Joint Unicef/WHO PQP 3rd meeting with manufacturers 24-26 Sept 2012

Expert Review Panel (ERP)

Dr M Stahl, ERP Coordinator, WHO/QSM
ERP (Expert Review Panel) - Outline

- Background/Fundamental principles
- Eligibility criteria
- ERP risk categories
- ERP experience so far
- Concluding remarks
Expert Review Panel (ERP)

- GF TOR for ERP approved by GF in March 2009; ERP established in April 2009 together with WHO.
- Objective: To review the potential risk/benefit for FPPs not yet WHO-prequalified or SRA-authorized, for the purpose of providing advise to help procurement decisions
- ERP risk categories developed by WHO/QSM.
- ERP is coordinated by the WHO/QSM
- ERP reviews are done by experienced regulatory professionals
ERP - Fundamental principles

- ERP is an advisory body only, ERP is not involved in procurement decisions.
- ERP positive opinion is not the same as prequalification, nor a substitute for PQP or SRA assessments. ERP products are potentially substandard products.
- GF recommendations based on ERP advice are valid for 12 months only - it is a temporary measure to enable supply - in the mean time the product should progress towards prequalification or SRA approval.
- Applicants submit filled out Pharmaceutical Product Questionnaire and supporting annexes as stipulated in GF invitations. This is not a full dossier.
- Within an ERP session the review is a one-off review (additional data is only requested if likely to improve the risk category, and only once).
- ERP communicates with GF, but not directly with the companies. This is for GF to do.
- ERP is separate from PQP but ERP reviewers may access information in dossiers submitted to PQP.
Criteria 1 (products included in WHO PQP EOI or eligible for SRA/Pepfar submission)
- A product dossier has been submitted to PQP or SRA/Pepfar and is accepted for assessment
- The FPP manufacturing site is compliant with Good Manufacturing Practices (GMP) as certified by WHO PQP, SRA or PIC/S inspectors.

Criteria 2 (products not included in WHO PQP EOI or eligible for SRA/Pepfar submission)
- The FPP manufacturing site is compliant with GMP as certified by WHO PQP, SRA or PIC/S inspectors.
ERP - possible outcomes of review

- "No objection" against procurement (Risk categories 1 or 2)
- "Objection" against procurement (Risk categories 3* or 4)
- Request for additional data

* Risk category 3 can be considered only if there is no other option and the risks of not treating the disease is higher than the risk of using medicines not meeting all quality standards.
The following major product attributes are used as the basis for risk categorization (assuming eligibility criteria are met):

a. FPP manufacturing process and FPP specification

b. Stability data

c. Evidence of therapeutic equivalence

d. API source and API quality
Criteria
Risk category 1

The product is described by all of the following:

- The FPP is tested with verified compendial tests/methods and validated in-house tests/methods or is tested with acceptable in-house specification and validated test methods.

- The submitted data support the claimed shelf life or at least an acceptable reduced shelf life can be assigned.

- Acceptable BE study (incl comparator) or multi-media dissolution data (for biowaiver-eligible products) have been submitted.

- The API is manufactured by a licensed site, and has acceptable specification. GMP certificate if available.
The product is described by one or more of the following:

- The FPP is tested with verified compendial tests/methods (without additional in-house tests such as related substances, loss on drying and ICH class III residual solvents)

- Stability data is submitted for a sufficient test period but test parameters (such as related substances and loss on drying) may not be complete. However the product is compendial and related substances and other tests are not controlled by the monograph.

- Therapeutic equivalence has been shown against a recommended comparator but source of the comparator is unknown or known to be outside of ICH, or the comparator itself is a generic product but prequalified by WHO or approved by SRA or PIC/s country.

- API is manufactured by licensed site (+GMP certificate, if available). The specification may not contain full set of tests and limits, but no major quality concern (e.g. residual solvents test for class III).
Criteria (cont'd)
Risk category 3

The product is described by one or more of the following:

- Acceptable in house specification but analytical methods are not sufficiently validated.
- BE study not submitted for a product (not eligible for biowaiver), but multi-media dissolution data show similarity (exception rifampicin containing products).
- BE shown but the comparator product is not acceptable (i.e. not included in PQP comparator list or is a generic which is neither prequalified nor SRA approved).
- In case of complicated products, only one batch stability data is submitted but a shelf life can still be considered.
- API is tested with acceptable specifications but there are GMP issues (w.r.t the API manufacturer).
Criteria (cont'd)
Risk category 4

The product is described by one or more of the following:

- The specification/analytical validation is not acceptable for critical test parameter.
- The available stability data does not allow assignment of shelf life.
- Therapeutic equivalence (BE or dissolution) not shown or data not acceptable/not submitted.
- The API specification is not acceptable for critical test parameter.
ERP review - process flow

