

Quality of Reproductive Health Medicines



Frequently Asked Questions

**The Prequalification of Medicines
for Reproductive Health**

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**Frequently asked questions
on the prequalification of
medicines for
reproductive health**

Concept Foundation
Bangkok, Thailand and Geneva, Switzerland

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Introduction

The United Nations Prequalification Programme for quality medicines is managed by the World Health Organization (WHO). It issued its first Expression of Interest for medicines for reproductive health in October 2006. Since then it has expanded its scope and following its most recent Expression of Interest (May 2010) will accept requests for prequalification of the following products:

1. Oral hormonal contraceptives

- ethinylestradiol + desogestrel, tablet 30 micrograms + 150 micrograms
- ethinylestradiol + levonorgestrel, tablet 30 micrograms + 150 micrograms
- levonorgestrel, tablet 30 micrograms
- levonorgestrel, tablet 750 micrograms (pack of two); 1.5 mg (pack of one)
- norethisterone, tablet 350 micrograms
- norgestrel, tablet 75 micrograms

2. Injectable hormonal contraceptives

- medroxyprogesterone acetate, depot injection 150 mg/ml, in 1-ml vial

- medroxyprogesterone acetate + estradiol cyprionate, injection 25 mg + 5 mg
- norethisterone enanthate, injection 200 mg
- norethisterone enanthate + estradiol valerate, injection 50 mg + 5 mg

3. Implantable contraceptives

- two-rod levonorgestrel-releasing implant, each rod containing 75 mg of levonorgestrel (150 mg in total)
- etonogestrel, implant, 68 mg of etonogestrel

4. Oxytocics

- oxytocin, injection 10 IU, 1-ml
- mifepristone 200 mg tablet (only to be used in combination with misoprostol)
- misoprostol 200 microgram tablet

5. Prevention and treatment of eclampsia

- magnesium sulphate, injection 500 mg/ml, in 2-ml and 10 ml ampoule

This document responds to the most frequently asked questions raised by manufacturers when con-

sidering prequalification of one or more products by WHO. Full details and information for applicants are to be found on the website of the WHO Prequalification of Medicines Programme,

<http://apps.who.int/prequal/default.htm> and WHO's Department of Essential Medicines and Pharmaceutical Policies has extensive documentation on all the issues raised below.

References are provided as footnotes throughout this document and they all can be downloaded from <http://www.who.int/medicines/publications/en/> in a pdf format. In particular, all the relevant reports of WHO's Expert Committee on Specifications for Pharmaceutical Preparations can be downloaded from:

<http://www.who.int/medicines/publications/pharmprep/en/index.html>.

We are keen to supply products internationally but have a valuable local market. What are the benefits in getting our products prequalified by WHO? We are concerned that if we have to increase our quality assurance costs, buy more expensive starting materials or significantly modify our facilities, this may result in us having to increase product price and lose market share because of the competition? How should we approach this?

1

The main donors, UNFPA and other key international procurement agencies, several developing country governments and technical agencies involved in the procurement of, access to, and appropriate use of medicines for reproductive health are members of the Reproductive Health Supplies Coalition (RHSC). Since its inception, members of RHSC have become critically aware of the need

to ensure that all reproductive health medicines being supplied to country programmes meet internationally accepted quality standards. The WHO Prequalification of Medicines Programme has played a pivotal role in ensuring that this has happened for drugs used for HIV/AIDS, TB and malaria and, more recently, has also been assisting the reproductive health community to achieve the same.

RHSC members are currently moving towards adopting a common procurement policy, similar to that used by the Global Fund to Fight AIDS, Tuberculosis and Malaria, and which has been approved by the Executive Board of the United Nations Population Fund (UNFPA). This policy states that Finished Pharmaceutical Products will only be procured if they have been prequalified by the WHO Prequalification of Medicines Programme or authorized for use by a Stringent Drug Regulatory Authority (SRA)¹.

Therefore, if a manufacturer would like to respond to a tender generated by UNFPA, and subsequently other procurement agencies that are members of the RHSC, and does not hold a product authorization from a SRA, it must meet the quality and safety and efficacy requirements of WHO's Prequalification Programme. These are stringent requirements (see point 3 below) and, as such, may require that a company has to invest in upgrading its quality assurance

procedures or even its manufacturing facility; or to change its source of Active Pharmaceutical Ingredients (APIs), excipients or other components of the FPP.

