WHO Prequalification of Medicines Programme – application fees

This document explains the fees that apply to applications to prequalify medicines or active pharmaceutical ingredients and applications for major variations to prequalified medicines

SUMMARY
Previously, the WHO Prequalification of Medicines Programme (PQP) relied entirely on external funding sources. In the current global financial environment it is an increasingly risky proposition to rely entirely on external funding sources. After having successfully implemented fees for the vaccines and diagnostics prequalification programmes, WHO has introduced fees for applications to prequalify a medicine (finished pharmaceutical product) or active pharmaceutical ingredient (API) and applications for major variations of a previously prequalified medicine.

As the majority of quality control laboratories (QCLs) are national laboratories or academic institutions, WHO will not charge an application fee for the prequalification of QCLs. At this stage WHO is not seeking to recover all of its costs from medicines and API manufacturers as this would lead to unsustainably high fees. As WHO continues to assess funding models to ensure the sustainability of the PQP, the scope of prequalification and related activities that will be subject to user fees may change in the future.

INTRODUCTION
The PQP, established in 2001, was originally intended to give United Nations procurement agencies, such as UNICEF, a choice of quality medicines. PQP supplements its internal expertise with experts from some of the best national regulatory authorities to provide a list of prequalified medicines that comply with accepted international standards. With time, the growing list of prequalified medicines has come to be seen as a useful tool for other organizations involved in the bulk purchase of medicines, including countries themselves.

Since its establishment, the PQP has also implemented the prequalification of APIs and QCLs. The former provides manufacturers of essential and other needed medicines with a list of quality assured ingredients for their medicines, the latter provides National Medicines Regulatory Authorities (NMRAs) with a list of
laboratories that are able to conduct testing and analysis of medicine samples consistently and reliably. Thus, the PQP has implemented a holistic approach to support the development of effective medicines regulation in all regions.

Any manufacturer wishing their medicines to be included in the WHO List of Prequalified Products list is invited to apply, provided the medicines are included in one of the invitations for Expressions of Interest (EoI). Each manufacturer must present extensive information on the product (or products) submitted to allow qualified assessment teams to evaluate its quality, safety and efficacy. In relation to QCLs, the assessment focuses on quality management systems and compliance with relevant guidelines.

Once an application is received it is screened and a determination made about whether it includes sufficient information to allow assessment of the product quality, safety and efficacy. The PQP applies a risk management approach during both the assessment of the product dossier submitted by the manufacturer as well as during inspection of the manufacturing facilities. Once a product or QCL has been deemed to meet all applicable requirements, it is added to the list of prequalified medicines, APIs or QCLs. The PQP also conducts capacity building activities with staff from NMRAs, manufacturers, contract research organizations and QCLs.

The PQP is not intended to replace NMRAs or national authorization systems for importation of medicines, but provides a mechanism for assuring the quality of medicines for which there is an urgent need in low- to middle-income countries. In addition, to minimize delays to the supply of critically needed medicines to the people who need them, PQP works with NMRAs to reduce national registration times.

Manufacturers are commonly required to pay fees when registering their products in different national jurisdictions. It is therefore reasonable to charge fees for applications to prequalify a medicine or API, or vary a previously prequalified medicine.

Quality control laboratories are generally operated by national governments or academic institutions, and the introduction of fees would be a significant disincentive, especially in low to middle income countries, where there is a demonstrated need for additional QCLs. Consequently fees will not be introduced for QCLs.

**FEE STRUCTURE**

**Key principles**

Many of the manufacturers that PQP deals with are small, local manufacturers with little or no experience in supplying international medicines markets. To fully recover the operating costs of the PQP, the fees would have to be significantly higher than those being implemented. Such costs are likely to be prohibitive for many of the manufacturers that PQP deals with. Therefore, the purpose of introducing PQP application fees is not to achieve full cost recovery, but to achieve a balance between external and internal funding.

When designing a fee structure it is important to consider ways to incentivize certain outcomes. For example, a key outcome is to have at least three medicines of each

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1 The current list of EoI medicines, APIs and QCLs is available at [http://apps.who.int/prequal/info_applicants/info_for_applicants_EOIs.htm](http://apps.who.int/prequal/info_applicants/info_for_applicants_EOIs.htm)
type available: increased competition reduces prices and the availability of products from multiple manufacturers ensures continuity of supply. With the PQP fees described here the main focus is on providing incentives in the form of reduced fees, or exemption from fees. WHO will provide the following incentives:

- **First time applicants are exempt from application fees**
  Any manufacturer who has not previously had an application accepted for assessment by PQP will be exempt from fees for their first application.

- **A sliding scale fee structure**
  No application fees are charged for the first application for an EoI medicine and reduced fees for second and third applications. Please note that this relates to applications accepted for evaluation by PQP and not applications received by PQP.

- **Reduced application fees for SRA approved products**
  Products that have been approved by a Stringent Regulatory Authority (SRA) will attract a lower evaluation fee as PQP does not require, or assess, a full dossier. This avoids duplication of regulatory effort and allows these products to be prequalified in shorter timeframes, typically less than 4 months.

- **Special circumstances**
  PQP will consider requests for fee waivers or reduced fees on a case-by-case basis. For instance, a small manufacturer from a low-income nation may be able to make a case that they should pay a reduced fee, or be exempt from fees.