- Invitation by GF
- Submission by manufacturers
- Pool of experts
- ERP coordinator: Organize a session
- GMP status (confirmation by PQP inspectors)
- GF: Eligibility screening
- ERP: Confirm eligibility
- ERP: Review submissions, Prepare reports incl risk categories
- ERP coordinator: Prepare final communication
- Report to GF
ERP experience so far

- Seven ERP sessions for GF;
  - ERP I - June 2009
  - ERP II - Oct 2009
  - ERP III - May 2010
  - ERP IV - Nov 2010 (+GDF)
  - ERP IV - Supplement - Dec 2010 (+GDF)
  - ERP V - March (HIV/MA) and June (TB) 2011 (+GDF + UNITAID)
  - ERP VI - November 2011 (+ GDF + UNITAID)
  - ERP VII - May 2012 (+GDF+UNITAID+UNICEF/WHO)
  - ERP VIII - Coming up (October-Nov 2012)

- Joint EOI GF-GDF in July 2010 (GDF aligned their QA policy with that of GF). ERP reviews for GDF started Feb 2009.


- ERP reviews for Neglected Tropical Diseases, NTD (WHO) (started April 2010)

- ERP reviews for Reproductive Health products (UNFPA) – October 2011, June 2012

- ERP reviews to advice on extension of the validity period (progress of dossiers?)

- ERP reviews of variations to prequalified and SRA approved products.
ERP experience

Number of eligible submissions reviewed by ERP (GF/GDF/UNITAID/Unicef/WHO)
Total 364 dossiers

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<tr>
<th>ERP</th>
<th>HIV</th>
<th>TB</th>
<th>Malaria</th>
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<td>ERP I</td>
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<td>ERP VI</td>
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<td>ERP VII</td>
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Criteria 1
Criteria 2

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Summary results for Criteria 1 products (ERP I-VII)

**TB products**
- Risk category 1: 18%
- Risk category 2: 18%
- Risk category 3: 38%
- Risk category 4: 26%
- Total: 96 submissions

**HIV products**
- Risk category 1: 39%
- Risk category 2: 29%
- Risk category 3: 0%
- Risk category 4: 32%
- Total: 59 submissions

**Malaria products**
- Risk category 1: 4%
- Risk category 2: 9%
- Risk category 3: 20%
- Risk category 4: 67%
- Total: 45 submissions
Summary results for Criteria 2 products (ERP III-VII)

TB Products
130 submissions

- Risk category 4: 38%
- Risk category 3: 62%

Malaria products
20 submissions

- Risk category 4: 70%
- Risk category 3: 30%
PQP/SRA progress of dossiers post ERP I and II (as of 18 Sept 2012 - after 2½-3 years) - Criteria 1 products

PQ-SRA progress of ERP "no objection" products

- HIV
- Malaria
- TB

PQ-SRA progress of ERP "objection" products

- HIV
- Malaria
- TB
PQP/SRA progress of dossiers post ERP III and IV (as of 18 Sept 2012-after 1½-2¼ years) - Criteria 1 products

PQP-SRA progress of ERP "no objection" products

- HIV
- Malaria
- TB

PQP-SRA progress of ERP "objection" products

- HIV
- Malaria
- TB

Legend:
- ERP "no objection"
- PQ-SRA approved

World Health Organization

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PQP/SRA progress of dossiers post ERP V and VI (as of 18 Sept 2012-after $0\frac{1}{2}-1\frac{1}{4}$ years) - Criteria 1 products

PQ-SRA progress of ERP "no objection" products

- HIV: 4
- Malaria: 6
- TB: 12

PQ-SRA progress of ERP "objection" products

- HIV: 1
- Malaria: 5
- TB: 25
Reproductive Health (RH) products

Difficult area;
- Few dossier submissions to PQP
- Limited progress in the PQP pipeline
- Few prequalifications
- Limited business incentive to improve quality?
- Many RH manufacturers outside of ICH region are currently non-GMP compliant (or no evidence of GMP as inspected by PQP/SRA)
- Many have limited experience of regulatory submissions to PQP/SRA

ERP was done for UNFPA to evaluate RH products using modified ERP eligibility criteria
Revised ERP eligibility criteria for RH products

GMP status

- Evidence of GMP compliance as inspected by but not limited to WHO PQP, SRA, PIC/S member inspectorate
  - As part of the submission applicants were also requested to submit any available inspection report even if negative and/or CAPAs

Dossier submission status

- Dossier has been submitted to PQP/SRA and accepted for assessment, or
- Commitment to submit dossier to PQP/SRA within three months from the date of publication of UNFPA EOI (13 April 2012) is provided
33 dossiers received by UNFPA by June 4, 2012
- 8 dossiers rejected on screening by UNFPA
- 20 dossiers received by WHO/QSM on June 11, 2012
- 5 additional dossiers were received by WHO/QSM on June 26, 2012

