Recommended comparator products: Anti-tuberculosis Medicines

Comparator products should be purchased from a well-regulated market with stringent regulatory authority [1].

Invited medicinal products (refer to EOI for more information e.g. requirements for scoring)	Recommended comparator product (Strength, Manufacturer)
Single ingredient first-line anti-tuberculosis medicines	
Ethambutol, 100 mg tablet and 400 mg tablet/capsule	Myambutol (400 mg tablet, Riemser Arzneimittel or Teopharma) Myambutol (100 mg, 400 mg tablet, Labatec Pharma, Switzerland[2]) Myambutol (100 mg, 400 mg tablet, STI Pharma LLC, US[3]) Myambutol/Ethambutol (400 mg tablet, Genus Pharmaceuticals Ltd, UK[4])
Isoniazid, 100 mg tablet and 300 mg tablet/capsule	Isozid (50 mg, 100 mg tablet, Fatol/Riemser Pharma) Isoniazid (100 mg, 300 mg tablet, Barr Laboratories Inc, US[3])
Pyrazinamide, 150 mg, 400 mg and 500 mg tablet	Pyrafat (500 mg tablet, Esteve) Pyrazinamide (500 mg tablet, Novitium Pharma LLC, US[3])
Rifampicin, 150 mg and 300 mg capsule	Rimactane (150 mg, 300 mg capsule, Novartis or Sandoz) Rifadin (150 mg, 300 mg capsule, Sanofi-Aventis) Rifampicin (150mg, 300 mg capsule, Sandoz, NL)
Rifabutin, 150 mg tablet/capsule	Mycobutin (150 mg capsule, Pfizer) Mycobutin (150 mg capsule, Pharmacia and Upjohn, US[3])
Rifapentine, 150 mg and 300 mg tablet	Priftin (150 mg tablet, Sanofi Aventis, US[3])
Fixed-dose combination products of first-line anti-tuberculosis medicines:	
Isoniazid/Rifampicin, 75 mg/150mg, and 150 mg/300 mg tablet/capsule	Rifinah (isoniazid/rifampicin 150mg/300 mg tablet, Sanofi-Aventis) Rifamate (isoniazid/rifampicin 150mg/300 mg capsule, Sanofi-Aventis, US[3])
Isoniazid/Rifampicin, 50 mg/75 mg tablet	Rifinah (isoniazid/rifampicin 100mg/150 mg tablet, Sanofi-Aventis)

For other invited fixed-dose combination products of anti-tuberculosis medicines, use appropriate combination of the recommended single ingredient comparator products

Single ingredient second-line anti-tuberculosis medicines	
Bedaquiline, 20 and 100 mg tablet	Sirturo (20 and 100 mg tablet, Janssen Therapeutics/Janssen-Cilag)
Clofazimine, 50 and 100 mg capsule/tablet	Lamprene (50 and 100 mg capsule, Novartis)
Cycloserine, 125 and 250 mg capsule	Seromycin (250 mg capsule, Purdue GMP, US[3]) Cycloserine 250mg capsules 'MEIJI' (Meiji Seika Pharma Co., Ltd., Japan[6])
Delamanid, 50 mg tablet Delamanid, 25 mg dispersible tablet	Deltyba (50 mg tablet, Otsuka Novel Products GmbH) Deltyba (25 mg dispersible tablet, Otsuka Novel Products GmbH)
Ethionamide, 125 and 250 mg tablet	Trecator (250 mg tablet, Wyeth)
Levofloxacin,100 mg, 250 mg, 500 mg and 750 mg tablet/capsule	Tavanic (250 mg and 500 mg tablet, Sanofi-Aventis) Levofloxacin (250 mg, 500 mg and 750 mg tablet, Aurobindo Pharma Limited, US[3])
Linezolide, 150 mg and 600 mg tablet	Zyvox (600 mg tablet, Pharmacia/Pfizer) Zyvoxid (600 mg tablet, Pharmacia/Pfizer) Zyvox (granules for oral suspension 100mg/5ml, Pharmacia/Pfizer)
Moxifloxacin, 100 mg and 400 mg tablet/capsule	Avelox (400 mg tablet, Bayer) Avalox (400 mg tablet, Bayer) Actira (400 mg tablet, Bayer) Moxifloxacin (400 mg tablet, Dr. Reddys Laboratories Ltd, US[3])
Para-aminosalicylate sodium, 5.52 g powder in a sachet (for oral solution)	P-Aminosalicylic acid (as sodium salt) (5.52 g powder for oral solution, Olainfarm JSC)
Pretomanid, 200 mg tablet	Dovprela (200 mg tablet, Mylan IRE Healthcare Ltd) Pretomanid (200 mg tablet, Mylan Ireland Ltd, US[3])
Protionamide, 250 mg tablet/capsule	Peteha (250 mg tablet, Fatol)
Terizidone, 250 mg capsule/tablet	Terizidon (250 mg capsule, Riemser Pharma GmbH) Terivalidin (250 mg capsule, Sanofi-Aventis, South Africa[5])

1 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; or
b) an ICH observer prior to 23 October 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or
c) 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.

2 Product should be obtained from the market of Switzerland.
3 The recommended comparator products are approved by US FDA; the comparator product should be obtained from the US market.
4 Product should be obtained from the market of UK.
5 Product should be obtained from the market of South Africa.
6 Product should be obtained from the market of Japan.

Obtaining Comparator

Comparator products should be purchased from a well-regulated market with stringent regulatory authority. If the recommended comparator cannot be located for purchase from the market of one of the identified countries, the applicant should consult with WHO regarding the sourcing of an acceptable comparator product.

Information Requirements

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. 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 or equivalent responsible for the application to the Prequalification Programme.

Dose Equivalence

In case the invited product has a different strength 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 between similar doses may be applied by dose normalisation.

Fixed-dose Combination Products

The bioequivalence of fixed-dose combination (FDC) product should be established following the same general principles. The submitted FDC product should be compared with the respective innovator FDC product as listed above. In cases where a FDC comparator product is not listed above, individual component products administered in loose combination should be used as a comparator. The principles of dose normalization as mentioned above are applicable.

Suitability of a comparator product for BCS-based biowaiver applications

Recommendation of an API for BCS-based biowaivers is made purely on the solubility, permeability, safety and related properties of the API (Class 1 or Class 3) – see the Biowaiver guidance documents on the WHO Prequalification website. It does not imply that the recommended comparator product(s) will be rapidly dissolving in case of Class 1 APIs (or very rapidly dissolving in case of Class 3 API), which is a requirement for BCS based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the Prequalification website is indeed suitable for a BCS based-biowaiver application before product development.

Note that rapidly dissolving (or very rapidly dissolving) properties of a product are not required for in vivo bioequivalence studies. Thus, though a listed comparator product may not be suitable for BCS-based biowaiver purposes, it is still suitable for in vivo bioequivalence studies.