Programme update - Prequalification of Medicines

UN Prequalification of Medicines, Diagnostics and Vaccines
6th Consultative Stakeholder Meeting
and Meeting with Manufacturers

Centre International de Conférences (CICG), 17 Rue de Varembé
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Content

• Background
• What medicines prequalification programme does
• Updates from various areas
• Challenges and opportunities
• Conclusions
• The **Millennium Development Goals** (MDGs):

• Eight international **development goals** that 192 United Nations member states and at least 23 international organizations have agreed to achieve by the year 2015
Medicines work in WHO HQ

• **Department of Essential Medicines and Pharmaceutical Policies (EMP)**
  – Two teams
    • Medicines Access and Rational Use (MAR)
    • Quality Assurance and Safety: Medicines (QSM)
  – Two units (teams) attached to Director’s office
    • Medicines Information and Evidence for Policy (MIE)
    • Medicine Programme Coordination (MPC)

• **Collaboration with other clusters/departments/units in HQ**
  – Vaccines and biologicals (IVB/QSS) – Vaccines prequalification programme
  – Essential Health Technology (EHT) – Diagnostics prequalification prequalification
  – Disease oriented programs (HIV/AIDS, malaria, TB, neglected diseases)

• **Collaboration with WHO regional and country offices**
QSM Technical Programmes

• International Nonproprietary Names (INNs)
• Quality Assurance
• Safety/Pharmacovigilance
• Regulatory support
• Prequalification Programme for Medicines
• Quality Assurance and Safety of Blood Products and Related Biologicals
• Anti SFFC (anticounterfeiting)
Active collaboration with other international, regional and national organizations

- UN family, international organizations and donors:
  - UNICEF, UNFPA, UNIDO etc.
  - BMGF, Global Fund, UNITAID
  - Manufacturers associations
  - MSF
- Regional
  - EMA/EU
  - Council of Europe/EDQM
  - NEPAD
- Professional and scientific
  - FIP, CIOMS, IUPHAR, ISPE
- National
  - National Medicines Regulatory Authorities (from all WHO Member States)
Prequalification of Medicines Programme

- The UN Prequalification Programme managed by WHO is ensuring that medicines procured with international funds are of assessed and inspected quality, efficacy and safety.

- The Prequalification Programme is an action plan for expanding access to priority essential medicines in the following four areas:
  - HIV/AIDS
  - Tuberculosis
  - Malaria
  - Reproductive Health
  - Flu
  - Selected individual products for other diseases (Zinc sulphate)

- A UN Prequalification Program of Quality Control Laboratories exists to facilitate the quality control of prequalified products.
Extensive collaboration with regulators

• Not duplicating work done by stringent regulatory authorities
  – SRA approval of new and generic products – abridged procedure
  – US FDA tentative approvals – based on confidentiality agreement including in the PQ products list
  – European Medicines Agency (EMA) – Art 58 … and beyond
  – Collaboration with EDQM, in particular in the area of APIs (confidentiality agreement to be signed)

• Active participation and involvement of
  – SRA experts
  – Regulatory authority experts from less resourced settings
PREQUALIFICATION PROGRAMME
A United Nations Programme managed by WHO

Vision
Good quality medicines for everyone.

Mission
In close cooperation with national regulatory agencies and partner organizations, the Prequalification Programme aims to make quality priority medicines available for the benefit of those in need.

This is achieved through its evaluation and inspection activities, and by building national capacity for sustainable manufacturing and monitoring of quality medicines.

Strategy

- Apply unified standards of acceptable quality, safety and efficacy.
- Comprehensively evaluate the quality, safety and efficacy of medicinal products, based on information submitted by the manufacturers, and inspection of the corresponding manufacturing and clinical sites.
- Prequalify quality control laboratories of pharmaceuticals.
- Build the capacity of staff from national regulatory authorities, quality control laboratories, and from manufacturers or other private companies, to ensure medicines quality.

Key output
The list of prequalified medicinal products used for HIV/AIDS, malaria, tuberculosis and for reproductive health produced by the Programme is used principally by United Nations agencies including UNAIDS and UNICEF to guide their procurement decisions. But, the list has become a vital tool for any agency or
The Expert Review Panel activities

• The Expert Review Panel (ERP) was created at the request of the Global Fund and is hosted and managed by WHO

• Not a substitute to prequalification or SRA approval

• Its purpose is to review the potential risks/benefits associated with the use of eligible for ERP finished pharmaceutical product that is not (yet) WHO pre-qualified or authorized for use by a stringent drug regulatory authority

• ERP uses regulatory experts who assess the information provided by applicants

• ERP like process has been applied also upon request from other parties in need for "quality risk assessment" guidance
Important points

• ERP review is not a substitute for PQ or SRA assessments

• An ERP session is a one-off review (additional data only requested once if this might improve the risk category).

