Reducing prequalification costs and maximizing opportunities

- identifying and understanding requirements and opportunities whilst avoiding some of the potential pitfalls!

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Shared objectives

Both product developers and manufacturers have some common objectives

• To bring effective safe quality products to market
• To commercialize their investment within the shortest possible and predictable timelines

And in the above process:
• Maximize the return on their investment
• Build and reinforce their reputations and sustainability

Whilst regulators need evidence to make judgements on the balances of quality, safety and efficacy

"God we trust, the rest have to bring evidence"
• And not just evidence, but good evidence meeting established and transparent regulatory standards
• But in a manner that does not unintentionally reduce or slow market access
Session objectives:

- Assist manufacturers in understanding the potential costs of seeking prequalification (PQ).
- Raise awareness of manufacturers of how those costs can be reduced.
- Encourage good submissions - right first time
- Discourage applications from manufacturers who have not thought through the cost implications of seeking for prequalification and who applications are less likely to be of adequate quality.
- Further raise profile of collaborative registration as means of optimizing investment in prequalification.
- Provide some examples and look to how both companies and the PQT product streams could facilitate efficient PQ submissions
Key messages for manufacturers:

- Investing in PQ = investing in a process and not simply a product. Product is simply an end point.
- Prequalification is a major investment: time; money; morale.
- The decision to seek PQ should not be taken lightly!
- Support is available to help manufacturers think through that decision.
- Support is available to help manufacturers optimize any investment they make in seeking prequalification.
- What’s already in the PQ pipeline?

For medicines: https://extranet.who.int/prequal/content/dossier-status
For Dx: http://www.who.int/diagnostics_laboratory/pq_status/en/
Potential benefits for a manufacturer participating in WHO medicines prequalification

Increased sales/market access including access to a large scale and growing market with Donor spend
- Access to donor-sponsored tenders
- Access to stringently-regulated markets, e.g. in Europe, USA
- Increased potential to compete successfully for contract manufacture for local markets
- Potential for collaboration to support local production
- Enable suppliers to expand business presence sub-regionally and regionally

Improved image/brand
- Quality-assured product status
- Improved external and internal image
- Improved positioning in home country

Reduced manufacturing costs
- Improved capacity utilisation
- Lower variable/commercial operating costs

Increased capacity/skills
- Development of human resources for ensuring and managing quality manufacture
- Capacity to ensure quality manufacture across range of products
- New or increased capacity to meet stringent regulatory requirements
Some questions manufacturers need to ask themselves

• Why are we going for PQ? What benefits do we foresee?
• How do we balance those benefits against the costs and risks?
• Risks associated with sustainability (E.g. in improving quality, production staff will have acquired greater skills and experience and leave for another position.)
• What value will PQ bring to the product and / or to the company?
• What product should we select for submission for evaluation for PQ?
• Are we primarily interested in a learning experience (so then should submit our company’s more complex products) or in finding a bigger market for an existing product?
• How long will it really take? (Knowing this will help with calculation of cost / opportunity cost.)
Some issues manufacturers need to consider

- Have substantial capital investments been made that require debt servicing or must a return be realized for equity providers?
- Will operating costs (in comparison with lower-quality peers), be high? E.g. to cover utilities needed to maintain the manufacturing environment.
- Working capital is a significant consideration given e.g. lead time, payment terms and the cost of trade financing.
- The “playing field” may not be level: international manufacturers may have to pay value added tax and import duties.
- Most inputs imported therefore ex factory prices include significant freight costs.
- Expanding product portfolio for international tenders prohibitively expensive (given most products require bioequivalence studies and given current availability of facilities).
- Competitive production requires optimizing capacity utilization.
UCL has readjusted its product selection processes after a failure in manufacturing Lamivudine + Zidovudine.

**Case study**

- UCL received WHO PQ for Lamivudine + Zidovudine
- Dedicated 3 years to submission
- Invested USD 3m in developing manufacturing processes
- Sold: ~30,000 packs in 2014
- Profit: ~$40,000 loss

**Revised strategy**

- Align product offering with international buyer demand
- Target low cost, high-volume products
- Evaluate competition in new product segments before entering markets
- Ensure high demand and UCL price competitive
Some questions manufacturers need to ask themselves

Technical issues include:

