



PQP

QUALITY MEDICINES FOR EVERYONE

PREQUALIFICATION OF
MEDICINES PROGRAMME
A UNITED NATIONS PROGRAMME
MANAGED BY WHO



Briefing note of 17 April 2012

WHO Prequalification of Medicines for Reproductive Health

Background

The WHO Prequalification of Medicines Programme (PQP) initiated prequalification of reproductive health (RH) medicines in 2006. As of 23 March 2012, it had prequalified 11 RH products. In other words, the list of WHO-prequalified RH medicines remains very limited; for many positions not a single prequalified medicine is yet available.

Weak “business case”

Why are manufacturers of RH medicines not motivated to apply for WHO prequalification? The overriding factor is the nature of the market for quality-assured RH medicines. This market is not only limited in size, but also fragmented. The market is limited because organizations and countries procuring RH medicines have not yet adopted a harmonized quality assurance policy. In brief, products of poor or insufficiently demonstrated quality, rather than quality-assured products, continue to be procured. The market is fragmented because procurement is carried out at different levels by a variety of organizations.

Thus a strong “business case” for producing quality-assured products does not exist. Building a strong business case will require harmonization and strengthening of the procurement practices and policies of key institutions, and a commitment from donors to ensure that any funds they provide for medicines procurement – whether at national or international level – are used to procure quality-assured medicines only.

PQP’s technical and regulatory support to manufacturers

When RH medicines manufacturers do express an interest in participating in WHO prequalification, PQP makes considerable efforts to help them meet prequalification requirements. This includes offering regulatory advice and making considerable technical information on production of quality-assured RH medicines available via its web site. It also organizes workshops for RH medicines manufacturers, focusing on general topics such as prequalification procedures, and on specific quality and efficacy/safety issues. Since 2008, 8 such technical and advocacy workshops have been organized in key producing countries of RH medicines; 3 more workshops are scheduled for 2012.

Additionally, PQP works with the Concept Foundation to organize technical assistance for targeted RH medicines manufacturers. Concept Foundation identifies and contracts technical experts, while PQP ensures the quality and content of any technical assistance provided. A memorandum of understanding delineating expectations and responsibilities in this area of work has been signed by both partners.



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Previous to collaboration with Concept Foundation, PQP organized technical assistance for 3 manufacturers (in Argentina, India and Indonesia), to help them improve their manufacturing quality.

Specific quality and efficacy/safety issues relating to RH medicines

PQP is well-positioned to advise manufacturers of RH medicines since it has an in-depth understanding of the quality and efficacy/safety issues that many of them find particularly challenging. These include problems in conducting bioequivalence studies (BE) and problems in ensuring safe manufacture of hormonal preparations.

For generic RH medicines, new clinical efficacy/safety studies are not needed. However, in most cases a BE study is necessary whereby the generic medicine is compared (in terms of blood concentrations of the medicine) with a product for which clinical documentation exists (the so-called originator). It is important that RH manufacturers understand the importance of conducting a BE study: a BE study provides the only evidence that the generic product is safe and efficacious. Furthermore, the comparator product and the study design must be acceptable, and the number of subjects included in the study must be appropriate. Some RH products, such as depot injectables, have specific design features that must also be taken into account by the BE study. And it is essential that the study is conducted according to good clinical and good laboratory practice, to ensure that the study results are reliable. (The proper conduct of the study must be verified by WHO PQP inspectors before the product can be prequalified.)

PQP is always available to assist RH manufacturers in designing appropriate BE studies: for example, by reviewing draft BE study protocols before a study is initiated. A document that advises on design of studies for RH products will be posted on PQP's web site shortly.

With respect to manufacture of hormonal contraceptives, sophisticated pharmaceutical expertise is key. Oral and injectable contraceptives require advanced manufacturing equipment and production techniques, strict adherence to quality assurance (QA) and compliance with good manufacturing practice (GMP). For example, due to the extremely small amount of active ingredients in each oral contraception tablet, production requires perfect integration of product formulation, starting materials, equipment, manufacturing processes and quality control procedures, if content uniformity is to be guaranteed. Additionally, hormonal contraceptive production can pose special risks for workers (due to exposure to the potent steroids) and for the environment in which they are produced (due to potential release, during production, of air and water that contain hormones). PQP can advise manufacturers on each of these issues.

An extensive document responding to the questions most frequently asked by RH medicines manufacturers interested in WHO prequalification is available on PQP's web site, as is its updated list of recommended comparator products. Guidance on quality risk management for RH medicines manufacturers is currently being developed by the WHO team that is responsible for development of pharmaceutical norms and standards. It is anticipated that it will be approved at the next meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (in October 2012) and will be posted on the PQP web site thereafter.