• Interested applicants submit filled Pharmaceutical Product Questionnaire and supporting annexes as stipulated in GF's invitation. This is not a full dossier.

• GF recommendations are valid for 12 months only, in the mean time the product should progress towards prequalification or SRA approval

• ERP is not part of the Prequalification Programme but may access information in dossiers submitted to the Programme
# Number of ERP dossiers reviewed in 2010

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>TB</th>
<th>Malaria</th>
<th>NTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Fund</td>
<td>13 New, 7 Add data, 3 Extension</td>
<td>84 New, 2 Add data, 7 Extension</td>
<td>16 New, 6 Add data, 2 Extension</td>
<td>-</td>
</tr>
<tr>
<td>GDF</td>
<td>-</td>
<td>8 New, 6 Add data</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>UNITAID</td>
<td>7 New, 2 Add data</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NTD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6 New, 3 Add data</td>
</tr>
<tr>
<td>Total</td>
<td>134 New, 26 Add data, 12 Extension</td>
<td>84 New, 2 Add data, 7 Extension</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Transparency – dossiers and their status information on the web

Status of product dossiers under assessment in the WHO Prequalification Programme

This sheet provides information on the status of submitted - not yet prequalified - dossiers; only includes dossiers that have been screened and accepted into assessment; includes several products with the same INN, strength, unit and dosage form. In such cases, the manufacturers differ; does not include inspection data at present. Such data are essential to be able to determine how close a product is to prequalification. For example, in cases where both dossier parts have been accepted, there may still be outstanding issues with respect to the manufacturing sites involved. Inspection data will be added as soon as possible; does not include prequalified products. Once a product is prequalified, it is included in a separate list of prequalified products (see links on the front page of the Prequalification Programme website).

<table>
<thead>
<tr>
<th>Product (INNs)</th>
<th>Strength</th>
<th>Unit</th>
<th>Dosage Form</th>
<th>Quality part</th>
<th>Efficacy/Safety part</th>
</tr>
</thead>
<tbody>
<tr>
<td>abacavir</td>
<td>20 mg/ml</td>
<td>solution, oral</td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>abacavir</td>
<td>20 mg/ml</td>
<td>solution, oral</td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>abacavir</td>
<td>300 mg</td>
<td>tablet</td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>abacavir + lamivudine + zidovudine</td>
<td>300/150/300 mg</td>
<td>tablet</td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>135/50 mg</td>
<td>tablet</td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>135/50 mg</td>
<td>tablet</td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>153 and 50 mg</td>
<td>tablet</td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>153/50 mg</td>
<td>tablet</td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>amodiaquine + artesunate</td>
<td>270/100 mg</td>
<td>tablet</td>
<td></td>
<td>×</td>
<td>×</td>
</tr>
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</table>
Overview of WHOPARs of prequalified medicinal products

The below WHOPARs are listed by WHO reference number and therapeutic area. The International Nonproprietary Name (INN), dosage formulation and dosage strength, as well as supplier are included.

- **HIV/AIDS products**
  - HA043: Lamivudine - 150mg Film-coated tablets - Cipla Ltd - INDIA
  - HA060: Lamivudine/Zidovudine - 150mg/300mg Film-coated tablets - Cipla Ltd - INDIA
  - HA097: Lopinavir (+ Ritonavir) - 133.3mg (+33.3mg) Soft capsules - Abbott Laboratories Ltd - USA
  - HA098: Lopinavir (+ Ritonavir) - 80mg (+20mg) Oral solution - Abbott Laboratories Ltd - USA
  - HA110: Lamivudine/Zidovudine - 150mg/300mg Film-coated tablets - GlaxoSmithKline - UK
  - HA111: Abacavir/Lamivudine/Zidovudine - 300mg/150mg/300mg Film-coated tablets - GlaxoSmithKline - UK
  - HA152: Lamivudine/Zidovudine - 150mg/300mg Tablets - Hetero Drugs Limited - INDIA
  - HA153: Lamivudine - 150mg Film-coated tablets - Hetero Drugs Limited - INDIA
  - HA210: Nevirapine/Lamivudine/Stavudine - 200mg/150mg/40mg Bi-layer uncoated tablets - Cipla Ltd - INDIA
  - HA249: Stavudine - 40mg Capsules - Aspen Pharmacare - SOUTH AFRICA
Transparency - WHOPIRs and NOCs

