



# PQP QUALITY MEDICINES FOR EVERYONE

PREQUALIFICATION OF  
MEDICINES PROGRAMME  
A UNITED NATIONS PROGRAMME  
MANAGED BY WHO



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## THE WHO PREQUALIFICATION PROGRAMME AND THE MEDICINES PATENT POOL: A PRIMER

The [World Health Organization Prequalification of Medicines Programme](#) (PQP) ensures the safety and efficacy of medicines. Since its beginning in 2001, the programme has evaluated medicinal products based on a stringent set of criteria, helping procurement agencies around the world to have confidence in the medicines they purchase.

The [Medicines Patent Pool](#), formed with the support of UNITAID in July 2010, is working to bring down prices of HIV medicines in developing countries and to encourage the development of needed new medicines, such as formulations for children, through voluntary licensing of critical intellectual property from patent holders. This provides potential generic manufacturers with a “one-stop shop” to access the intellectual property they need to enter into HIV medicines markets or to do research on new formulations and combination drugs. It will also spur competition that brings down prices and encourages innovation. The Pool is working with WHO on several levels, and will be closely cooperating with the WHO/UN Prequalification of Medicines Programme to ensure that medicines made with licences obtained from the Pool meet international quality and safety standards and are acceptable for UN procurement.

This document intends to answer frequently asked questions about the Prequalification of Medicines Programme, and how it relates to the Pool.

### WHY IS PREQUALIFICATION IMPORTANT?

WHO prequalification of medicines is a strong indicator of quality. In a recent study of antimalarials collected in Cameroon, Ethiopia, Ghana, Kenya, Nigeria and Tanzania, only 3.6 percent of the WHO-prequalified product samples deviated from pre-specified quality criteria (and none of the deviations represented serious threats to health), compared with 39.7 percent of the non-prequalified product samples. In other words, provided procurement and distribution practices are sound, procurement agents, health workers, patients and funding agencies can view WHO-prequalified medicines with confidence.

### WHAT DOES WHO MEDICINES PREQUALIFICATION INVOLVE?

In order for a finished pharmaceutical product to be prequalified by WHO, the Prequalification of Medicines Programme (PQP) carries out a comprehensive, scientific evaluation of that product. The evaluation is based on information submitted by the manufacturer and on an inspection of the corresponding manufacturing facilities and clinical sites (i.e. contract research organizations). Products found to comply with WHO norms and standards are added to the *WHO List of Prequalified Medicinal Products*, which is posted on the WHO web site.<sup>1</sup>

Medicines Patent Pool licensees will be required to submit their products to either PQP or to a stringent regulatory authority for evaluation.

<sup>1</sup> [http://www.who.int/prequal/info\\_general/notes.htm](http://www.who.int/prequal/info_general/notes.htm)



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### WHAT PHARMACEUTICAL PRODUCTS ARE ELIGIBLE FOR WHO PREQUALIFICATION?

The Prequalification of Medicines Programme focuses primarily on medicines for treating HIV/AIDS, malaria and tuberculosis. It also evaluates zinc for managing acute diarrhoea in young children, and products for reproductive health and influenza-specific antiviral medicines. In 2010, it initiated prequalification of active pharmaceutical ingredients.

In order to be eligible for prequalification, a medicinal product must be listed in an *Invitation to Manufacturers to Submit an Expression of Interest for Product Evaluation to the WHO Prequalification of Medicines Programme* (EOI).<sup>2</sup> The medicines listed in EOIs have been identified as vital to public health programmes by the respective WHO disease, child health or reproductive health department. Most products listed in an EOI are already included in the *WHO Model List of Essential Medicines* and/or in WHO treatment guidelines, which set out respectively the medicines needed for a basic and effective public health system, and best practices for the treatment of particular illnesses. However, since the processes for updating the *Model List* and WHO treatment guidelines can lag behind evolving treatment needs, exceptions are sometimes made. Thus, at the request of a WHO disease programme, a medicine may exceptionally be included in an EOI that is not yet listed in the *Model List* and/or not included in the relevant WHO treatment guideline.

In 2009 and 2011, the Medicines Patent Pool along with UNITAID and the WHO HIV/AIDS Department submitted a document containing a list of missing medicine formulations for HIV treatment to be reviewed by the WHO Expert Committee on the Selection and Use of Essential Medicines. The document in particular highlighted several needed fixed-dose combinations. It was also endorsed by nine members of the WHO Treatment 2.0 Initiative for meeting current and future needs of people living with HIV. In the context of Treatment 2.0, further prioritization is taking place to identify the most urgent priority medicines for future development.

