EXPERT REVIEW PANEL PROCEDURE: ADDITIONAL SUPPORT TO PROCUREMENT AGENCIES UNDER EXCEPTIONAL CIRCUMSTANCES

Introduction
The WHO Prequalification of Medicines Programme (PQP) was established to provide UN procurement agencies with a quality assurance mechanism on which to base their procurement decisions. Other procurement agencies and nations now also rely on this mechanism when deciding which medicines to procure.

Since 2009 the WHO has coordinated the Expert Review Panel (ERP) on behalf of the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). The ERP was established as a mechanism to provide procurement agencies with information about the level of risk and advice to aid procurement decisions regarding pharmaceuticals for which there is an urgent need but no available WHO prequalified or Stringent Regulatory Authority (SRA)-approved products. The WHO now also coordinates ERPs on behalf of UNFPA and UNITAID and other procurement organizations.

The procurement agency releases an expression of interest, inviting manufacturers to submit an application for an ERP assessment of their medicine. The application must provide specified information, which includes:

- Product details (active pharmaceutical ingredient, dosage form and formulation).
- Applicable pharmacopoeial standards and evidence that the product meets these.
- Data to demonstrate product stability in support of claimed shelf life and storage conditions.
- Summary information on product safety and efficacy.
- Information about the GMP status of the manufacturing site.

After assessing this information the ERP provides a risk category rating to the procurer in question, be it Global Fund or UNFPA or any other procurement organization. Risk categories 1 and 2 are given to products that have demonstrated sufficient quality, safety and efficacy and for which a full dossier is under assessment by WHO PQP or an SRA (or in case of RH products, there is a commitment to submit a full dossier to WHO PQP or SRA within 3 months following conclusion of the ERP assessment). An ERP risk rating of 1 or 2 for a product translates to an ERP no-objection to procurement of the product, valid for a period of 12 months, meaning the product can be supplied for this period if the procurer decides to do so.

A risk category rating of 3 or 4 indicates that ERP objects to the procurement of the product. However, in the case of risk category 3, a procurer may proceed with procurement if the risk of no treatment outweighs the risk of treatment, as determined by the procurer, with a medicine that has not yet met all the quality standards. The

criteria applied by ERP to determine a product risk category are provided at Attachment 1.

The problem

The ERP has provided procurement agencies with a mechanism on which to base their procurement decisions about priority medicines for which no WHO PQP or SRA approved product is available. Although this mechanism is achieving its objectives, there are nevertheless exceptional circumstances where procurers do not have access to urgently needed medicines that have achieved an ERP risk category of 1, 2 or 3, and for which there are no alternative treatments.

This places procurement agencies in a difficult situation, as not procuring the medicine may have a significant adverse impact on important health programmes in low- to middle-income nations. It is timely therefore, to assess whether it is possible to leverage from WHO and ERP expertise in identifying and managing risks associated with medicines to develop a mechanism that would allow procurement agencies to meet their health objectives.

When considering a solution to these exceptional circumstances the following should be noted:

- **Assessing all relevant information**: Although in some cases an ERP application is in relation to a product for which a full dossier has also been submitted to WHO PQP or a SRA, the ERP process is designed to review the information the manufacturer is required to submit to ERP and accelerate access to priority medicines that have not yet completed the regulatory approval processes. Recognizing that ERP in general has access to the full dossier submitted to WHO PQP, it can be envisaged, however, that WHO, the manufacturer or other stakeholders may hold additional information about the medicine that might be pertinent to a risk/benefit assessment; information that is not included in the ERP application or in the full product dossier.

  For example, where a product has been registered and/or supplied in a number of countries, relevant information may include registration details, volumes of the medicine supplied (including batch data that would allow tracking of any reported adverse events), risk management plans for the supply of the medicine and safety information collected. Any data published in peer reviewed professional publications would be well regarded, as would unpublished but appropriately validated data. The nature of the additional information will determine the expertise that will be required for the assessment (further discussed below).

- **Risk management plans**: Current approaches to medicines regulation recognize that post-authorization risk management activities are as important as pre-authorization quality, safety and efficacy assessments. A case in point is the regulation of new innovator medicines: an authorization of such a medicine is based on a limited data set and more safety information will come to light as the medicine is distributed to larger numbers of patients. A key element of the post-authorization activities is the risk management plan, which
specifies a range of pharmacovigilance and other activities that the manufacturer is responsible for to ensure any safety signals are detected, reported and acted upon immediately.