- Access to affordable investment capital for manufacturers
- Increased amount of skilled and semi-skilled human resources across requisite disciplines
- Access to know-how and expertise for upgrading
- Increased regulatory oversight of the marketplace
- Defragmented markets (see African Medicines Regulatory Harmonisation) and quantification of market opportunities
- “Level playing field” with international imports
- Time-limited incentives
- Baseline GMP assessment which provides benchmark for development and basis for corrective and preventive actions

Issues from a coordination/implementation perspective include:

- Multiple partners need to work together
- National leadership is required
- Collaboration across organs of government is a necessity (e.g. Joint Steering Committee)
- Regulator needs to be credible authority to enforce requirements

To achieve objectives must recognize:

- Manufacturing occurs within a system where multiple parties influence the context.
- Upgrading of site and quality systems requires investment and access to expertise
- Coordination of multiple parties requires moving beyond conceptual notions

Quality assurance requires GMP AND stringent approval of products
Direct costs that need to be controlled

- Direct product-specific development costs
- Indirect development costs
- Specific product dossier costs
- Systematic improvements facilitated by and prompted by a submission for stringent assessment
- Ongoing maintenance costs
- Ongoing quality improvements
  - Variation costs
  - Maintaining sustainable GMP standards
- Market specific authorizations either post-PQ or in parallel with PQ
Supply and demand side initiatives, and a business environment could see increase in number of leading companies and Q/A products

**Supply Side**
- **Portfolio expansion:**
  - Regulatory pathway defined for PQ of products produced under license (inc. SRA-approved products?) & expedited country approval
  - Companies attract partners to conduct rigorous tech transfer
- **Technical assistance:**
  - Identify interested companies (inc. for additional forms)
  - Gap closure for GMP certification
  - Operational excellence to improve efficiency

**Business Environment:**
- Affordable investment capital
- Level playing field with imports
- Time-limited incentives (inc. tax shields)

**Demand Side**
- **Market Signalling**
  - Forward-looking statements from international procurement funds, recognizing….
- **Details of sourcing mechanisms e.g.**
  - Considers total cost not ex-factory
  - Longer-term contracts
  - Agreed delivery schedules
  - Good payment terms (e.g. 60 days)

Increased number of internationally-certified manufacturers producing expanded range of Q/A priority products that are commercially viable
Commercial viability within the global public health sector – is about more than purely commercial factors

Company-driven:
* A significant proportion of suppliers combine a commercial perspective with an approach based on corporate social responsibility

Government-driven:
* The economic environment needs to be stable, open and supportive. Incentives to invest and level of taxation can be an issue

Market-driven:
* Commercially the market must provide a viable return on investment even if margins are below market norms
Indirect costs due to delays that need to be controlled

• Lost opportunity costs due to failures to understand
  • Failure to understand the requirements
  • Failure to understand how the requirements are expected to be implemented/interpreted
  • Failure to perform gap analysis
• Dossiers that are incomplete (validation checks)
• Studies or modules that are deficient in content
• Studies that use inappropriate standards
• Failures to obtain early GMP clearances such that GMP inspection and CAPA become critical path items, resulting in prequalification decision delays
• Incomplete validations at a commercial scale at the time of inspection
## Cost of formulation development

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation development</td>
<td>If formulation not already being used, has to be developed (to mimic the existing product).</td>
</tr>
<tr>
<td>Lot production (no API)</td>
<td>Production of 3 lots of material at a lot size representative of full-scale production. These materials are used in all PQ studies. (Cost of all materials, packaging, labour and overhead estimates.)</td>
</tr>
<tr>
<td>Cost of API</td>
<td>About 75% of the cost of production.</td>
</tr>
<tr>
<td>Stability studies</td>
<td>Ongoing real time and accelerated stability studies. Need to calculate person year(s): possibly one person for two years.</td>
</tr>
<tr>
<td>Head count</td>
<td>3 regulatory and administrative personnel for 6 months.</td>
</tr>
<tr>
<td>Local regulatory</td>
<td>Cost of getting local regulatory approval for countries to which company wants to export product.</td>
</tr>
<tr>
<td>Agent fees and samples</td>
<td>Cost of managing the registration process within a country, including the cost of samples.</td>
</tr>
<tr>
<td>Dossier preparation for prequalification</td>
<td>Preparing bioequivalence documentation for submission for prequalification.</td>
</tr>
<tr>
<td>Ongoing communication</td>
<td>Equivalent of one person over two years.</td>
</tr>
<tr>
<td>Prequalification fees</td>
<td>Application and maintenance.</td>
</tr>
</tbody>
</table>
Investments will vary depending on experience of company

