Recommended comparator products: Reproductive Health medicines

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

Invited medicinal products (refer to EOI for more information e.g. requirements for scoring)	Recommended comparator product (Strength, Marketing authorization holder)
Oral hormonal contraceptives	
Desogestrel 75 µg tablet	Cerazette (75 µg tablet, MSD)
Ethinyl estradiol/desogestrel 30 µg/150 µg tablet	Marvelon (Organon) Varnoline (Organon)
Ethinyl estradiol/levonorgestrel 30 µg/150 µg tablet	Microgynon 30 (Schering AG) Levora 0.15/30-28 (Mayne Pharma LLC, US[1])
Levonorgestrel 30 µg tablet	Microlut (30 µg tablet, Bayer Schering AG) Norgeston® (30 µg tablet, Bayer Plc, UK[3]) 28 Mini® (30 µg tablet, Jenapharm)
Levonorgestrel 750 µg tablet (pack of two)	Postinor-2 (two tablets each containing 750 µg levonorgestrel, Gedeon Richter) NorLevo (two tablets each containing 750 µg levonorgestrel, Laboratoire HRA Pharma) Levonorgestrel 750 µg tablet (L Perrigo Co, US[1])
Levonorgestrel 1.5 mg tablet (pack of one)	Postinor-1, Levonelle (levonorgestrel 1.5 mg tablet, Gedeon Richter/Bayer) NorLevo (levonorgestrel 1.5 mg tablet, Laboratoire HRA Pharma) Plan B One-Step (levonorgestrel 1.5 mg tablet, Foundation Consumer Healthcare LLC, US[1])
Norethisterone 350 µg tablet	Micronor (Janssen-Cilag) NOR-QD (Teva Branded Pharmaceutical Products R and D Inc, US[1])
Norgestrel 75 µg tablet	Opill (75 µg tablet, Laboratoire HRA Pharma, US[1])
Ulipristal 30 mg tablet	Ella (30 mg tablet, Laboratoire HRA Pharma, US[1]) Ella (30 mg tablet, HRA Pharma)

Injectable hormonal contraceptives	
Medroxyprogesterone acetate (DMPA), depot injection (subcutaneous) 104 mg/0.65 ml	Sayana/Sayana Press (depot injection 104 mg/0.65 ml, Pfizer) Depo-SubQ Provera 104 (Pharmacia and UpJohn, US[1])
Medroxyprogesterone acetate (DMPA), depot injection 150 mg/ml	Depo-Provera (medroxyprogesterone acetate, depot injection 150 mg/ml, Pharmacia/Pfizer)
Medroxyprogesterone acetate (DMPA)/estradiol cypionate, 25 mg/ 5 mg (0.5 ml injection)	Cyclofemina (medroxyprogesterone acetate/estradiol cypionate 25/5 mg inj, Millet Roux Ltd, Brazil[2])
Norethisterone enanthate, injection 200 mg	Noristerat (200 mg/ml, solution for intramuscular injection, Bayer)
Norethisterone enanthate/estradiol valerate, injection 50 mg/5 mg	Mesigyna (norethisterone enanthate/estradiol valerate, 1 ml injection 50 mg/5mg, Bayer Schering Pharma[2])
Hormonal intra-uterine device	
Levonorgestrel intra-uterine system (reservoir 52 mg)	Mirena (Bayer)
Implantable contraceptives	
Two rod levonorgestrel-releasing implant; each rod containing 75 mg of levonorgestrel	Jadelle (two-rod levonorgestrel implant, each rod containing 75 mg of levonorgestrel, Bayer Schering Pharma)
Etonogestrel, implant containing 68 mg of etonogestrel	Implanon NXT(implant containing 68 mg of etonogestrel, Organon) Nexplanon (implant containing 68 mg of etonogestrel, Organon USA LLC[1])
Intravaginal contraceptives	
Progesterone vaginal ring (2.074 g)	Progering (Laboratorios Andromaco S.A./Grunenthal)
Utero-tonics	
Carbetocin, injection 100 µg/ml	Duratocin (carbetocin 100 µg/ml injection, Ferring) Pabal (carbetocin 100 µg/ml injection, Ferring)
Oxytocin, injection 10 IU	Syntocinon (oxytocin 10 IU/ml injection, Novartis or Sigma Tau, Spain) Pitocin (oxytocin 10 IU/ml injection, PAR Sterile Products LLC, US[1]) Oxytocin 10 IU/ml injection (West-Ward Pharmaceuticals Int Ltd, US)[1] Oxytocin 10IU/ml injection (Fresenius KABI LLC, US[1])
Mifepristone 200 mg tablet	Mifegyne (mifepristone 200 mg tablet, Exelgyn SA) Mifeprex (mifepristone 200 mg tablet, Danco Labs LLC, US[1])
Misoprostol 25 µg and 200 µg tablet	Cytotec (misoprostol 100 µg, 200 µg tablet, Searle/Pfizer)