**Expanding the ERP process**

The above therefore suggests that where a medicine is urgently needed, but it has not achieved an ERP risk category rating of 1, 2 or 3, and no alternative treatments exist, a mechanism could be invoked that involves the assessment of other available information relevant to the determination of a ERP risk category rating and the development of a risk management plan under which the medicine could be procured and supplied within priority countries.

**Eligibility criteria**

To ensure that the expanded ERP process is applied only in genuinely exceptional circumstances, the following criteria must be satisfied:

- The risk of providing no treatment is greater than the risk of treatment with medicines that meet some but not all quality standards.
- There is no alternative treatment available in priority countries.
- There is additional information available to inform the determination of an ERP risk category.

This raises the question about how the determination will be made that the above criteria apply in relation to a product, including what additional information may be available in relation to a specific product. Given WHO’s role as the coordinator of the ERP, it is more appropriate for the procurement agency to make this determination. The expanded ERP process described in this document does not prescribe a specific mechanism for procurement agencies to make this determination. However, one option may be to invite interested parties not involved in the manufacture of medicines to make submissions about whether a specific product may qualify for the expanded mechanism and the kind of additional information that is available. This could be done prior to the release of the expression of interest, or in parallel.

**Access to relevant additional information**

It is envisaged that information may exist that is not contained within an ERP application or is otherwise unavailable to ERP but may nevertheless be relevant to the risk categorization of the medicine. Experience to date is that in the majority of ERP applications, the current application form provides sufficient information for ERP to develop a risk category rating. There is therefore no case to be made for expanding the scope of the ERP application, as this would create an additional regulatory burden for manufacturers and administrative burden for procurers and ERP.

Given the small number of cases in which this mechanism will be invoked, it makes more sense to assess each on a case-by-case basis and make a determination about what additional information might be available and how this might be obtained within a timely fashion. In addition to any advice provided by the procurer (see above), WHO’s extensive network of contacts, collaborators and country and regional offices will facilitate accessing additional information that may be relevant to the risk/benefit assessment.
Access to relevant expertise - advisory group

When considering a mechanism to allow ERP to provide advice to procurers in exceptional circumstances, we need to ensure that appropriate expertise is available for the assessment of any additional information and development of the risk management plan. In relation to the former, the WHO has access to significant expertise within the Essential Medicines and Health Products (EMP) Division, the clinical treatment areas and its extensive list of experts and expert committee members.

A key aspect of the proposed mechanism will be speed; as indicated this would only be invoked in exceptional circumstances where any undue delays may have adverse health impacts in low- to middle-income nations. To ensure timely responses to exceptional circumstances each will be assessed on a case-by-case basis and appropriate experts identified based on the nature of the additional information. For instance, should additional information include history of use of the medicine, clinical expertise would be sought. However, if the additional information includes product quality data, appropriate scientific expertise would be sought.

These experts will be convened as an advisory group to the ERP, either face-to-face or via tele- or videoconferences. Their advice will be provided to ERP, who will then assess the medicine in the light of their previous assessment and the advisory group advice.

Developing risk management plans

It must be noted that although this mechanism is designed to provide support to procurement agencies in exceptional circumstances where WHO-prequalified or SRA-approved urgently needed medicines are not available, it is not intended to be a ‘supply at all costs’ option. The situation may arise that even after the expanded ERP process, ERP objects to the procurement of the medicine under any circumstance (ie. risk category rating 4) on the grounds of serious quality and/or safety concerns that would pose a higher risk to health programmes than not supplying the medicine. Recognizing the difficult position in which this would place the procurement agency, WHO would naturally provide any advice and assistance requested.

The WHO has significant expertise in the areas of medicine risk management planning and pharmacovigilance. In particular, the Uppsala Monitoring Centre is a WHO Collaborating Centre, which allows for rapid information exchange in priority circumstances, such as when a safety signal is detected. The WHO also has staff, and access to a network of external experts, with experience in developing risk management plans.

WHO has applied this experience to the development of strategies for monitoring post-market safety in resource limited settings. This, together with WHO’s knowledge of local capabilities, will allow WHO to respond to requests from procurers for assistance in the development of appropriate risk management plans.
Application of the expanded ERP process

The expanded ERP process is not intended to provide a mechanism for reviewing past decisions. Therefore, it will apply only to new expressions of interest for manufacturers to submit applications to ERP.

Expanded ERP process with mechanism for exceptional circumstances

Based on the above, a process flow illustrating the expanded ERP process is presented at Attachment 2.

