Prequalification of essential medicines (update)

Consultation with pharmaceutical manufacturers on essential medicines procurement
October 30th – November 1st, 2006,
Copenhagen, Denmark

Anton Norder
Technical Officer, World Health Organization, Geneva
Quality Assurance and Safety: Medicines (QSM)
Medicines Policy and Standards (PSM)
nordera@who.int
Prequalification of essential medicines

- The UN prequalification program is an action plan for expanding access for the hardest hit by
  - HIV/AIDS
  - Tuberculosis
  - Malaria

- by ensuring quality, efficacy and safety of medicines procured using international funds (e.g. GFTAM)
Why the prequalification is needed

- **Problems**
  - Millions of people living with HIV/AIDS, tuberculosis and malaria, have no or limited access to treatment
  - Substandard and counterfeit products in different countries
  - Weak or absent QA systems of medicines supply chain
  - Lot of money invested in procurement
    - no harmonized quality assurance system available for procurement organizations/initiatives yet;
    - products with very different quality sourced

- **Risks**
  - Sourcing of poor quality products or even counterfeit medicines
    - risk to patients, toxic reactions, treatment failure, resistance
    - bad quality (generic) products undermine public confidence
Prequalification programme:

- **Objective**
  - To ensure Access to Antimalarial, Antituberculosis and HIV/AIDS Drugs and HIV/AIDS Diagnostics of Acceptable Quality
Prequalification basic principles

- **Voluntary** for participating manufacturers
- **Legitimate** - General procedure and standards approved through WHO Expert Committee system involving all WHO Member States and WHO Governing bodies
- **Widely discussed**
  - FIP Congress, Nice 2002
  - Supported by International Conference of Drug Regulatory Authorities (ICDRA) in 2002 and 2004, representing more than 100 national drug regulatory authorities; discussed also in 12th ICDRA 2006
- **Transparent** (all information available on the web site [http://mednet3.who.int/prequal/](http://mednet3.who.int/prequal/))
- **Open** to both innovators and multisource/generic manufacturers
- **No cost** for applicants as per today (in future fees considered)
Expected outcome of prequalification

- Public lists of products and manufacturing units
  - Meeting international norms and standards on quality, safety, and efficacy

- Capacity building and harmonization
  - National Drug Regulatory Authorities (DRAs), manufacturers, WHO treatment programs, NGOs, procurement organizations

- Ongoing quality monitoring
  - Ongoing monitoring of prequalified products
  - Prequalification of quality control laboratories (pilot project, focus on AFRO at present with 3 QC labs prequalified – see web site for more information)

- Facilitate access to treatment
  - Through fair procurement mechanisms (e.g. tender, competition based on the same quality standards)
  - WHO commitment to developing better access to quality medicines
How prequalification is organized?

- **Role of WHO**: Managing and organizing the project on behalf of the United Nations.
  - provides technical and scientific support and guarantee that international norms and standards are applied all through the process including assessment, inspection (GMP, GCP, GLP) and quality control

- **Partners**:
  - UNICEF, UN Population Fund (UNFPA), UNAIDS and with the support of the World Bank
  - Anti-malarial and anti-TB products: Roll Back Malaria and Stop TB (Global Drug Facility); HIV/AIDS Department

- **Actors**: Mainly qualified assessors and inspectors from National DRAs (also from National Quality Control Laboratories) of ICH and associated countries, and inspectorates belonging to PIC/S
Assessment procedure

- **Assessment of products dossiers** i.e. quality specifications, pharmaceutical development, bioequivalence etc.
  - teams of professionals from national drug regulatory authorities (DRA): *Brazil, China, Canada, Denmark, Estonia, Finland, France, Germany, Hungary, Indonesia, Malaysia, Philippines, Spain, South-Africa, Sweden, Switzerland, Tanzania, Uganda, UK, Zimbabwe ...*

- **Copenhagen assessment week**
  - 8 to 16 assessors together during one week at least every two months at UNICEF in Copenhagen
  - Every dossier is assessed by at least two assessors.
  - An assessment report is issued; signed by two assessors
  - Letter summarizing the findings and asking for clarification and additional data if necessary; signed by two assessors
  - Letter is sent first by e-mail to the applicant followed by surface mail
Assessment procedure- Product dossiers

- **Innovator products**
  - Abridged procedure if approved by stringent authorities like EMEA and US FDA
  - Assessment report from DRAs, WHO Certificate of Pharmaceutical Product (CPP), batch certificate, update on changes
  - Trusting scientific expertise of well-established DRAs

- **Multisource products**
  - Full dossier with all data and information requested
  - **Quality**: information on starting materials and finished product including API details, specifications, stability data, formulation, manufacturing method, packaging, labelling etc
  - **Efficacy and safety**: Bio-equivalence study or clinical study report
    - US FDA tentative approvals for ARVs – recognition scientific assessment based on information exchange (Confidentiality agreement between US FDA and WHO); the same approach will soon apply for EU Art58 and Canadian JCPA procedure

- **Commercial sample**
  - Requested, but not always analysed before prequalification.
Prequalification: generics or not?