Hence an application to WHO to get a product prequalified is a business decision which can only be taken by the manufacturing company as it determines the implications, including possible investment, of meeting WHO requirements. However, in addition to the national/international tender markets, any manufacturer seriously considering exporting product to high income countries would be required to meet similar standards for quality assurance. Moreover, even in countries which currently have less stringent drug regulatory agencies, companies would be well placed if they obtained prequalification of products by WHO. There is a wind of change across many low and middle income countries, where governments increasingly want to ensure the importation of quality products.

1 Stringent Drug Regulatory Authority (SRA) means a regulatory authority which is (a) a member of ICH (as specified on www.ich.org); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by Swiss Medic, Health Canada and World Health Organization (WHO) (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).

How do we apply for prequalification? How does the process for prequalification work and how long does it take?

2

Information on the process for prequalification can be found on the website of WHO's Prequalification of Medicines Programme, (also see²). <http://apps.who.int/prequal/default.htm>. This gives full instructions on what information should be submitted and how to do so.

WHO recently issued updated guidelines for the submission of documentation for generic FPPs, including those necessary for the APIs used³. Subject to receipt of all necessary information and its satisfactory review, product prequalification takes 18 to 24 months.

Our quality assurance practices, in particular, GMP, have been certified by our national authorities and the certificate states they conform to WHO GMP, will we need to make any changes before we can get a product prequalified?

3

This depends on the GMP requirements of your national drug regulatory agency. Quality assurance, of which GMP is a key component, is a dynamic and constantly evolving issue. As such, WHO's Expert Committee on Specifications for Pharmaceutical Preparations meets annually and reviews the current state of the art in assuring the quality of pharmaceutical products. This includes not only the requirements

for manufacture of FPPs but also APIs and other key constituents of the products. Moreover, the Expert Committee reviews requirements of all other good practices that impact upon the product and its use. This includes requirements for Good Laboratory Practices (GLP) as well as for quality control laboratories; and for Good Clinical Practices (GCP) and the requirements that must be met to determine safety and efficacy

- 2 WHO Expert Committee on Specifications for Pharmaceutical Preparations, 43rd report. Technical Report Series 953, 2009. Annex 3. Procedure for prequalification of pharmaceutical products
- 3 WHO Expert Committee on Specifications for Pharmaceutical Preparations, 45th report. Technical Report Series 961, 2011. Annex 15. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product: general format: preparation of product dossiers in common technical document format.

of a product. The recommendations and requirements of the Expert Committee and published at regular intervals by WHO in its Technical Report Series. WHO's GMP requirements were updated and published in 2007⁴ and updated for hazardous substances and for sterile FPPs in 2010⁵.

The current WHO guidelines related to pharmaceutical production can be accessed on the following links:

http://apps.who.int/prequal/assessment_inspect/info_inspection.htm#2; and

http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/production/en/index.html

Unfortunately, some national drug regulatory agencies do not

regularly update national GMP requirements plus the skills and systems to evaluate and enforce the requirements. Although you may have received a Certificate of Pharmaceutical Product (CoPP) that states that your facilities and operations conform to GMP as recommended by WHO, it may not refer to current GMP (CGMP) requirements. For example, a recently issued CoPP from a major pharmaceutical producing country refers to GMP requirements issued by WHO in 1992 – they have changed substantially since then! It is therefore essential that you ensure that you comply with CGMP, which may well mean that you will need to change your quality assurance procedures or even have to make changes to your manufacturing processes, raw materials or even your physical facility.

4

Does our API manufacturer need to have its API prequalified?

Having the source of your API (API manufacturer) prequalified is not mandatory. The prequalification of an API source is a separate process

to FPP prequalification and is open to API suppliers who wish to take advantage of the benefits of this process⁶.

4 WHO, 2007 Quality Assurance of Pharmaceuticals - A Compendium of Guidelines and Related Materials - Volume 2, 2nd Updated Edition - Good Manufacturing Practices and Inspection. World Health Organization, Geneva, pp 416

5 WHO Expert Committee on Specifications for Pharmaceutical Preparations, 44th report. Technical Report Series 957, 2010. Annex 2. WHO good manufacturing practices for active pharmaceutical ingredients. Annex 3. WHO good manufacturing practices for pharmaceutical products containing hazardous substances. Annex 4. WHO good manufacturing practices for sterile pharmaceutical products.

6 http://apps.who.int/prequal/info_applicants/API_info_applicants.htm.

To support the quality of the API used in your FPP information regarding the API can be supplied in three ways. These are: the provision of a certificate of suitability of the European Pharmacopoeia (CEP) with some additional data in the product dossier; the provision of an active pharmaceutical ingredient master file (APIMF) through the APIMF procedure with some additional data in the product dossier; or the inclusion of a complete Module 3.2.S as part of the product dossier. If a CEP is not available the provision of an APIMF is strongly encouraged.