• These are published in response to the WHA Resolution WHA57.14 of 22 May 2004, which requested WHO, among other actions:
  – "3. (4) to ensure that the prequalification review process and the results of inspection and assessment reports of the listed products, aside from proprietary and confidential information, are made publicly available;"

• A WHO Public Inspection Report (WHOPIR) provides a summary of the inspection (where found to be GMP complaint)

• A Notice of Concern (NOC) is a letter reflecting areas of concern where the non-compliances require urgent attention and corrective action by the manufacturer or contract research organization.
Prequalified medicines April 2011

Countries that have submitted and had products prequalified: Belgium (1); China (3); France (26); Germany (6); Hungary (1); Iceland (2); India (141); Netherlands (5); Pakistan (2); South Africa (9); Spain (7); Switzerland (15); United Kingdom (26); USA (2); Zimbabwe (2).

Countries of manufacture of prequalified products: Australia; Belgium; Canada; China; Finland; France; Germany; Hungary; India; Latvia; Morocco; Netherlands; Pakistan; South Africa; Spain; Switzerland; Uganda; United Kingdom, USA; Zimbabwe.

Prequalified Products
Total = 256

- 191 = 76% HIV
- 8 = 2.5% Tuberculosis
- 17 = 7% Malaria
- 29 = 12% Reproductive Health
- 7 = 2.5% Influenza
Communication

• ... is the key and needs constant improvement

Prequalification: Global Meeting

WHO Medicines Prequalification in a New Decade

Copenhagen, Denmark 26 - 27 July 2010

Programme [pdf]

The meeting will be an opportunity to hear about common dossier and GMP deficiencies, and new or revised WHO guidelines, from expert assessors, inspectors and other manufacturers. There will also be an opportunity to discuss your experiences with the WHO prequalification programme and help identifying possible opportunities for improvement.

The focus of the meeting will be on multisource (generic) medicines as innovative medicines are mostly prequalified relying on the scientific assessments carried out by stringent authorities. An interactive style of meeting is proposed, with presentations, panel discussions and workshops.
WHO Prequalification Programmes

WHO Prequalification of Medicines Programme: survey of service quality provided to manufacturers

Established in 2001, the Prequalification of Medicines Programme (PQP) is a service provided by the World Health Organization (WHO) to facilitate access to quality medicines for treating priority diseases. In order to be prequalified, medicines must meet WHO-specified standards for quality, safety and efficacy. PQP is supported by various United Nations agencies (e.g., UNAIDS, UNICEF, UNFPA) and the World Bank.

WHO prequalification of medicines is a multi-step process whereby a manufacturer submits extensive information that is then evaluated by a WHO assessment team with respect to product quality, safety and efficacy, site(s) of manufacture and any clinical studies that may have been carried out during development. Products that successfully pass PQP evaluation are listed on the WHO List of Prequalified Medicinal Products (see: http://www.who.int/prequal). This list provides UN agencies with a single source of reference for quality-assured priority medicines and is also used by a variety of entities, both country-specific and international, that purchase medicines in bulk quantities.

The Prequalification of Medicines Programme has conducted a comprehensive survey among pharmaceutical manufacturers to assess its level of service. PQP assessment and inspection activities reflect those carried out by national regulatory...
Technical assistance – increasing need

Technical assistances organized by PQP

- 2006: 2 (REG), 3 (GPCL), 1 (GCP), 2 (GMP)
- 2007: 10 (REG), 1 (GPCL), 3 (GCP), 2 (GMP)
- 2008: 8 (REG), 1 (GPCL), 2 (GCP), 6 (GMP)
- 2009: 7 (REG), 0 (GPCL), 2 (GCP), 7 (GMP)
- 2010: 14 (REG), 4 (GPCL), 1 (GCP), 8 (GMP)
Technical assistances organized by PQP in individual countries
Technical assistances organized by PQP in WHO regions (2006-2010)
Training and capacity building – important part of the programme since its start

Trainings organized or supported by PQP

- PQP supported
- PQP organized
Trainings – reaching more than 1200 participants globally from 76 countries in 2010

Participants in trainings organized or co-organized/supported by PQP

World Health Organization

QUALITY MEDICINES FOR EVERYONE
Training activities covering all WHO six regions

Trainings organized by PQP in WHO regions (2006-2010)
Trainings organized by PQP focusing on specific therapeutic categories of medicines (2006-2010)
Quality monitoring projects (1)

- Quality survey of antimalarials Africa
  - Cooperation with NDRAs in Cameroon, Ethiopia, Ghana, Kenya, Nigeria, Tanzania
  - ACTs and sulfadoxine-pyrimethamine
  - 935 samples collected and screened by Minilab, 306 tested in laboratory
Quality monitoring projects (2)