### Fees for applications to prequalify a finished pharmaceutical product (FPP)

The following schedule of fees applies to applications to prequalify a FPP:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>First application accepted for evaluation in relation to an EoI medicine (FPP)</td>
<td>No fee</td>
</tr>
<tr>
<td>Second application accepted for evaluation relation to an EoI medicine (FPP) OR Application to prequalify a medicine that has been approved by an SRA</td>
<td>USD 3,000</td>
</tr>
<tr>
<td>Third application accepted for evaluation in relation to an EoI medicine (FPP)</td>
<td>USD 6,000</td>
</tr>
<tr>
<td>All other applications to prequalify an EoI medicine (FPP)</td>
<td>USD 8,000</td>
</tr>
</tbody>
</table>

### Fees for applications to prequalify an active pharmaceutical ingredient (API)

The following schedule of fees applies to applications to prequalify an API:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>First application accepted for evaluation in relation to an EoI API</td>
<td>No fee</td>
</tr>
<tr>
<td>Second application accepted for evaluation relation to an EoI API</td>
<td>USD 3,000</td>
</tr>
<tr>
<td>Third application accepted for evaluation in relation to an EoI API</td>
<td>USD 6,000</td>
</tr>
<tr>
<td>All other applications to prequalify an EoI API</td>
<td>USD 8,000</td>
</tr>
</tbody>
</table>
Fees for applications to vary a prequalified medicine

In relation to fees for applications to vary an existing prequalified medicine, WHO will limit fees only to major variations, i.e. no fees will be charged at this time for minor variations. This is because WHO effort in relation to major variations can be significant. Any change that could have a major effect on the overall quality, safety and efficacy of the prequalified medicine, including some changes to formulation or dosage form, are considered to be major changes. For detailed guidance on the classification of variations to prequalified medicines please refer to http://apps.who.int/prequal/info_press/pq_news_10April2013_Variation.htm.

The WHO recognizes that there may be times that a manufacturer will seek to have their variation application treated as a priority to avoid interruptions to their participation in the market for the medicine. Due to the additional effort involved in managing such applications with limited resources, a higher fee will apply.

The following schedule of fees applies to major variation applications in relation to prequalified medicines or APIs:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard process for major variations</td>
<td>USD 1,500</td>
</tr>
<tr>
<td>Expedited process for major variations</td>
<td>USD 3,000</td>
</tr>
</tbody>
</table>

The usual timeframe for deciding major variations is 90 days, where the application includes the required information. PQP will endeavour to complete expedited reviews of major variation applications within 45 days, but will commit to taking less than 60 days. Clearly, PQP’s ability to complete the expedited assessment will be reliant on application quality and manufacturer responsiveness to PQP requests for information. PQP will review these timelines during the impact assessment (see below).

Special circumstances

As described in the key principles, where a manufacturer provides justification, WHO may reduce or waive the application fee. To ensure that WHO can be flexible in this regard, it is not proposed to develop a detailed list of criteria for fee reductions or exemptions at this time. However, it is expected that justifications for exemptions from fees or reduced fees should relate to circumstances such as the establishment of a quality medicines manufacturing capability within a low-income country, or a demonstrable adverse impact on the financial viability of the manufacturer.

PQP will collate these specific circumstances as they arise, with the view of developing criteria for fee exemptions or reductions once sufficient experience with the fees system has been obtained.

Process for payment of fees

Manufacturers are NOT required to pay a fee when they lodge an application. The fee becomes due only after the application screening step and only if the application has been deemed to be acceptable for assessment by PQP.

An invoice will be sent to the manufacturer together with the notification that their application is suitable for further consideration by PQP. The application will not be formally accepted, or issued with an application number, until the application fee has been received by WHO, or appropriate evidence of payment has been provided by the manufacturer and accepted by WHO.
The notification letter will include detailed instructions about the applicable fee and payment methods.

**Determining whether other applications have been accepted for evaluation**

PQP understands the need for manufacturers to be able to determine whether one or more applications for a specific FPP or API have already been accepted for evaluation. To this end a list of all EoI FPPs and APIs is provided which shows the number of prequalified products and the number of applications under evaluation. This list is available on the WHO Internet site at [http://apps.who.int/prequal/info_applicants/info_for_applicants.htm](http://apps.who.int/prequal/info_applicants/info_for_applicants.htm)

**DATE OF EFFECT**

This fees schedule applies to all applications to prequalify an FPP or API and applications for major variations to a prequalified medicine received on and after 1 September 2013.

**IMPACT ASSESSMENT**

Following the implementation of these fees, WHO will review the operation of the fee schedule. This review will be initiated 18 months after implementation. The objectives of the review will include assessing:

- Impact on number of applications received after the introduction of the fees, including number of applications from first time applicants to PQP.
- Impact on quality of applications.
- Resource implications for PQP (e.g. large number of applications for expedited variation process).
- Complaints and other feedback received.
- Feasibility to expanding the schedule of fees to include inspection fees, annual fee for maintaining a product on the prequalified list of medicines/APIs.
- Other fees-based incentives that could be introduced.
- Whether fees-based disincentives should be introduced (e.g. screening fee that would not be refundable if the dossier is not accepted for evaluation).

Following the review, the schedule of fees may be revised. This may involve either changing the value of the fees, revising the exemptions or by adding further fees to other activities in the evaluation process and any combination of these and other issues identified during the review. It should be noted that the impact assessment may be conducted as part of a broader WHO consideration of fees and cost recovery issues in general.