Update on UN prequalification of medicines

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Is quality of medicines a problem?

Substandard drugs is a big problem - antibiotics, antimalarials, antituberculosis antiretrovirals drugs included

- Incorrect ingredient: 16%
- Incorrect amount: 17%
- Other errors: 7%
- No active ingredient: 60%

Percentage breakdown of data on 325 cases of substandard drugs - reported from around the world to WHO database
Prequalification of essential medicines

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

- for ensuring quality, efficacy and safety of medicines all the way through the medicines supply chain.
Why the prequalification is needed

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

- **Risks**
  - Sourcing of poor quality products or even counterfeit medicines → risk to patients, treatment failure, resistance
Challenges of prequalification

- **Demand** for affordable antiretrovirals, anti-malaria drugs and anti-tuberculosis drugs is increasing
- Increasing number of generic manufacturers offering products
- **Challenges** for UN family and procurement agencies/organizations to ensure supply of quality products
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 ICDRA in 2002 and 2004, representing more than 100 national drug regulatory authorities
- **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 during pilot phase
Expected outcome of prequalification

- List of products and manufacturers
  - Meeting international norms and standards on quality, safety, and efficacy (Q, S & E)

- Harmonization
  - Co-operation, training, capacity building – NDRAs, WHO treatment programs, NGOs, procurement organizations

- Facilitate access to treatment
  - Through fair procurement mechanisms (e.g. tender, competition)
  - Ongoing monitoring of Quality, Safety & Efficacy of essential medicines
  - WHO commitment to developing better access to quality medicines
Prequalification: misunderstandings and critics

- Too high standards increasing prices
  - … Too high and unnecessary standards for developing countries
  - … Too bureaucratic and slow, not proactive and not able to provide products…

- Too low standards
  - … "This leaves the impression with readers that the ARVs approved by WHO are in fact generic products that are interchangeable with their innovator cousins. From available documents, however, we conclude that they are copy products with unknown quality, safety and efficacy profiles".
Objectives

- Propose a list of prequalified products linked and manufacturers of which the quality, efficacy and safety have been assessed, inspected and controlled to meet international norms and standards.
- Gives assurance that international norms and standards are applied at all the steps of the prequalification and at the process itself.
- Make possible and speed up access to good quality of medicines. Fast track process for listing can take as little as two months from the date of application.
Objectives cont...

- **Follow-up** and regular monitoring of the quality of manufacturers and products
- **Ensure** re-qualification and update of the list of prequalified products and manufacturers as new products and manufacturers meet the standards
- **Ensure** the appropriate control of variations and changes
- **Develop** the local capacity for quality production
  - National regulatory authorities (DRA) are involved in dossier assessment and inspections
  - Producers receive invaluable specific technical feedback
- **Help** the national DRA to build up capacity in assessment, inspection and control meeting international norms and standards
How prequalification is organized

- **Role of WHO**: Managing and organizing the project on behalf of the United Nations.
  - provide 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 assessors and inspectors of National DRAs as well as National Quality Control Laboratories of PIC/S and ICH member countries
Steps of prequalification

1. **Expression of interest (EOI)** from a prospective supplier interested in a voluntary participation in the program.

2. **Explicative notes and guidelines** are published on the WEB in order to explain how to bring together a product dossier meeting the requirements for prequalification.


4. **Screening** of the dossier, "Quality" part, "Clinical" part and samples.

   ➔ Listed for the possible inspection

5. **Assessment of the dossier** and writing of the assessment report and assessment letter.

6. Outcome of the evaluation **communicated to supplier**
Steps of prequalification cont...

7. **Inspection of the site(s)** of manufacturing and follow-up inspection when necessary ➔ **GMP compliant list of manufacturers**

8. **Inspection** of the Research Laboratory or Contract Research Laboratory (CRO) where the bioequivalence study has been performed ➔ **GCP compliant list of CROs**

9. **Conclusion and listing** of the product in the prequalification list

10. **Publication** of the Public Assessment and Inspection Reports

11. **Assessment of the variation** when submitted, market survey, de-listing if necessary

12. **Re-qualification** after 3 years
Assessment procedure

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

- **Copenhagen assessment week**
  - 8 to 12 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
  - Assessment report from DRAs
  - WHO Certificate of Pharmaceutical Product (CPP)
  - Batch certificate
  - Update on changes.