### DO WHO REQUIREMENTS FOR MEDICINES PREQUALIFICATION DIFFER FROM THE APPROVAL REQUIREMENTS OF OTHER MEDICINES REGULATORY AGENCIES?

The norms and standards used as the basis for prequalification have been evaluated and adopted as international standards by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Committee members include individual, national technical experts and medicines regulators from different countries in all WHO regions. Other stakeholders, with a range of professional expertise, are linked to the Committee as observers. They include representatives of nongovernmental organizations and the pharmaceutical industry.

Wherever possible, WHO prequalification seeks to harmonize its requirements with the approval requirements of stringent medicines regulatory agencies. For example, the Prequalification of Medicines Programme has adopted the common technical document

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<sup>2</sup> current invitations are listed here:

[http://www.who.int/prequal/info\\_applicants/info\\_for\\_applicants\\_EOIs.htm](http://www.who.int/prequal/info_applicants/info_for_applicants_EOIs.htm)



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format<sup>3</sup> for product dossier submissions of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), a project that brings together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US to make recommendations on the technical guidelines of registering medicines. The common technical document format is also used increasingly by the regulatory authorities of countries such as Indonesia, Jordan, Kenya, Saudi Arabia, Singapore and Thailand. Beginning in September 2011, all applicants to PQP must submit their product dossier using the common technical document format.

WHO good manufacturing practice requirements are also very similar to those required by stringent regulatory authorities.

### DOES WHO MEDICINES PREQUALIFICATION TAKE THE FINDINGS OF OTHER REGISTRATION SYSTEMS INTO ACCOUNT?

PQP applies an abbreviated procedure for products that have already been approved and registered by a "stringent regulatory authority." That is, a regulatory authority that is (a) a member of the [International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use \(ICH\)](#), (b) an ICH Observer, or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement (this currently includes Australia, Norway, Iceland and Liechtenstein).

If a product has been assessed and approved by a stringent regulatory authority WHO applies an abridged procedure to evaluate the product, to verify that it is essentially the same product as already approved by one of these agencies. Duplication of scientific assessment is therefore avoided. In addition, products that are tentatively approved by the US FDA (US President's Emergency Plan for AID Relief, commonly known as PEPFAR) or approved by the EMA through the EU Article 58 mechanism, are added to the WHO List of Prequalified Medicinal Products without further assessment.

The abbreviated procedure helps speed medicines through prequalification that have already been through an equivalent regulatory process and approved.

### HOW LONG DOES WHO PREQUALIFICATION TAKE?

The length of time taken to prequalify a medicine is highly dependent on the quality of information contained in the product dossier submitted by the manufacturer, the length of time taken to respond to any requests for additional information made by WHO, and the length of time taken to respond to any observations made during the inspection of the relevant manufacturing site, and/or to carry out any required additional studies or corrective actions. In 2010, the median time to prequalify an innovator product was 4.3 months, and 31.6 months to prequalify a generic product. As noted above, PQP applies an abridged procedure to products already registered at a stringent regulatory authority, which is frequently the case with innovator products.

<sup>3</sup> <http://www.ich.org/products/ctd.html>



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The Medicines Patent Pool is working to facilitate the development of new fixed-dose combinations that are essential to scale up HIV treatment in resource-poor settings. Several of these "missing combinations" have specifically been identified by WHO (see above). Because of the urgency of the need for these new medicines, WHO PQP has indicated that it will prioritize the assessment of any of these newly developed fixed-dose combinations.

### HOW IS PREQUALIFICATION STATUS MAINTAINED AND VERIFIED?

Manufacturers are obliged to submit any significant changes (variations) they have made to a prequalified product to PQP for review.<sup>4</sup> Assessment of variations provides assurance that any changes made to WHO-prequalified products – either to their development or manufacture – have not entailed an unacceptable reduction in product quality.

PQP arranges for the products and manufacturing sites included in its list of prequalified products to be re-inspected at regular intervals. The frequency of re-inspection is determined on a risk basis.

Additionally, manufacturers of WHO-prequalified products must submit a quality review to PQP either 5 years from the date of prequalification of the product, or when requested to do so by PQP (whichever date is earlier), in order to be "requalified". Requalification incorporates review of certain summary information and key documents (i.e. not the full dossier), to verify the continued acceptability of the product and its conformity with WHO norms and standards.

Other mechanisms for ensuring that prequalification status is maintained include an internal procedure for investigating complaints about quality, irrespective of the source from which they have been received, and random quality control sampling on a project basis.

