

FAQ: Prequalification of Medicines for Reproductive Health

(updated and expanded, 20 March 2012)

United Nations prequalification for quality medicines is managed by the World Health Organization (WHO). It issued its first Invitation to Manufacturers to Submit an Expression of Interest for Product Evaluation for medicines for reproductive health in October 2006. Since then it has expanded its scope and has included a number of medicines in its EOI (link for EOI). This document responds to the most frequently asked questions raised by manufacturers when considering 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 Team: medicines (PQTm), and WHO's Department of Essential Medicines and Health products 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 relevant annexes of the reports of WHO's Expert Committee on Specifications for Pharmaceutical Preparations can be downloaded from PQTm's website.

- 1. What are the benefits in getting our products prequalified by WHO? We are keen to supply products internationally but have a valuable local market. 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?**

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. PQTm has played a pivotal role in ensuring that this is the case for medicines used for HIV/AIDS, TB and malaria and, more recently, has also been assisting the reproductive health community to achieve the same goals.

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. This is being submitted for approval 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 PQTm 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 PQTm's quality and safety and efficacy requirements. These are stringent requirements (see point 3 below) and, as such, may require a company invests in upgrading its quality assurance procedures or even its manufacturing facility; or change its source of active pharmaceutical ingredients (APIs), excipients or other components of the finished pharmaceutical product (FPP).

Until a number of generic products have been prequalified, an interim Expert Review Panel will continue to allow the use of products for a time-limited period. This process applies only to products

¹ Stringent drug regulatory authority (SRA) An SRA is the regulatory authority of a country officially participating in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The current ICH members are Canada, the European Union, Japan, Switzerland and the USA. Other countries associated with ICH (through legally binding mutual recognition agreements) include Australia, Norway, Iceland and Liechtenstein.

that have already been accepted for review by PQTm can be shown to meet the required quality standards.

A prequalification application to WHO 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. Even in countries which currently have less stringent drug regulatory agencies, companies could benefit from WHO prequalification of products as the governments of many low- and middle-income countries are increasingly interested in ensuring the quality of imported health products.

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

Information on the process for prequalification can be found on the website of PQTm's website at www.who.int/prequal.²

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 used.³

3. How can we get technical assistance to improve our dossiers and GMP status?

PQTm may be able to arrange technical assistance for manufacturers who have demonstrated firm interest and have submitted or intend to submit dossiers for evaluation. WHO PQTm has a Memorandum of Understanding with Concept Foundation,⁴ which is being funded through the RHSC to provide technical assistance in the areas of dossier improvement and compliance with Good Manufacturing Practices (GMP).

4. 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?

This depends on the GMP requirements of your national medicines regulatory agency (NMRA). 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 ensuring 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 of a product. The recommendations and requirements of the Expert Committee are published at regular intervals by WHO in its Technical Report Series.

² Procedure for prequalification of pharmaceutical products. WHO Technical Report Series 961, Annex 10, 2011.

³ See also: Annex 15. Guidelines on submission of documentation for a multisource (generic) finished product. Preparation of product dossiers in CTD format, WHO Technical Report Series 961, Annex 15, 2011 and, Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for WHO prequalification: quality part, WHO Technical Report Series 970, Annex 4, 2012.

⁴ Email: p.procter@conceptfoundation.org

WHO's GMP requirements were updated and published in 2014⁵ and updated for hazardous substances and for sterile FPPs in 2010 and 2011.⁶ Unfortunately, some NMRAs do not regularly update national GMP requirements and 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 make changes to your manufacturing processes, raw materials or even your physical facility.

5. Does our API manufacturer need to have its API prequalified?

Having the source of your API 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 process.⁷ However, using a prequalified API should make completion of your dossier for submission easier.

To support the quality of the API used in your FPP, information regarding the API can be supplied in four ways. These are: the provision of a confirmation of API prequalification document with some additional data in the product dossier; 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 prequalified API or CEP are not available the provision of an APIMF is strongly encouraged.