Detailed information on the preparation and submission of drug substance information to support

an FPP application for prequalification can be found in the new guidance document *Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP)*^{3,7}.

Information on the use of the APIMF procedure can be found in the World Health Organization, WHO Technical Report Series, No. 948, 2008, Annex 4, Guidelines on active pharmaceutical ingredient master file procedure⁸.

Please note that the API manufacturer may be inspected by WHO as part of the prequalification process, but is expected to follow the recently issued GMP requirements for APIs⁵.

What is the situation regarding excipients?

5

All excipients must be at least equivalent to an officially recognized pharmacopoeial standard. Requirements for excipients can be found in the new *Guideline on Submission of Documentation for a*

Multisource (Generic) Finished Pharmaceutical Product (FPP)^{3,7}. Novel excipients are not accepted. Only excipients with an officially recognized pharmacopoeial monograph should be used⁹.

7 http://apps.who.int/prequal/info_general/documents/generic_guide/GenericGuideline_Quality.pdf.

8 http://apps.who.int/prequal/info_general/documents/TRS948/TRS_948.

9 Those pharmacopoeias recognized by the WHO Prequalification of Medicines Programme (the International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the British Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP))pdf#page=113

6

Our manufacturing batches are less than 100,000 tablets. Is this acceptable for submission for manufacturing process validation and stability study data requirements?

The production of batches of 100,000 tablets or less may indicate that a manufacturer has limitations in its production capacity, due to constraints of the size of one or more of items of processing equipment, such as, granulator, dryer, blender, or tablet press. It may also be that market demand for the product is limited or the market for the product is just beginning to be developed. While product used for stability testing should originate from a

batch of at least 10% of the industrial/commercial production scale or 100,000 tablets, whichever is the greater, it is acceptable to use product from batches of 100,000 tablets or less, as long as it is a full production batch and an adequate justification is provided. If the production batch is less than 100,000 tablets, the biobatch must be produced at the final production scale and there should be no subsequent scale-up.

7

We have been producing our product for more than 3 years and manufacture more than 10 batches per year, but process validation was only performed using current requirements in the past 12 months. Can we submit annual product quality review data for batches manufactured in the past instead of recent validation data?

With regard to documenting product quality, there is a significant difference between retrospective data derived from previous batches and concurrent or prospective validation. While retrospective data is useful for preliminary quality assessment, in

general, historic data using only retrospective results or a limited number of batches are often incomplete and sometimes biased.

As such, WHO discourages any attempts at retrospective validation and data from batches made prior

to process validation should be treated as part of periodic product review. Hence, you must not only supply your recent validation/qualification results and data from all batches but ensure that it meets the recommendations made in WHO TRS 937 (annex 4, part 5.1.2)¹⁰

To submit a product quality review in lieu of the process validation, the product must meet the criteria of an established multisource product, i.e. a product that has been marketed for at least 5 years, and either 10 batches were produced in the past year, or 25 batches were produced in the past 3 years. See the recent Prequalification Update¹¹.

We are manufacturing a broad range of pharmaceutical products in our facility, does our hormonal contraceptive production line need to be in a separate building?



WHO has recently revised its GMP for pharmaceutical products containing hazardous substances⁵. The highly potent steroids contained in hormonal contraceptives must be treated according to these requirements, which state that:

“The production of certain products containing hazardous substances should generally be conducted in separate, dedicated, self-contained facilities.

These *self-contained facilities* may be in the same building as another facility but should be separated by a physical barrier and have,

e.g. separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services should be determined by risk assessment.”

While this states that, subject to meeting the necessary requirements, the self-contained facilities can be in the same building that is manufacturing other pharmaceutical products, you should be aware that certain national drug regulatory agencies, including ANVISA in Brazil, do require that hormonal products are manufactured in a completely separate building.

10 Pharmaceutical Preparations, 40th report, Technical Report Series 937, 2006. Annex 4.

11 http://apps.who.int/prequal/info_general/documents/generic_guide/GenericGuideline_Quality.pdf

9

If we obtain prequalification of one of our products, does that apply to all products and all our production sites?

No, prequalification of a product is specific to that product as manufactured at a certain site at a certain point in time. Even if an identical product with the same APIs and all other ingredients are produced with clearly demonstrable and acceptable quality assurance procedures at a different site, this product is not covered under the

prequalification. Furthermore, if a similar product is being produced, even within the same facility, but uses APIs or any other components that are different from the prequalified product, it will require to be prequalified as a separate product. In other words only products are prequalified, not manufacturing sites.