Last but not least, procurement agencies and organizations conduct pre- and post-shipment sampling and testing of purchases of prequalified medicines. If this testing reveals the failure of a product to meet the specifications of the procurer, the procurer can provide the details to PQP, for immediate investigation and further action, if necessary.

If, as a result of ongoing re-evaluation, a product and/or specified manufacturing site is found to no longer comply with the WHO-recommended standards, the product and manufacturing site(s) will be removed from the list.

### HOW WIDELY RECOGNIZED IN COUNTRIES IS WHO PREQUALIFICATION OF MEDICINES?

PQP is currently collecting data on how individual country regulatory authorities handle the dossiers of medicines that are submitted for national registration and that have already been prequalified by WHO. In several countries, an abridged procedure is used to handle

<sup>4</sup> See *Guidance on variations to a prequalified product dossier* at:  
[http://www.who.int/prequal/info\\_general/documents/TRS943/TRS943.pdf#page=121](http://www.who.int/prequal/info_general/documents/TRS943/TRS943.pdf#page=121)



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an application for registration of a WHO-prequalified product, meaning that the national authorities concerned take into account the scientific assessment already undertaken by PQP and do not consider it necessary to carry out another full assessment.

Efforts to promote joint assessment by WHO in conjunction with national medicines regulatory authorities are under way. Two products have been assessed jointly by WHO and regulators of the East African Community. The products were prequalified by WHO in consultation with national regulators and the results of the joint evaluation integrated into the national decision-making processes, including registration, of the countries who participated in the assessment. This meant that manufacturers of these products had immediate access to the markets of countries that had participated in the joint assessment. Such projects reduce the burden of assessment for both the regulatory authorities and manufacturers and ensure that patients gain access to medicines more quickly.

PQP is hoping to use the same model for assessing selected, technically complex, new high-priority products. Several partners and stakeholders see joint assessment as an effective means of speeding up access to much needed products. It is very likely that new fixed-dose combinations identified as "missing" by the WHO Expert Committee and developed through the Patent Pool initiative, will also fall into this category.

### WHY WOULD A MANUFACTURER SUBMIT A DOSSIER FOR EVALUATION TO WHO AS WELL AS TO AGENCIES SUCH AS THE UNITED STATES FOOD AND DRUG ADMINISTRATION AND THE EUROPEAN MEDICINES AGENCY?

Some national authorities consider that listing of a product as WHO-prequalified confers added value on that product. And some research-based international companies recognize that WHO-prequalification of a product is beneficial when seeking national registration and/or participating in procurement tenders. In some countries, review by the national medicines regulatory authority of a WHO-prequalified product will take precedence over review of a US FDA- or EMA-approved product. In other countries, the reverse is true. Thus manufacturers may need to adapt their strategies for seeking regulatory approval depending upon the country in which they plan to operate.

PQP is willing to discuss these issues with individual manufacturers, to help them take an informed decision as to which regulatory pathway is best for their product.

### WHAT ARE THE REQUIREMENTS FOR WHO PREQUALIFICATION?

Any manufacturer of medicinal products listed in the EOIs can express an interest in having a finished pharmaceutical product and the relevant manufacturing site assessed by the prequalification programme. A product dossier for a product listed on a current EOI must be submitted to PQP and be accompanied by a covering letter, a product sample and the site master file of the manufacturing site of the medicinal product. Comprehensive and up-to-date information about the documentation required can be found on the [PQP web site](#) in the section headed *Information for applicants*.



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### WHAT LEVEL OF ASSISTANCE CAN PQP PROVIDE TO MANUFACTURERS WHO ARE USING NEW FORMULATIONS OBTAINED FROM THE MEDICINES PATENT POOL?

PQP has a very extensive website that contains useful technical material for medicines manufacturers. This includes material used in PQP training courses. In addition, PQP can advise companies on development issues before they submit their product dossier to PQP for assessment and can organize technical assistance for a manufacturer, provided that the manufacturer is committed to producing quality products that meet PQP requirements, and has the potential capacity to do so. PQP can also meet with applicants after the submission of a dossier, to discuss any outstanding issues. Applicants can send questions or a request for a meeting to [prequalassessment@who.int](mailto:prequalassessment@who.int).

PQP organizes some training courses on pharmaceutical development, including a course on development of paediatric dosage forms.

WHO will continue to work closely with the Medicines Patent Pool on quality assurance issues, and will provide advice to the Pool and assistance to its potential sub-licensees to ensure that their medicines meet international quality and safety standards.