A good way of identifying API manufacturers with a complete Drug Master File (DMF) and acceptable GMP status is to check whether there are suppliers that hold a valid CEP as issued by EDQM. EDQM maintains a database of approved APIs and their manufacturers which can be accessed via <http://www.edqm.eu> (see "Databases" and click the "Certification" database button). Since starting its approval process for APIs, a similar approach is being taken by WHO PQTm and a list of prequalified APIs is now published on the PQP website (see "Quick Links" and click the "Prequalified APIs" button). Partners working on the quality of medicines, such as Concept Foundation, may also have information on potential API suppliers that may be able to supply DMFs and meet expected GMP requirements for APIs.

Detailed information on the preparation and submission of API information to support an FPP application for prequalification can be found in the guidance document [Guidelines on submission of documentation for a multisource \(generic\) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part](#).

Information on the use of the APIMF procedure can be found in the [Guidelines on active pharmaceutical ingredient master file procedure](#). Please note that the API manufacturer may be inspected by WHO as part of the prequalification process, and is expected to follow the GMP requirements for APIs.

⁵ [Good manufacturing practices for pharmaceutical products: main principles](#). WHO Technical Report Series 986, Annex 2, 2014.

⁶ [Good manufacturing practices for pharmaceutical products containing hazardous substances](#). WHO Technical Report Series 957, Annex 3, 2010; [Good manufacturing practices: sterile pharmaceutical products](#). WHO Technical Report Series 961, Annex 6, 2011.

⁷ See PQTm website (www.who.int/prequal): Procedures and Fees for Prequalification, Active Pharmaceutical Ingredients.

6. We have bioequivalence and stability data collected on batches manufactured with APIs obtained from our current supplier(s). However, the supplier(s) has (have) failed to provide us with a complete DMF. In this case, can we use the available data to support our application even though we may propose a different API supplier for prequalification?

The data collected on batches manufactured using your current supplier can be submitted to support the dossier in some cases (e.g. API is high BCS⁸ solubility, or API from the proposed supplier has the same polymorphic form and similar particle size distribution to that of the batch used in clinical/bioavailability studies). In these cases, you should also include in the dossier data demonstration of comparability of the API from the existing and the proposed source (in terms of batch analysis data and key physicochemical properties, such as polymorphism and PSD when applicable). In some cases additional information may be requested, for example comparative dissolution profile data and/or a commitment to place batches of the FPP manufactured with the API from the proposed source on stability studies. For more information applicants should consult the relevant section of the WHO PQTm variation guideline.

7. What is the situation regarding excipients?

All excipients must be at least equivalent to an officially recognized pharmacopoeial standard. Requirements for excipients can be found in the generic guideline ([Guidelines on submission of documentation for a multisource \(generic\) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part](#) under section 3.2.P.4). Novel excipients are not accepted. In general, only excipients with an officially recognized pharmacopoeial monograph should be used.⁹

8. 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.

9. We have stability data that may not conform to current requirements in terms of testing frequency and/or test parameters. Can we submit our dossiers with the existing data and commit to perform stability studies in accordance with current requirements?

You are requested to refer to the note on the PQTm website, "Accelerated procedure for accepting reproductive health product dossiers for assessment for WHO prequalification". This note describes the reduced requirements for the stability data in reproductive health dossiers at the time of submission

⁸ BCS: Biopharmaceutics Classification System.

⁹ Those pharmacopoeias recognized by PQTm: (the International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the British Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP)).

10. We have been producing our product for more than three 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 i.e. up to or beyond three years instead of the 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 992 (Annex 3).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 five years, and either 10 batches were produced in the past year, or 25 batches were produced in the past three years. See the recent Prequalification Update.¹¹

11. 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?

In 2010, WHO revised its GMP for pharmaceutical products containing hazardous substances. 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 ANVISA¹² in Brazil, do require that hormonal products are manufactured in a completely separate building.