- FDA requirements for generic drugs ([www.fda.gov/cder/ogd](http://www.fda.gov/cder/ogd))
  - **Generic drugs must:**
    1. contain the same active ingredients as the innovator drug
    2. be identical in strength, dosage form, and route of administration
    3. have the same use indications
    4. meet the same batch requirements for identity, strength, purity and quality
    5. be manufactured under the same strict standards of GMP required for innovator products.
    6. be bio-equivalent

- **Prequalification requirements for generics** – fully line with major regulatory agencies

- **What if not generics** – full data set to prove the safety (including preclinical toxicology) and efficacy has to be presented

- **Not all non-innovator products in prequalification pipeline can be defined as generics** – no innovator may be available
Inspection procedure

- **Inspections**
  - Manufacturing site (final product, packaging)
  - Active pharmaceutical ingredient (API)
  - Research laboratory or Contract Research Organization (CRO)
  - Teamwork of inspectors
    - WHO representative (qualified GMP inspector)
    - Inspector from well-established inspectorate (Pharmaceutical Inspection Co-operation Scheme countries – PIC/S)
    - National inspector(s) invited to be part of the team but have NO decision making power (different GMP standards, potential conflict of interest)

- **Quality control analysis** - upon need, but not always necessarily before prequalification and supply, increasingly as part of proactive follow-up
Capacity building (Training activities)

- In 2005 three one week comprehensive training courses on quality of TB drugs and ARVs (Malaysia, China, Ukraine)
- Three GMP training courses (South-Africa, China), GMP training course in Tanzania (with PQ participation)
- Training of QC lab officials
- Specific to antimalarial medicines (ACTs) training courses for regulators and industries (in 2004 - Thailand, in January 2006 – China, in August 2006 - Tanzania)
- Introduction to the prequalification course in Vietnam (January 2006)
- All training course materials are posted on the web site to assist manufacturers to prepare quality dossiers and readiness for inspections
Current status

- Started with HIV/AIDS products in 2001 – malaria and TB products joined later

- Prequalified products (Sept 2006) "Active" dossiers in pipeline (2006)
  - 152 HIV related medicines 200 (April -06)
  - 8 anti-tuberculosis medicines 65
  - 5 anti-malarial medicines 40
  - 134 305

- Ongoing assessments and follow-up
  - Products
  - Manufacturing sites (both for APIs and finished dosage forms)
  - CROs
Measures taken to get more products prequalified

**General**
- Very limited resources
- PQ programme started with only ONE professional, today it has four and by the end of 2006 it will have at least six to eight (three will be secondments from Governments)
- Business plan created and funding proposals created

**Specific**
- Internal SOPs and work procedures to facilitate process created
- Specific for antimalarials "Note for Applicants" prepared
- More direct discussions with manufacturers started
- Additional work that could help manufacturers under way
- Specific training workshops for manufacturers producing antimalarials
Prequalification of national quality control laboratories in priority regions

Why?
- Capacity building to ensure continuous monitoring of quality

How?
- Auditing and assisting to get up to the standards
- Linked to already existing activities, such as external quality assessment scheme (focuses on methods whereas PQ focuses on internal quality systems), International Pharmacopoeia work (monographs and international chemical reference substances) etc.
Are there alternative regulatory pathways for products of public health needs?

EU legal basis

- Article 58 Regulation (EC) 726/2004
- WHO as "gate keeper"
- Committee for Human Medicinal Products (CHMP)
- Scientific opinion in cooperation with WHO
- Part of the EU response
  - To the need to protect public health
  - To give assistance to non-EU countries
  - Rapid access to important medicines
Scope

- Vaccines to be used in the WHO Expanded Programme on Immunization
- Vaccines for WHO public health priority diseases or for emergency response
- Medicines for WHO target diseases such as HIV/AIDS, malaria, tuberculosis, lymphatic filariasis, trachoma, leishmaniasis, schistosomiasis, African trypanosomiasis, onchocerciasis, dengue fever, Chagas disease, leprosy.
Regulatory Framework

- Only medicinal products for human use
- Intended exclusively for markets outside the Community
- Has to be confirmed with WHO
- Scientific opinion
- No marketing authorisation (MA) will be granted
- No data protection to be taken into account
Are there alternative regulatory pathways for products of public health needs (2)?

- US FDA tentative approvals linked to PEPFAR
- Canadian Access to medicines scheme
  - WHO cooperation with the above mentioned
News regarding prequalification programme

- Programme is winning more support

- Expectations to the programme are increasing, includes paediatric medicines

- Need for more
  - Capacity building targeting both regulators and manufacturers
  - NEW things planned
    - Technical assistance to manufacturers – need for minimizing potential conflicts of interest, setting criteria of eligibility
    - Planned involvement of inspectors from developing countries
    - Potential MOUs with selected national regulatory authorities
    - …
Summary and conclusion

Good news

- Relatively large number of products and suppliers comply with the standards (mostly ARVs so far)
- Many potential suppliers appreciating feedback and willing to improve
- Unique technical knowledge obtained about products, especially about generic antiretrovirals and antimalarials
- Capacity building component a lot appreciated

Bad news

- Only limited number of products have met the required standards (especially malaria and TB products)
- Takes time to get into compliance
  - Data to be generated, tests to be carried out …
  - GMP upgrade needed
- Quality has its price
Summary and conclusion cont...

Quality can not be assessed, tested or inspected into the product, BUT

It has to be

built into it!

More technical help to manufacturers in developing countries is needed
Welcome to the web site of the Prequalification project managed by the World Health Organization (WHO)

General information

Key facts on Prequalification

Steps on how to be prequalified

Follow the quick links below for general information on the prequalification of products and manufacturers, focusing on HIV/AIDS, Tuberculosis and Malaria.