10

Since our products are generics, will we be required to undertake bioequivalence studies? Can we apply for a BCS based biowaiver for any oral solid dosage form reproductive health product?

As well as demonstrating that products meet cGMP, the WHO Prequalification of Medicines Programme requires that a manufacturer demonstrates that its products meet acceptable quality standards and are proven to be safe and effective. For a generic product, safety and efficacy are established by demonstrating bioequivalence with the innovator product. This requires that a study of adequate sample size to provide sufficient power is undertaken to demonstrate that the generic

product is bioequivalent to the innovator.

This is often one of the more challenging requirements faced by manufacturers. A study by Hall et al (2007)¹² of generic hormonal contraceptive manufacturers in lower and middle income countries identified that “there was a significant difference between companies in their understanding of bioequivalence and most had not considered the need for such studies. Few companies have un-

12 Hall PE, Oehler J, Woo P, Zardo H, Chinery L, Singh JS, Jooseery SH and, Essah NM. A study of the capability of manufacturers of generic hormonal contraceptives in lower and middle income countries. *Contraception* 2007. 75:311-317

undertaken bioequivalence testing programmes, most supplying untested biosimilar products. Some companies had undertaken pharmacokinetic/pharmacodynamic studies in local university clinical departments but it was difficult to ascertain what had been the comparator products used and how the investigators applied Good Clinical Practice (GCP) in the conduct of the studies or GLP for the analysis of blood specimens collected." Questions and answers addressing the conduct of bioequivalence studies are found below.

The WHO Prequalification of Medicines Programme will accept a Biopharmaceutics Classification System (BCS) based biowaiver in

lieu of undertaking a bioequivalence study for some drugs, however, none of the products currently listed in WHO's current Invitation for Expression of Interest for Reproductive Health Medicines qualify for a BCS-based biowaiver at this time. It is important to note, however, that it may be possible to justify the waiver of the requirement to conduct a bioequivalence study for aqueous solution for injection products such as oxytocin and magnesium sulfate (WHO TRS 937)¹³. Hence for generic formulations of all the products listed, except for oxytocin and magnesium sulfate injections, it is necessary to show that they are bioequivalent to the innovator product.

How should a bioequivalence study be designed? Is there a common protocol? How many subjects are required? 10.1

WHO's Prequalification of Medicines Programme will provide advice on the design of a bioequivalence study as you are finalizing the protocol. However, it must be in a close to final format, with a

clear description of the proposed design and a statistical justification for the sample size. Obviously, the design is dependent on several factors, such as the type of product, route of administration, duration of action, etc.

13 WHO Expert Committee on Specifications for Pharmaceutical Preparations, 40th report, Technical Report Series 937, 2006. Annex 7. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability.

The design and requirements for bioequivalence studies are to be found in WHO TRS 937¹⁴ and in the European Medicines Agency's (EMA) "Guidance on the investigation of bioequivalence"¹⁵

The components of a common protocol for a specific reproductive health product type have been agreed upon. For combined oral contraceptive tablets, progestogen-only and emergency contraceptive pills, a randomized, single-dose, two-period, two-treatment, cross-over bioequivalence study is required. However, the injectable contraceptive, depot medoxyprogesterone acetate (DMPA), is administered every 90 days either as a deep intramuscular or subcutaneous injection. The duration of action of the drug may be longer than 90 days and measurable levels of MPA may be found in the blood up to 140 days. Therefore, it is recommended that a study with a randomized, single dose, parallel design should be undertaken for this product.

One of the major issues relates to the number of subjects. Annex 7 of TRS 937 and the EMA guidance both state the required parameters

for determining bioequivalence and that "The number of evaluable subjects in a bioequivalence study should not be less than 12". However, it is necessary to obtain an adequate sample size calculation from a professional statistician in order to determine the number of subjects that should be included in a study.

The parameters to be analysed from the study data are the area under the curve ($AUC_{(0-t)}$ and $AUC_{(0-\infty)}$) and the maximum plasma/serum concentration (C_{max}). It is also useful to measure time to maximum plasma/serum concentration (t_{max}) and terminal phase half-life time ($t_{1/2}$) but statistical evaluation of these two parameters is not required.

For the test product to be in the acceptance limit for bioequivalence with the innovator, the 90% confidence interval of the mean ratio of C_{max} and of AUC of the two products must be within 80.00% to 125.00%. Knowledge of the expected within-subject (for crossover studies) or between-subject (for parallel studies) variability for these parameters for the particular drug will allow a statistician to calculate the sample size required for a study to have the power to meet these criteria.

