The Expert Review Panel (ERP)

The Expert Review Panel (ERP) is an independent advisory body of technical experts, coordinated by WHO.

ERP assesses the quality risks of pharmaceutical products that do not meet all stringent quality requirements, based on transparent criteria and provides advice for the purpose of aiding procurement decisions regarding time limited procurement. Products are classified in one of four risk categories:

- risk category 1 or 2: No objection to time-limited procurement
- risk category 3: Objection to procurement but may be considered when there are no alternatives, and provided the benefit outweighs the risk of procuring a product which is not fully quality assured.
- risk category 4: Objection to procurement.

Depending on the number of submissions, ERP may review products in pre-planned sessions, or ad-hoc, as requested by the procurer.

ERP members

ERP members are technical experts in the field of pharmaceutical quality (chemical, manufacturing and controls) and safety/efficacy, with extensive regulatory experience. They are currently employed as regulatory dossier reviewers. Additional expertise is sought as needed.

ERP clients

ERP clients are procurement agencies that procure and/or fund procurement, such as the Global Drug Facility, the Global Fund to Fight AIDS, Tuberculosis or Malaria (Global Fund), or UNITAID, that need the advice of an independent body to aid their procurement decisions.

ERP may also assist procurers in identifying deficiencies in dossiers and areas of needed improvement with respect to the quality of products that they are interested in procuring.

ERP clients receive the full assessment reports of the products for which they have commissioned an ERP review.

Basic principles

ERP is a service to procurement or funding agencies. ERP does not interact directly with applicants/manufacturers. This is in contrast to the way in which a regulatory function such as WHO prequalification or a stringent regulatory authority operates (SRA). Instead, communication with applicants is handled by the procurer, including receipt of dossiers, communication of the ERP review outcome, and receipt of any responses from the applicant.

ERP clients are expected to have a clearly defined quality assurance (QA) policy that indicates under which conditions ERP-reviewed products, in the absence of stringently approved products, are to be procured. (In other words, ERP can only ever be one element in the QA policy of a procurement agency.) The policy should state that ERP-reviewed products are to be procured only on a time-limited basis, during which time the products are expected to progress in a stringent regulatory pipeline, such as WHO prequalification, or stringent regulatory review, with concomitant improvements in quality.

A typical QA policy includes the following procurement options (ranked in order of priority):

1. products prequalified by WHO, or approved by an SRA
2. ERP-reviewed products[1] but only if no WHO-prequalified or SRA-approved products are available.

[1] risk category 1 or 2, or in certain cases risk category 3 – see above

Unlike the regulatory process of WHO prequalification or an SRA, ERP is not continuous or iterative. Rather ERP makes a statement as to the quality of a given product at a certain point in time, based on the data available at that time, for the purpose of identifying urgently needed products for procurement. In some cases, the applicant may be invited to address issues if these issues can be expected to be resolved within a short time and the applicant's response is likely to improve the risk category. The applicant is free to resubmit a (new) application following the issuance of a subsequent Invitation to Manufacturers to Submit an Expression of interest for Product Evaluation (EOI) by the procurement agency.

An ERP risk category 1 or 2 product is not equivalent to a prequalified or SRA-approved product, nor is ERP an alternative to prequalification or SRA approval. ERP is intended to identify products suitable to meet urgent supply need in the absence of WHO-prequalified or SRA-approved products. However, since an important objective is improvement in quality over time, and ultimately full quality assurance, it is expected that the product progresses along an SRA or WHO prequalification pipeline, during the (time-limited) procurement period. This is why the eligibility criteria for ERP review include acceptance of the product dossier for assessment by WHO prequalification or an SRA. The eligibility criteria also include evidence of compliance with Good Manufacturing Practices (GMP), as inspected by WHO's Prequalification Team: medicines (PQTm), an SRA or a PIC/s member inspectorate.

ERP may also review products that are not invited for WHO prequalification or expected to be submitted for approval by SRA. Such products include certain anti-TB products used specifically in the Indian TB programme, or some antimalarial products, such as quinine tablets, for which demand may be limited, and which are therefore not included in the relevant WHO prequalification EOI, but which may still be needed in certain regions at certain times.

Eligibility criteria

Criteria 1 products (medicines included in a WHO prequalification EOI):

a. the product dossier has been submitted to and accepted for assessment by PQTm or an SRA

b. the manufacturing site is GMP-compliant as inspected by PQTm, an SRA or PIC/s[2] member inspectorate.

Criteria 2 products (medicines not included in a WHO prequalification EOI):

c. the finished pharmaceutical product (FPP) manufacturing site is GMP-compliant as inspected by PQTm, an SRA or a PIC/s member inspectorate.

The fact that the product dossier of a criteria 2 product is not under assessment in a stringent regulatory pipeline is perceived as an added risk by ERP, as compared to the situation for a criteria 1 product. ERP will therefore not assign a risk category better than risk category 3 to a criteria 2 product.

Under some circumstances (currently only products in reproductive health, neglected tropical diseases, and certain products of interest to the UN Commission on Life-saving Commodities for Women and Children), ERP may perform a GMP risk assessment, and accept a commitment to submit a dossier to PQTm or SRA within a specified period and, rather than applying the standard eligibility criteria, accept a commitment to submit a dossier to WHO for prequalification or to an SRA.