- Manufacturers experienced in dealing with global regulatory agencies will have fewer investments in both capital and formulation development
- Manufacturers with existing dossiers will have fewer investments to make
- Formulation development may be necessary and depends upon the complexity of the medicine
- Companies without a WHO GMP-standard facility, will require renovations to meet GMP standards
- Companies new to the pharmaceutical industry will have to make major investments in capital infrastructure
Controlling your timelines to reduce opportunity costs
Getting earlier to PQ (e.g. your product is first or second product to be prequalified) may mean you capture more of the market

- Historical example of an ARV fixed dose revenue through Global Fund (lamivudine + nevirapine + stavudine – FDC)
- The first three companies to be approved by PQP captured 93% share of the total revenue for years 2007–2010

<table>
<thead>
<tr>
<th>Company</th>
<th>Year PQP’d</th>
<th>Share 2007-2010 revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2005</td>
<td>53%</td>
</tr>
<tr>
<td>2</td>
<td>2003</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>2005</td>
<td>5%</td>
</tr>
<tr>
<td>4</td>
<td>2007</td>
<td>1%</td>
</tr>
<tr>
<td>5</td>
<td>2009</td>
<td>2%</td>
</tr>
<tr>
<td>6</td>
<td>2008</td>
<td>2%</td>
</tr>
</tbody>
</table>

Market share and Global Fund revenue

<table>
<thead>
<tr>
<th>Year</th>
<th>Share 2007-2010 revenue</th>
</tr>
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<tbody>
<tr>
<td>2007</td>
<td>$5,469,939</td>
</tr>
<tr>
<td>2008</td>
<td>$13,526,468</td>
</tr>
<tr>
<td>2009</td>
<td>$26,528,034</td>
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<tr>
<td>2010</td>
<td>$24,419,009</td>
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<th>2009</th>
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<tr>
<td>1</td>
<td>$5,469,939</td>
<td>$13,526,468</td>
<td>$26,528,034</td>
<td>$24,419,009</td>
</tr>
<tr>
<td>2</td>
<td>$26,565</td>
<td>$7,860,441</td>
<td>$13,327,621</td>
<td>$25,208,137</td>
</tr>
<tr>
<td>3</td>
<td>$3,298</td>
<td>$721,049</td>
<td>$3,777,804</td>
<td>$2,408,739</td>
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<tr>
<td>4</td>
<td>$1,429,562</td>
<td>$144,251</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$1,680,880</td>
<td>$159,426</td>
<td>$958,202</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>$988,116</td>
<td>$1,144,943</td>
<td>$239,018</td>
<td></td>
</tr>
</tbody>
</table>
Changing regulatory paradigm

• Regulators’ behaviour and attitudes have changed over the time
• Regulatory systems in many recipient markets are becoming more robust
  
  *Today there is much more dialogue, including regulatory advice: from concepts of product development, to final submission of data sets for regulatory assessment*

• **NOT GETTING IT RIGHT FIRST TIME** brings avoidable additional cost and can be very expensive for both manufacturer and the regulatory system –
• Setting clear requirements and their interpretation and implementation is imperative
• Appropriate regulatory advice can shorten assessment time and get needed products to patients faster
• Adaptive licensing concepts for some medicines to meet major unmet health needs
NOT GETTING IT RIGHT FIRST TIME brings avoidable additional cost and can be very expensive for both manufacturer and the regulatory system.

<table>
<thead>
<tr>
<th>Year</th>
<th>(FPPs prequalified, including generics)</th>
<th>Number of WHO days to PQ</th>
<th>Number of mfr. days to PQ</th>
<th>Number of stop-clock* days to PQ</th>
<th>Total number of days to PQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>All products</td>
<td>Median time (Full Assessment)</td>
<td>223</td>
<td>624</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median time (Abridged Assessment)</td>
<td>37</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Products accepted in or after 2014</td>
<td>Median time (Full Assessment)</td>
<td>239</td>
<td>366</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median time (Abridged Assessment)</td>
<td>32</td>
<td>73</td>
<td>30</td>
</tr>
<tr>
<td>2015</td>
<td>37 generic FPPs prequalified</td>
<td>Number of WHO days to PQ</td>
<td>Number of mfr. days to PQ</td>
<td>Number of stop-clock* days to PQ</td>
<td>Total number of days to PQ</td>
</tr>
<tr>
<td></td>
<td>All products</td>
<td>Median time (Full Assessment)</td>
<td>206</td>
<td>506</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median time (Abridged Assessment)</td>
<td>78</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Products accepted in or after 2014</td>
<td>Median time (Full Assessment)</td>
<td>164</td>
<td>255</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median time (Abridged Assessment)</td>
<td>69</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>
Times for manufacturers to deal with dossier deficiencies have been progressively getting longer. Why?