Ongoing review and process improvement

It is recognized that the current process relies on treating each exceptional circumstance on a case-by-case basis. Given the current lack of experience in the suggested mechanism and the need for this to be timely, this is an appropriate starting point. WHO will conduct a review of the process after each instance and it is anticipated that with more experience it will be possible to develop more detailed procedures.

WHO will not identify individuals who contribute to the advisory group. However, in the interest of transparency, WHO will publish information about the technical expertise involved in the assessment of the additional information.
### Attachment 1: ERP criteria

<table>
<thead>
<tr>
<th>Quality:</th>
<th>No objection to procurement (Risk category 1, applicable only to products under assessment by WHO PQP or an SRA)</th>
<th>No objection to procurement (Risk category 2, applicable only to products under assessment by WHO-PQP or an SRA)</th>
<th>Objection to procurement, but can be procured if benefit outweighs risk (Risk category 3)</th>
<th>Objection to procurement (Risk category 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finished product manufacturing process and specifications</td>
<td>Acceptable specifications (in-house or compendial + additional in-house tests, and verified compendial /validated in-house methods). For sterile products, manufacturing processes are adequately validated</td>
<td>Acceptable specifications as per official monograph but missing certain additional in-house tests. For sterile products, manufacturing processes are adequately validated</td>
<td>Acceptable specification but analytical methods not sufficiently validated</td>
<td>Unacceptable specification or analytical validation for a critical test parameter. For sterile products, manufacturing process were not adequately validated</td>
</tr>
<tr>
<td>Stability and shelf life</td>
<td>The submitted data support the claimed shelf-life or an acceptable shelf life during which the product will comply with acceptable specifications</td>
<td>The submitted data support the claimed shelf-life or an acceptable shelf life during which the product will comply with compendial specifications</td>
<td>Shelf life is supported by insufficient stability data (e.g. submission of data on only one batch of a product with potential stability problems).</td>
<td>The available stability data does not allow any assignment of shelf life</td>
</tr>
<tr>
<td>Safety and efficacy: For generics:</td>
<td>Acceptable evidence of safety and efficacy OR demonstrated in vivo bioequivalence with an acceptable comparator product. OR (for oral products exempt from bioequivalence studies) acceptable multi-media dissolution data</td>
<td>Bioequivalence demonstrated or for biowaiver eligible oral products similarity in multi-media dissolution studies. The source of the comparator product is unknown or known to be outside of ICH OR comparator itself is a generic but prequalified by WHO or approved by SRA</td>
<td>Bioequivalence data not submitted, but for orally administered products, multi-media dissolution data show similarity (for non-oral products other in vitro data, as applicable, indicate similarity), AND/OR comparator is a generic product not prequalified or SRA-authorized</td>
<td>Efficacy and safety data not submitted, or unsatisfactory (e.g. several major deficiencies)</td>
</tr>
<tr>
<td>Source and quality of active pharmaceutical ingredients (API)</td>
<td>API has acceptable specifications and is manufactured at a GMP compliant facility as inspected by WHO, SRA or PIC/s member inspectorate</td>
<td>API has acceptable specifications with no major quality concern and is manufactured at a licensed site with no known GMP issues</td>
<td>API has acceptable specifications but there are GMP issues</td>
<td>API specification not acceptable for a critical test parameter</td>
</tr>
</tbody>
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1 Where the procurer has determined that the eligibility criteria for the expanded mechanism have been met, additional information will be sought and an advisory group formed, as described in the process flow in Attachment 2.
Attachment 2 – ERP process flow with mechanism to deal with exceptional circumstances

**Manufacturer actions**

- Application submitted to ERP

**Procurer actions**

- Procurer publishes EoI
- Proceed with procurement
- Medicine supplied to procurer

**ERP/WHO actions**

- ERP review of application information
- ERP risk category 1, 2 or 3?
  - No
  - IF: Risk of no treatment > risk of medicines that meet some but not all quality standards AND No alternative is available AND Stakeholder holds information relevant to risk assessment THEN: Convene advisory group to develop advice for ERP taking into account all relevant information and draft risk management plan
  - Yes
  - ERP risk category 3?
    - No
    - Medicine supplied to procurer in accordance with risk management plan
    - Implement appropriate response
    - Advice regarding eligibility criteria and additional information
    - Safety/quality risks identified?
      - Yes
        - WHO QMS advises on appropriate response
      - No
        - Medicine supplied to procurer
        - Proceed with risk-managed procurement
        - Is supply necessary?
          - Yes
            - Proceed with risk-managed procurement
          - No
            - Proceed with procurement