- A total of 25 dossiers received by ERP covering 11 of the 17 invited medicines (1 implant, 5 injectables, 19 tablets)
- Subject to confirmatory screening and GMP risk assessment by ERP
- 23 of 25 dossiers went into full review (one GMP risk level 4, one already SRA approved)
The following aspects were considered

- Site location and related NMRA status (SRA/PIC/S or not)
- Available FPP site GMP certification, Inspection reports and/or CAPAs
- Information on API GMP status
- Other possible discriminating factors (simple/complex site & process; company known to WHO PQP/SRA, recalls? complaints? etc)
## GMP risk assessment-risk categories

<table>
<thead>
<tr>
<th>Risk rating level</th>
<th>Input from current Inspection Findings</th>
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<tbody>
<tr>
<td>0</td>
<td>Product manufactured within a SRA territory</td>
</tr>
<tr>
<td>I</td>
<td>Site considered acceptable from the GMP standpoint with an assured level of supervision by SRA International or WHO inspection programme OR A Category II site where there is strong discriminating evidence factors indicating robust controls within the manufacturing organisation</td>
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<tr>
<td>II</td>
<td>Site considered acceptable from the GMP standpoint but with a lower assurance level of continuing compliance than category I OR A Category III site where there is strong discriminating evidence factors indicating robust controls within the manufacturing organisation</td>
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<tr>
<td>III</td>
<td>Site is outside an SRA/PIC/s territory and has not yet been subject to a SRA/WHO/PIC/s inspection OR A site within an SRA/PIC/s territory where there is currently no or minimal robust evidence of current compliance with GMP BUT with a positive agreed action plan awaiting confirmation by reinspections by an SRA/WHO</td>
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<tr>
<td>IV</td>
<td>Site is either inside or outside an SRA/PIC/s territory and has been found to be NON-COMPLIANT/Subject to on-going regulatory action e.g. Consent decree/warning letter/NOC by SRA/WHO/PIC/s Or where follow up inspection has shown inadequate progress to previous regulatory action</td>
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# Outcome of GMP risk assessment

- Products manufactured at the sites of GMP risk level of 0, 1, 2 and 3 were taken for dossier review.

- Note:
  - The best possible ERP risk category for a product falling in risk category 3 on dossier review is 3 (irrespective of the GMP risk level - 0, 1, 2 or 3).
  - Likewise, the best possible ERP risk category for a product manufactured at a GMP risk level 3 site is 3.

<table>
<thead>
<tr>
<th>GMP risk rating level</th>
<th>No of manufacturers</th>
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<tbody>
<tr>
<td>0</td>
<td>1</td>
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<tr>
<td>1</td>
<td>4</td>
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<td>2</td>
<td>3</td>
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<tr>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>1 (not considered eligible for dossier review )</td>
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ERP initial results

Outcome
23 products

- Add data not requested
- Add data requested

<table>
<thead>
<tr>
<th>Risk Cat</th>
<th>Count</th>
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<tbody>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>3</td>
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<td>3</td>
<td>1</td>
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<tr>
<td>4</td>
<td>5</td>
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Expert Review Panel (ERP)
After additional data

- So far 10 additional data submissions have been received and reviewed
  - 5 products improved from risk category 4 to 2
  - 1 product improved from risk category 4 to 3
  - 1 product remained in risk category 3
  - 3 are currently under review.

- 2 manufacturers indicated a need for additional time and the requests were accepted by ERP.
ERP – concluding remarks

- ERP provides advice to help procurement decisions but is independent of procurement
- ERP uses a uniform submission format, uniform and transparent criteria for eligibility and risk categorization of products
- ERP is fast and meets all agreed timelines. ERP's mode of working is transparent (SOP; full reports provided – full insight into how each review was done)
- ERP has high capacity – close to 600 product reviews (reports) so far (approx. 432 dossier submissions covering 256 different products)
- ERP capacity-builds manufacturers and helps them prepare for prequalification
- ERP stimulates progress of dossiers under assessment in PQP (Criteria 1 products)
- ERP has also provided feedback on the quality of Criteria 2 products
- ERP "no objection" means future prequalification/SRA approval is likely (predictive value)
- ERP reviews are currently done jointly for GF, GDF and UNITAID (+ UNICEF and WHO procurement in the most recent ERP). ERP reviews of RH products are ongoing with UNFPA.
- ERP encourages establishment and harmonization of QA policies across procurement agencies, eg. GF and GDF QA policies
Expert Review Panel

A rapid quality risk assessment mechanism for assessing needed pharmaceutical products that have not completed a stringent assessment

http://apps.who.int/prequal/info_press/pq_news_27April2012_ERP.htm