• Quality survey of anti-TB medicines in NIS
  – Cooperation with NDRAs in Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, Uzbekistan
  – Rifampicin, Isoniazid, Rifampicin/Isoniazid, Ofloxacin, Kanamycin
  – 291 samples collected and tested

• None of 38 samples of WHO-prequalified products failed
Prequalified QCLs:
- South Africa, RIIP+CENQAM (2005)
- Algeria, LNCPP (2005)
- South Africa, Adcock Ingram (2007)
- Morocco, LNCM (2008)
- Kenya, NQCL (2008)
- India, Vimta Labs (2008)
- France, CHMP (2008)
- Vietnam, NIDQC (2008)
- Kenya, MEDS (2009)
- Singapore, HSA (2009)
- Singapore, TÜV (2009)
- Canada, K.A.B.S. Laboratories (2010)
- Ukraine, CLQCM (2010)
- Ukraine, LPA (2010)
- Peru, CNCC (2010)
- Uruguay, CCCM (2010)
- Bolivia, CONCAMYT (2010)
- SGS, India (2011)
- TFDA, Tanzania (2011)
Prequalified / interested laboratories

March 2011

National QCLs
Other QCLs

39
11

QCLs interested
QCLs prequalified

AFRO AMRO EMRO EURO SEARO WPRO
Key accomplishments in 2010

• Prequalified 36 products (total 256): first artesunate powder for injection prequalified; tenofovir disoproxil fumarate/lamivudine and the first generic emtricitabine

• Initiated prequalification of active pharmaceutical ingredients (APIs)

• Six quality control laboratories (QCLs) prequalified

• Provided training for over 200 regulatory participants, 200 QCL participants and over 800 manufacturing participants; significant capacity building in China with manufacturers of anti-TB medicines

• Pilot joint assessment of 2 products with EAC countries

• Completed an in-depth analysis of the quality survey results of antimalarials circulating in 6 African countries

• Completed a survey of manufacturers to assess PQP’s level of service
Problems

• **Known problems continue to exist:**
  – Immature submissions – takes time to get to the maturity needed
  – Relative lack of motivation from applicants
  – Relative lack of new innovator products
  – GMP non compliance (both for finished dosage form and API)
  – Quality part of the dossier – specifications, stability data etc incomplete
  – API quality
  – Safety and efficacy – poor clinical and safety data, poor quality information, poor information for users
Challenges

• Meeting the needs for **highly qualified staff** under the conditions prescribed by the environment
• **Availability of national experts** (qualified assessors and inspectors) in forthcoming years
• Increasing demand for **capacity building and TA** – shift from general to more specific and technical
• Increasing **demand for prequalified products** for medicines of high public health value (new product groups, individual products, NTD products)
• Increasing demand of **ad hoc services** regarding quality risk assessment (ERP)
• Constant need to **improve communication and collaboration** (resource demands for this purpose remain underestimated)
• **Reform of IT services** – more complexity, more investment
Summary remarks (1)

• The main objective of the prequalification programme remains to make a list of good quality, safe and effective medicines available for public health needs in resource limited settings

• The program has had huge impact on:
  – **Access to quality medicines** – especially for HIV/AIDS
  – it has been a **powerful engine for pulling QUALITY of medicines agenda** ahead internationally

• It has had major impact on **increasing national regulatory capacity**, including QC laboratories and inspectorates, on country level

• It has **promoted regulatory collaboration and harmonization** and should continue to do so even more

• **Technical assistance** to manufacturers of selected priority essential medicines is available but needs review and resources to improve efficiency.
Summary remarks (2)

• Close cooperation with international procurement and financial institutions
  – quality as prerequisite for procurement decision
  – financial instruments to support quality production

• Prequalification program needs supportive and flexible environment to serve better Global Public Health

• Main aim of PQ – to increase choice and access to quality products without compromising requirements for quality, safety and efficacy should remain unchanged
A BIG THANK YOU!

• We wish gratefully to acknowledge the assistance and help provided by our many partners/collaborators in and outside WHO, donors (such as BMGF and UNITAID) and many other organizations (such as Global Fund and UNICEF) and individuals

• Especially we are grateful to the staff from National Medicines Regulatory Authorities who have provided us experts and expertise since the start:

  Australia, Austria, Botswana, Brazil, Canada, China, Estonia, Ethiopia, France, Germany, Ghana, Hungary, Italy, Kenya, Netherlands, Poland, Saudi Arabia, Singapore, South Africa, Spain, Sweden, Switzerland, Tanzania, Uganda, Ukraine, United Kingdom, and Zimbabwe …