ERP can review a few dossiers within days. But for a larger number of dossiers, ERP typically reports its findings within six weeks from the date it received the dossiers from the procurement agency.

[2] The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as **PIC/S**) are two international instruments between countries and pharmaceutical inspection authorities, which together provide an active and constructive co-operation in the field of GMP.

The dossier review process and risk assessment principles

ERP reviews are primarily performed on the basis of dossier information compiled by the manufacturer using the interagency product questionnaire, which is widely used among the UN and other international procurement agencies. In addition, ERP reviewers have access to the relevant product dossiers submitted for WHO prequalification.

The review of each ERP dossier involves two assessors, the second assessment is a quality assurance review. Before providing the review outcome to the procurer, all ERP reports are reviewed by a dedicated assessor to ensure consistency in assessment and consistency in the application of risk categorization criteria.

ERP reviews available information and identifies deficiencies in each product dossier. The impact of each deficiency on the quality, safety and efficacy of the product is assessed in the context of the intended use of the product, duration of use, as well as product specific attributes such as formulation, specification, stability, bioequivalence and release profile. The product is then allocated to one of four risk categories based on the extent and perceived impact of observed deficiencies, in accordance with the criteria given in the table below.

Extension reviews

ERP's opinion in terms of a favourable risk category of a given product (see footnote 1) is valid for 12 months. During the validity period, the product dossier submitted to an SRA or WHO prequalification is expected to progress towards approval by the SRA or prequalification by WHO. Extension of the favourable ERP risk category beyond 12 months for the product may only be considered based on the procurer's assessment of a continued need to procure the product while at the same time considering the number of available prequalified or SRA approved products at that time. If the procurer deems that there is a continued need to procure the product, then a two-step process is followed to consider extension of the ERP risk category of the product for another 12 months;

Step 1: ERP's review of the progress (or absence of it) made by the manufacturer in terms of the application submitted to PQTm or SRA. If the manufacturer has shown acceptable progress, he will be invited by the procurer to submit an updated ERP dossier. [3]

Step 2: ERP's review of the updated ERP dossier, as received via the procurer for a possible extension of the ERP risk category for another 12 months.

[3] For criteria 2 products (i.e., medicines not included in a WHO prequalification EOI), only step 2 is applicable.

Table 1 ***Overview of ERP assessment criteria***

	RISKCATEGORY 1 ****No objection to procurement (risk category 19)*** *Product described by all of the below.*	***RISK CATEGORY 2*** ****No objection to procurement (risk category 2)*** *Product described by any of the below*	***RISK CATEGORY 3*** ***Objection to procurement,*** *but can be procured if benefit outweighs risk* ***(risk category 3)*** *Product described by any of the below*	***RISK CATEGORY4*** ***Objection*** *to procurement* *Product described by any of the below*
Finished product manufacture and controls	Acceptable specifications (in-house or compendial + additional in-house tests, and verified compendial / validated in-house methods). For sterile products, manufacturing processes adequately validated	Acceptable specifications as per official monograph but missing certain additional in-house tests; for sterile products, manufacturing processes are adequately validated	Acceptable specification but analytical methods not sufficiently validated	Unacceptable specification or analytical validation for a critical test parameter; for sterile products, manufacturing process not adequately validated
Stability and shelf life	The submitted data support the claimed shelf life or an acceptable shelf life during which the product will comply with acceptable specifications	The submitted data support the claimed shelf-life or an acceptable shelf life during which the product will comply with compendial specifications	Shelf life is supported by insufficient stability data (e.g. submission of data on only one batch of a product with potential stability problems).	The available stability data does not allow any assignment of shelf life
Safety and efficacy: *For generics*: Evidence of therapeutic equivalence an acceptable comparator	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 multimedia dissolution data	Bioequivalence demonstrated or for biowaiver-eligible oral products similarity in multimedia dissolution studies; the source of the comparator product is unknown or known to be outside of ICH** **OR** comparator itself is a generic but WHO-prequalified or SRA-approved	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	Efficacy and safety data not submitted, or unsatisfactory (e.g. several major deficiencies)
Source and quality of active pharmaceutical ingredients (API)	API has acceptable specifications and is manufactured at a GMP-compliant facility as inspected by WHO, SRA or PIC/s member inspectorate	API has acceptable specifications with no major quality concern and is manufactured at a licensed site with no known GMP issues	API has acceptable specifications but GMP issues have been identified	API specification not acceptable for a critical test parameter such as impurities

**applicable only to products under assessment by PQTm or an SRA*

*** ICH: The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. See: ww.ich.org/*

Contact for ERP coordinator: Dr Matthias Stahl. E-mail: stahlm@who.int

Links

Current invitations to ERP review as well as lists of current risk category 1 or 2 products can be found on the websites of ERP clients. For information on products with current risk category 3, ERP clients (Global Drug Facility, Global Fund, UNFPA, UNICEF UNITAID and WHO's Department of Neglected Tropical Diseases) should be contacted directly.

Global Fund: information on ERP-reviewed products

UNFPA: information on ERP-reviewed products