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Product evaluation pipeline

Since prequalification is a voluntary process¹ and the business case for prequalification of RH medicines is weak, the number of applications for evaluation that is being received from manufacturers continues to be relatively low.

Seven products – all generic – are currently under assessment. The applications for evaluation were received in 2007 (for 1 product), in 2010 (for 5 products) and in 2012 (for 1 product). For some of these products, dossier assessment has revealed a wide range of quality and efficacy/safety problems that will require significant effort on the part of the manufacturer if they are to be overcome.

In terms of applications received per product/recommended dosage form/strength invited for evaluation, the situation is as follows:

- PQP has not received a single application for 6 of the 16 products currently invited for evaluation
- PQP has received a single application for some products invited for evaluation and that single product has been prequalified; but no additional applications have been received
- for the remaining products, 2 or 3 applications for evaluation have been received; a product in one of these product categories is close to meeting PQP requirements (following joint efforts by the manufacturer and PQP), but each of the other products continues to demonstrate major deficiencies that remain to be rectified by its manufacturer.

Ensuring supply

The lack of prequalified RH medicines is evidently of great concern to WHO and to partner organizations working to improve reproductive health. However, the lack of prequalified products – irrespective of therapeutic category – does not impede supply of products in the short term since WHO's Quality and Safety: Medicines team, and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) have created a mechanism known as the Expert Review Panel (ERP), that provides risk-based advice to aid decisions about procurement of products that are in the PQP "pipeline", but that have not yet been prequalified. ERP is managed by PQP.

Each ERP is a discrete operation, consisting of an invitation to manufacturers to submit a product for ERP evaluation, followed by assessment of product dossiers submitted.

ERPs to date have ranged widely in the number of products assessed: from a few up to 80 product dossiers. Assessment is carried out by highly experienced assessors and covers manufacturing process and specification, stability data, evidence of therapeutic equivalence, and quality and source of active pharmaceutical ingredient. An assessment report is issued for each product. Most importantly

¹ Applications for evaluation are invited via an *Invitation to Manufacturers of RH Products to Submit an Expression of Interest for Product Evaluation to the WHO Prequalification of Medicines Programme*. The current invitation is the 5th such invitation.



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for procurers, each assessment report includes categorization of the level of risk associated with use of the product in question.

Today, the ERP mechanism is used not only by the Global Fund but also by the Global Drug Facility, UNITAID, UNFPA and several WHO departments. Assessment usually takes up to 4 weeks, but can be as short as several days when products and suppliers are few.

Accelerating national registration of WHO-prequalified products

In order to facilitate availability and minimize regulatory delays during registration of RH medicines in recipient countries, PQP has drafted, in co-operation with several national medicines regulatory authorities, a procedure for accelerated registration of WHO-prequalified medicines. In 2012 this will be piloted with prequalified generic RH products, as well as with products in other therapeutic categories.

Outreach to industry associations and individual manufacturers

PQP is in regular contact with industry associations such as the European Generics Association and the International Generic Pharmaceutical Alliance. It actively encourages these associations to support their members in their efforts to attain WHO prequalification of their products. It also seeks to engage individual manufacturers that have significant manufacturing capacity with respect to RH medicines. Outreach consists of face-to-face meetings, teleconferences and regular communication via email.

Funding and collaboration

PQP's activities focusing on RH medicines are currently financed by the Bill & Melinda Gates Foundation. Concept Foundation's activities in support of WHO prequalification are financed by the Department for International Development. Both organizations and both donors consult together regularly to ensure that activities of PQP and Concept Foundation are aligned and effective.

PQP is seeking additional funding for a sampling and testing survey. When oral contraceptives "fail", the failure is more likely to be falsely attributed to failure to use the product as indicated, rather than to the actual inadequate quality of the product. Sampling and testing of RH products could help to highlight this issue and to underscore the need for procurers to rigorously apply (harmonized) QA procurement principles. Increased procurement of quality-assured products would expand the market for those products, which would stimulate manufacturers to participate in WHO prequalification.



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Further information:

Questions and answers relating to WHO prequalification of medicines for RH

http://www.who.int/prequal/info_press/pq_news_21March2012_QA-RH.htm

Accelerated procedure for accepting RH dossiers for assessment

http://www.who.int/prequal/info_press/pq_news_21March2012_noteRH.htm

Recommended comparator products for RH medicines

http://www.who.int/prequal/info_applicants/BE/Comparator-RH2012-20March.pdf

Concept Foundation

<http://www.conceptfoundation.org/>

Contacts:

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