14 WHO Expert Committee on Specifications for Pharmaceutical Preparations, 40th report, Technical Report Series 937, 2006. Annex 7. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Annex 9. Additional guidance for organizations performing in vivo bioequivalence studies.

15 European Medicines Agency, 2010. Guidance on the investigation of bioequivalence. Doc ref: CPMP/EWP/QWP/1401/98Rev1/Corr.

For combined oral contraceptives (COCs), progestogen-only pills (POPs), emergency contraceptives (ECPs) and certain other short-acting products, a single-dose, two-treatment, cross-over study will normally require 24 - 30 subjects.

Unfortunately, for injectable contraceptives, such as DMPA, there is significant inter-subject variation in blood levels. It may be necessary to have 60 subjects in each arm of a single dose, parallel treatment

study. Because this is a large number of subjects compared with most bioequivalence studies and they require to be followed for a long period, this study could be extremely expensive. It has been suggested that an interim analysis of data from 25-30 subjects per arm might help in estimating the total number of subjects that would be required to establish bioequivalence, however, we would not expect that bioequivalence could be established based on a dataset of that size.

Where can we undertake bioequivalence studies? How do we choose a Clinical Research Organization (CRO)? Are there approved CROs that must be used?

10.2

A bioequivalence study must be undertaken by a CRO that can be shown to meet Good Clinical Practice (GCP)¹⁶ requirements and have a laboratory or access to a laboratory that meets Good Laboratory Practice (GLP)¹⁷ and is certified under ISO17025¹⁸ for the analytes to be measured. There are many CROs around the world with the capability to undertake bioequivalence studies of reproductive medicines, ranging

from large international organizations to smaller independent organizations. Many multinational pharmaceutical companies are undertaking their clinical research with CROs in lower and middle income countries.

However, as in any field, some CROs may provide better quality services which must be balanced with cost. If a manufacturer decides to use a CRO but is unsure of its quality

16 WHO, 2005. Handbook for Good Clinical Research Practice (GCP). World Health Organization, Geneva, pp125

17 WHO TDR. Handbook for Good Laboratory Practice (GLP). World Health Organization, Geneva, pp243 http://apps.who.int/prequal/info_general/documents/GLP/glp-handbook.pdf

18 ISO/EC 17025:2005 General requirements for the competence of testing and calibration laboratories. International Standards Organization, Geneva

standards, it may be necessary to commission an independent GCP audit of the clinical research facilities and services and a GLP audit of the laboratory of the CRO. The aim of the audit would be to assess

the compliance of the CRO with internationally recognized regulations and guidelines, such as those of WHO and EMA, that relate to the services it offers.

10.3

We manufacture two types of combined oral contraceptives: a 21-day pack, with pills containing estrogen and progestogen, and a 28-day pack which contains 7 placebo pills. Would we need to submit separate dossiers for the two products and, if so, why? What additional requirements are there for the placebos and would placebo tablets containing either lactose or ferrous fumarate be treated differently?

No additional safety and efficacy (clinical) data are required for the placebo products - only quality (chemistry and manufacturing) information would be required for those tablets. Placebo tablets must be designed to ensure that they have ingredients, process, controls, specifications and stability, and other requirements that conform

to acceptable quality standards and cGMP for oral solid dosage forms. However, the use of a compound such as ferrous fumarate is not included in the current Expression of Interest but would require that safety and efficacy are addressed in a similar manner to the hormonal tablets.

What do we do if the approved comparator product is not available in our country? In such a case, how do we obtain the product if the manufacturer of the comparator refuses to supply it to us or we cannot get an import certificate from our national authorities because the product is not registered?

10.4

For studies to be submitted to the Prequalification of Medicines Programme, comparator products must be purchased from the market of an ICH or ICH-associated country. Innovator products obtained from local markets that are not ICH or ICH-associated country markets are not acceptable. There are pharmaceutical distribution companies in the USA, Europe, and other ICH-associated countries that are licensed to sell pharmaceutical

products to companies for scientific study. Many national drug regulatory agencies have information requirements for products that are being imported for clinical trials and most CROs have experience in dealing with these issues. However, if a national authority will not allow the import of the necessary comparator product, consideration must be given to conducting the study at a CRO located elsewhere.

Concept Foundation
17 chemin Louis-Dunant
1202 Geneva
Switzerland
Tel: +41-22-734 2560/1