Management of hypertensive disorders of pregnancy	
Alpha Methyl dopa 250 mg tablet	Methyldopa 250 mg tablet (Rising Pharma Holding Inc., US[1]) Aldomet (methyldopa, 250 mg tablet, Aspen Pharmacare/ H.A.C. Pharma/Phardis B.V.)
Hydralazine 5 mg Injection (5 mg/ml in 2ml ampoule)	Hydralazine hydrochloride 20 mg/ml (solution for injection, Fresenius Kabi USA LLC, US[1]) Apresoline (hydralazine, 20 mg, powder for solution for injection, Amdipharm)
Labetalol 100 mg tablet	Labetalol hydrochloride 100 mg tablet (Aiping Pharmaceutical Inc., US[1]) Trandate (labetalol, 100 mg tablet, Aspen Pharma)
Labetalol 10 mg Injection (5mg/ml in 2ml ampoule)	Labetalol hydrochloride 5 mg/ml (solution for injection, Hospira Inc., US[1]) Trandate (labetalol, 5 mg/ml, solution for injection, several MAHs)
Nifedipine 10, 20 mg tablet	Nifedipine 10 mg capsule (Heritage Pharma Labs Inc., US[1]) Adalat (nifedipine, 10 mg capsule, Bayer)
Magnesium sulphate, injection 500 mg/ml	Magnesium sulphate 500 mg/ml (solution for injection, 1g/2ml, 5g/10ml, Fresenius Kabi, US[1])
Treatment of maternal syphilis and prevention of congenital syphilis	
Benzathine benzylpenicillin, for reconstitution for i.m. injection, 2400000 IU/dose, 1200000 IU/dose and 150000 IU/dose	Bicillin L-A (2.4 million units/4ml, 1.2 million units/2ml and 600000 units/1ml suspension for i.m. injection, Pfizer/King Pharmaceuticals LLC)
Procaine benzylpenicillin 150000 IU (for reconstitution for i.m injection)	Penicillin G Procaine (300000 IU/ml for i.m. injection, King Pharmaceuticals, LLC, US[1])
Benzylpenicillin 150000 IU (for reconstitution for i.v. administration)	Penicillin G sodium (5000000 IU/vial for i.v. administration, Sandoz, US[1]) Benzylpenicilline 1000000 IU (powder for reconstitution for i.v. administration, Sandoz)
Treatment of antifibrinolytics	
Tranexamic acid 100 mg/ml	Cyklokapron (tranexamic acid 100mg/ml, Pharmacia and UpJohn Co/Pfizer)
Management of severe iron deficiency anemia during pregnancy	
Ferric carboxymaltose, 50 mg/ml iron	Injectafer (50 mg/ml iron, American Regent Inc., US[1])
Iron sucrose, 20 mg/ml iron	Venofer (20 mg/ml iron, American Regent Inc., US[1]) Venofer (20 mg/ml iron, Vifor France)

* 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.

[1]The recommended comparator product is approved by US FDA; the comparator product should be obtained from the US market.
[2]Product should be obtained from Brazil.
[3] Product should be obtained from the UK.

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.