12. If we obtain prequalification for 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 this 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 [Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation](#). WHO Technical Report Series 992, Annex 3, 2015.

¹¹ [Guidelines on submission of documentation for a multisource \(generic\) finished pharmaceutical product for WHO prequalification: quality part](#). WHO Technical Report Series 970, Annex 4, 2012.

¹² Agência Nacional de Vigilância Sanitária: Brazil's regulatory agency.

13. 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, PQTm requires that a manufacturer demonstrate 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)¹³ 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 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 PQTm 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. It may be possible, however, to justify the waiver of the requirement to conduct a bioequivalence study for aqueous solution for injection products such as oxytocin and magnesium sulfate.¹⁴ 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 WHO comparator product.

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

PQTm 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.

The design and requirements for bioequivalence studies are to be found in Annex 9 of WHO TRS 937¹⁵ and Annex 7 of WHO TRS 992.¹⁴

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 in study design relates to the number of subjects. Annex 7 of TRS 992 states 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

¹³ 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.

¹⁴ [Guidelines on registration requirements to establish interchangeability](#). WHO Technical Report Series 992, Annex 7, 2015.

¹⁵ [Guidance for organizations performing in vivo bioequivalence studies](#). WHO Technical Report Series 937, 2006. Annex 9.

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 within the acceptance limits for bioequivalence with the WHO comparator, the 90% confidence interval of the mean ratio of C_{max} and of AUC of the two products must be within 80.00–125.00%. 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.

For combined oral contraceptives, progestogen-only pills, emergency contraceptives 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 must be followed for a long period, this study could be 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. More information on a two-stage design can be obtained from Annex 7 of TRS 992.

13.2 Where can we undertake bioequivalence studies? How do we choose a clinical research organization (CRO)? Are there approved CROs that must be used?

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 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.

¹⁶ WHO. [Handbook for Good Clinical Research Practice \(GCP\)](#). World Health Organization, Geneva, 2005.

¹⁷ UNDP/World Bank/WHO/TDR. [Handbook for Good Laboratory Practice \(GLP\)](#) Handbook for Good Laboratory Practice (GLP). World Health Organization, Geneva.

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

13.3 We are making a film-coated tablet but the comparator is sugar-coated, what happens if we cannot show similar dissolution profiles?

Oral contraceptives can be sugar-coated, film-coated or uncoated. It is not a requirement that a product employ the same non-functional coat as the appropriate comparator product e.g., the comparator may be a sugar-coated tablet while the product under development can be a film-coated tablet. The use of a different non-functional coat may impact the dissolution characteristics of a product relative to the comparator, however, this is not considered to be important if in vivo bioequivalence is demonstrated for the two products.

It is important to note that manufacturers must use a suitable method and information in the quality dossier should include multi-point dissolution profiles for the lot used in bioequivalence studies in three media across the physiological pH range. Recommendations for conducting and assessing comparative dissolution profiles are to be found in Appendix 1 of Annex 7, WHO TRS 992.¹⁴

13.4 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.

Similarly, it has been accepted that the addition of seven tablets of 60 mg or 75 mg of ferrous fumarate instead of placebo tablets represents an iron supplement and not a therapeutic dose. Therefore, from the clinical perspective, the same requirements can be applied for ferrous fumarate as those for placebo tablets stated above.

From the quality perspective, information on the placebo should include full information on the manufacture and the control of the product (P.1, P.3, P.4, P.5, as well as P.7 if a separate packaging system is proposed). The information can be submitted in the same dossier, using the same sections as the hormonal tablet, e.g. P.5.1 a) hormonal tablet information, b) placebo information.

Where the ferrous fumarate tablets are used instead of placebo, the above is required plus relevant additional information such as P.2 (e.g. API-excipient compatibility), P.6 and P.8 (e.g. results of stability studies).

13.5 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 if we cannot get an import certificate from our national authorities because the product is not registered?

For studies to be submitted to PQTm, comparator products must be purchased from the market of an ICH1 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 NMRAs 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.