- Multisource products (generics)
  - Full dossier with data and information
  - Quality: information on starting materials and finished product including API details, specifications, stability data, formulation, manufacturing method, packaging, labelling etc
  - Efficacy: Bio-equivalence study or clinical study report
  - US FDA tentative approvals – recognition based on information exchange (Confidentiality agreement)

- Commercial sample
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 drugs 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
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 Convention Scheme countries)
    - National inspector(s): *Canada, India, China, France, Italy, Switzerland, South-Africa*…

- **Quality control analysis** - upon need but not always necessarily before prequalification and supply, increasingly as part of follow-up
Inspection procedure cont...

- Inspection of the manufacture of
  - the **finished pharmaceutical products (FPP)** or
  - the **active pharmaceutical ingredients (API)**.

- **Good Manufacturing Practice (GMP)** conformity of production and Quality Control Laboratory according to WHO, (ICH or EU guidelines).

- **Areas covered**: Conformity of the manufacturing to the assessed dossier: batch review, stability studies, specifications, analytical methods, validations…
Inspection procedure cont...

- Inspection of CROs

- Inspections looking at the conformity of bio-equivalence (BE) studies with
  - Good Clinical Practice (GCP) and
  - Good Laboratory Practice (GLP) and
  - Good Quality Control Laboratory Practice (GCCLP)

- Study specific and/or site specific

- **Areas covered**: verification of ethical aspects, analytical data, verification of source documents and associated raw data, methods, controls, calculations, all relevant validations etc. according to GCP, GLP and GCCLP requirements.
Prequalification of quality control laboratories

- Quality Control Laboratories in sub Saharan Africa as priority
- WHO norms and standards for QC laboratories
- Prequalification process
  - Expression of Interest (EOI)
  - Laboratory Information File (LIF), evaluation
  - Inventory Audit – help/evaluate
  - Inspection with the team of inspectors
  - Prequalified laboratories list public in WHO web site (2 listed)
  - Reassessment system
Training activities

- In 2005 two one week comprehensive training courses on quality of TB drugs and ARVs (Malaysia, China)
- Two more courses in pipeline (Ukraine, China)
- Three GMP training courses (South-Africa, China)
- Upcoming GMP training course in Tanzania (with PQ participation)
- Training of QC lab officials
Quality Assurance (QA) of WHO prequalification process

- Internal Quality Assurance system
  - Quality Assurance and Safety: Medicines (QSM)
  - Standard Operating Procedures (SOPs)
  - Manuals and guidelines
  - General Procedure for Prequalification
  - Norms and standards (product dossiers, manufacturers etc)
Current status - September 2005

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

- Prequalified products (Sept 2005)
  - 98 HIV related medicines
  - 8 anti-tuberculosis medicines
  - 2 anti-malarial medicines
  - Total: 108

- Dossiers arrived (July 2005)
  - 289 (Feb-05) to 316 (Aug -05)
  - 153 to 156
  - 46 to 48
  - Total: 488 to 520

- Ongoing assessments and follow-up
  - Products
  - Manufacturing sites
  - CROs
Current status – Manufacturers of finished products

- In the prequalification list: **13 sites** of generics

  - Asia: 9 sites
  - Europe: 3 sites
  - Africa: 1 site

- Observations during inspections mainly: mix-ups, validation, qualification, HVAC, cross-contamination, contamination, documentation, QC procedures …
Ongoing monitoring and requalification

- Samples taken after supply – QC and checks
- Routine inspections and additional inspections
- Changes and variations controlled
  - Products and manufacturers
- Requalification (re-assessment) every 3 years
- World Health Assembly resolution: WHA57.14 of May 2004
  - Public reports requested
  - WHOPIRs and WHOPARs now on the web
  - Increasing interest in WHO Public Inspection Reports (WHOPIR)
Recent news and new challenges

- 2005 changes in GFTAM procurement policy – challenges for prequalification
- Confidentiality Agreement with the US FDA
- Recognition of US FDA tentative approval process for ARVs based on the scientific assessment done by FDA
- Additional fields of cooperation with European Directorate of the Quality Medicines (responsible for European Pharmacopoeia)
- Jointly funded post established with UNICEF to help managing the assessment weeks in Copenhagen from Sept 2005
- Constant upgrading guidelines and guidance documents increasing workload
- Resources for 2006/2007
Summary and conclusion

- **Good news**
  - Relatively large number of products and suppliers comply with the standards
  - Many potential suppliers appreciating feedback and willing to improve
  - Unique technical knowledge obtained about products, especially about generic antiretrovirals and antimalarials

- **Bad news**
  - Only limited number of products have met the required standards
  - Takes time to get into compliance
    - Data to be generated, tests to be carried out …
    - GMP upgrade needed
  - Bad quality generics may undermine the public confidence in generics
  - 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)

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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.