WHO and manufacturer time to PQ
- FPP full assessment -

Number of calendar days

2013 2014 2015 2016

Number of WHO days to PQ
Number of mfr. days to PQ
The Prequalification Team publishes implementation guidance and provides regulatory advice

Several layers and mechanisms for advice are provided:
- Contributes to the development of WHO norms and standards
- Regulatory advice for product development - clinical, BE, API, formulation, regulatory pathway etc. e.g. “Points to consider”
- Regulatory advice for defined topics/issues
  - Passive – following additional guidance issued on website specific to concrete products/product groups/topics
  - Active – applications for regulatory advice Pre-submission consultations, etc.
- Inspectional guidelines and Q&As
- Methods: revised website, physical meetings, TC and VCs, written communications – continuous
- Annual meetings including one-to-one meetings
Types of documented technical assistance

- Norms and standards
  - *e.g.* GMP guidance and annexes
- Points to consider
- General Questions and Answers
- Training materials *e.g.*
  - Mock dossiers
  - Mock protocols
  - Mock site master files
  - GMP training modules
- What is missing over the various PQ product streams, either individually or collectively
Opportunities from collaborative systems

- Use of APIs that have been assessed through API PQ or collaborative procedures such as CEP
- Common market specific core dossiers for specific products
- Higher complexity in collaborative assessment vs. outcome of a single decision taken into account by NRAs according to defined and predictable schedules
- Lower complexity of regulatory approvals of ongoing process and quality improvements
  - Variation timelines are easier to manage
Regulatory advice: medicines

Quality (APIs) – starting material

- In the area of API assessment the area significantly benefitting from seeking regulatory advice is the selection of the API starting material.
- The API starting material defines the point at which GMP must be applied in manufacture. The selected starting material directly impacts:
  - the viability of the proposed manufacturing chain
  - the information required to be submitted in the drug substance module
- Redefinition therefore requires significant manufacturing chain changes (potentially new suppliers of intermediates) and documentation reformatting.
- This significantly lengthens the time taken to obtain approval.
Regulatory advice: medicines

Quality (APIs) – intended manufacturing chain

- The API manufacturer should consider carefully where they intend to undertake commercial preparation.

- Scale and location of manufacture can be changed post-approval, but the site responsible for the pilot scale manufacture specified in the API information must be available for inspection if the API information is to be accepted.
Regulatory advice: medicines

Bioequivalence (BE) examples

There are many examples of the value of seeking advice regarding comparator products for BE studies:

1. **Possibility of a bio waiver (one example)**
   PQ will advise a company whether a BCS-based bio waiver may be possible for a product if sufficient information is provided by the company for consideration. This can avoid the conduct of unnecessary BE studies.

2. **Comparator products** are sometimes purchased in the local market of the manufacturer. Consultation will prevent the use of an unacceptable comparator. Acceptable comparators for PQ are listed on the website.

- List indicates Rifampicin 300 mg capsules from Sandoz purchased in the Netherlands is an accepted comparator. Company purchased Rifampicin (Rifampin) 300 mg capsules from Sandoz from the USA and used them in a BE study.
Regulatory advice: medicines

BE study design examples

If requested, PQ will provide comments on near-to-final drafts of BE study protocols.

1. The sample size (number of subjects) estimate for a planned BE study for an anti-malarial product was calculated incorrectly because it failed to consider the larger than normal expected difference in Cmax between the products, as demonstrated in a pilot study. The error was caught during a PQT review of the study protocol. If the error had not been corrected, the study would have been underpowered and therefore, may not have met the BE acceptance criteria.

2. In a recent protocol for a study with albendazole, the company did not plan to measure the parent compound (albendazole) in the study because it did not believe it could be measured. PQT was able to inform the company that albendazole can be measured and is the analyte upon which the BE decision will be made.
Regulatory advice: medicines

Clinical examples
1. Any product which is "first in class" in a generic application. Implantable contraceptives, for example, are not easily studied via BE route, and may require clinical trials, not merely literature support. PQT advice could have avoided early missteps in the levonorgestrel implant PQ application, which initially came in with dubious literature support only. This could have been excluded a priori and earlier discussions had on the eventual clinical trial.

