Recommended comparator products: Treatment of bacterial infections in children

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, Marketing authorization holder)
Single ingredient medicine to treat possible serious bacterial infection (PSBI) in newborn and young infants and pneumonia in children	
Amoxicillin, 125 and 250 mg dispersible tablet	Amoxil/Clamoxyl (amoxicillin 125mg/5ml, 250mg/5 ml, and 500mg/5ml powder for oral suspension (bottle), 250 and 500 mg powder for oral suspension in sachet, GlaxoSmithKline Pharmaceuticals) Amoxicillin pediatric 50mg/ml powder for oral suspension (Teva Pharmaceuticals Inc., US[2])
Medicine for treating lower urinary tract infections in children	
Nitrofurantoin, 5 mg/unit dose, orodispersible multi-particulates (minitablets or sprinkles), 5 mg and 10 mg dispersible tablet	Furadantin (nitrofurantoin 25mg/5ml, 50mg/5ml oral suspension, Casper Pharma LLC, US[2])
Medicine for treating children with cholera, enteric fever, trachoma and yaws; also as a second choice for acute invasive bacterial diarrhoea, and potentially other infections	
Azithromycin, 50 mg/unit dose, orodispersible multi-particulates (minitablets or sprinkles), 50 mg and 100 mg dispersible tablet	Zithromax (azithromycin 100mg/5ml, 200 mg/5ml powder for oral suspension, Pfizer)

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 The recommended comparator products are approved by US FDA; the comparator product should be obtained from the US market

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.