling. The name of the product, name and address of the manufacturer, batch number, and expiry date should be clearly visible on the labelling.

2. Copy of the invoice from the distributor or company from which the comparator product was purchased. The address of the distributor must be clearly visible on the invoice.

3. Documentation verifying the method of shipment and storage conditions of the comparator product from the time of purchase to the time of study initiation.

4. A signed statement certifying the authenticity of the above documents and that the comparator product was purchased from the specified national market. The certification should be signed by the company executive responsible for the application for registration of pharmaceutical product.

In case the invited product has a different dose compared to the available acceptable comparator product, it is not always necessary to carry out a bioequivalence study at the same dose level; if the active substance shows linear pharmacokinetics, extrapolation may be applied by dose normalization.

The bioequivalence of fixed-dose combination (FDC) should be established following the same general principles. The submitted FDC product should be compared with the respective innovator FDC product. In cases when no innovator FDC product is available on the market, individual component products administered in loose combination should be used as a comparator.

[11] Countries officially participating in ICH are the ICH members European Union, Japan and USA; and the ICH observers Canada and Switzerland.