2. Products in therapeutic areas such as HIV and hepatitis B/C, where rapid changes in clinical guidelines are occurring. Products "on the way out" (e.g. zalcitabine, d4T) and "on the way in" (e.g. integrase inhibitors) often have issues which need close attention during the workup of data for the application.

3. Products where use is considerably different in the developing versus developed world (e.g. malaria products used for treatment versus prophylaxis, or efavirenz used as first-line versus "alternative").
Regulatory advice: medicines

Quality (FPPs): 1

1. Applicants have made assumptions based on outside regulatory requirements, they said it was a requirement in their country: e.g. applicant assumed the biobatch must include API from each supplier, therefore performed an unnecessary additional BE study because of an additional API supplier (only required in exceptional circumstances, e.g. insoluble API with different polymorphic form).

2. Applicants initiate stability studies without consulting PQT or our guidelines, and have the wrong storage conditions or batch numbers/sizes. The incorrect data can only be supportive, which is of limited use, and they have to initiate the proper studies, which sets their studies and establishment of shelf-life back by the length of time before they switched to proper parameters.

3. Applicants have not consulted PQT or its guidelines on primary batch requirements, and may have unnecessarily manufactured production batches according to old guidelines, rather than the required pilot batches. This may mean they could have submitted the dossier much earlier with adequate data.
Regulatory advice: medicines

Quality (FPPs): 2

4. Applicants have not consulted PQT or PQT / WHO guidelines regarding excipients, and have formulated with a novel excipient (excipient not used in a similar level/same route in a product approved by an SRA or WHO) and have to reformulate and/or face significant delays as PQT does not have the capacity to review the necessary safety studies.

5. For artesunate suppositories, PQT guidelines and prior consultation has helped define a developmental and regulatory pathway for generic manufacturers supported by MMV, to make available generic versions of the product developed by WHO TDR. Applications expected soon.

6. For atypical products (e.g. implant), failure to consult guidelines and failure to make appropriate use of feedback, necessitated new development and validation activities subsequent to submission. It took the applicant more than 2 years to deal with some of the issues and some are yet to be addressed. A development and submission plan agreed with PQT would have been beneficial in terms of prequalifying this product sooner.
Regulatory advice: vaccines

- Pre-submission discussions with PQT of the first vaccines produced by China — Japanese encephalitis vaccine, triggered a working group composed by several stakeholders.

- We started discussion even before Chinese regulator was declared functional (pre-condition for vaccines PQ) and identified the needs for additional clinical studies and needs for additional info.

- When the manufacturer submitted the dossier, clinical studies were ongoing (we agreed to start the review with the clinical data available pending submission of the additional studies), we advanced with the evaluation and when the clinical data was available we reviewed it and we PQed the product.
Regulatory advice: diagnostics

It is extremely useful and helpful that manufacturers applying for PQ for the first time consult PQT before submitting a product dossier: can save much time in dossier screening, review and post-review phase.

Many IVD manufacturers have never compiled a product dossier of the type required for PQ. We have seen several examples of companies (especially those not used to compiling dossiers for stringent review) failing to submit the information in the necessary format, with the prescribed content and level of detail.

**Positive example:** Cases of very experienced manufacturers discuss with dossier compilation with PQT before submitting the dossier. Manufacturers realise that particular dossier sections must be documented in such a way to reflect reality and needs in resource-limited settings. For example, the risk assessment, flex studies and stability studies are critical components of a PQ dossier which must be robust.
Regulatory advice: diagnostics

Manufacturers developing new products and planning to submit to PQ should consult PQ in the R&D phase.

Many manufacturers, especially smaller companies with little or no experience in the regulatory world, lack understanding of available reference documents, such as standards and guidelines.

In our dossiers we have seen a huge number of badly-designed studies (number of specimens used, specimen characterization, elected comparator device, etc.) Manufacturer must identify standards and guidance documents to assist them in this piece of work and discuss with PQT at early stage of development to ensure that documentation development is appropriate.

**Positive example:** A company developing an HIV RDT approached PQT before design lock-down to seek information on PQ approach and requirements. Also requested information on leveraging stringent regulatory approvals for PQ.

**Challenging example:** Most companies developing IVDs for PQ submission still do not approach PQT early enough to be guided with regard to requirements and process. Not doing so can cause considerable delay.