Antiretroviral quality – WHO actions
Prequalification of drugs for priority diseases

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HIV/AIDS Crisis.
Demand for affordable antiretrovirals is increasing. Numerous generic manufacturers offering products. Challenges for UN family and procurement agencies/organizations

- Which way to go to get the best possible protection of public health with the resources available?
Pre-qualification

What is the problem?

- Sub-standard drugs purchased
  - weak or absent quality assurance systems

- Lot of money invested in procurement
  - no harmonized quality assurance system available for procurement organizations/initiatives

- Duplication of work
  - lack of harmonized standards (GMP inspections)

- Risk: Sourcing sub-standard drugs, waste of money and, health risks to patients
Joint project with other UN organizations

Prequalification of HIV/AIDS Drugs - UN joint activity

- Partners*
  - UNAIDS
  - UNICEF
  - UNFPA
  - WHO
- With the support of World Bank
  * All organizations are also members of the International Pharmaceutical Co-ordination Group (IPC)

- WHO role
  - Technical assistance based on WHO norms and standards, plus ICH and other standards, where applicable
**Procurement, Quality and Sourcing Project**

The prequalification part of the project has two major activities: countries are providing expertise

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

- **II. Manufacturing site inspections: teamwork of inspectors:** WHO representative (qualified GMP inspector), inspector from well-established inspectorate (Pharmaceutical Inspection Convention Scheme countries) and national inspector(s): Canada, France, Italy, Switzerland, The Netherlands ...

**Quality control analysis** - upon need but not always necessarily before prequalification and supply, increasingly as part of follow-up
Procurement, Quality and Sourcing Project

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** in many fora
  - 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://www.who.int/medicines/](http://www.who.int/medicines/))
- **Open** to both innovators and multisource/generic manufacturers
- **No cost** for applicants during pilot phase
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".
Prequalification: generics or not?

- FDA requirements for generic drugs (www.fda.gov/cder/ogd)

Thus, a generic drug 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. be bio-equivalent
5. meet the same batch requirements for identity, strength, purity, and quality
6. be manufactured under the same strict standards of GMP required for innovator products.
General procedure: Prequalification

What will be required for generic drugs (1) ?

1. Details of the product
2. Regulatory situation in other countries
3. Active pharmaceutical ingredient(s) (API)
   3.1 Properties of the active pharmaceutical ingredient(s)
   3.2 Sites of manufacture of API(s)
   3.3 Route(s) of synthesis
   3.4 Specifications
       - API described in a pharmacopoeia
       - API not described in a pharmacopoeia
   3.5 Stability testing
       http://www.ifpma.org/ich5q.html#stability
General procedure: Prequalification

- What will be required (2)?
  - 4. Finished product
  - 4.1. Formulation
  - 4.2. Sites of manufacture
  - 4.4. Manufacturing procedure
  - 4.5. Specifications for excipients
  - 4.6. Specifications for the finished product
  - 4.7. Container/closure system(s) and other packaging
  - 4.8. Stability testing
General procedure: Prequalification

What will be required (3)?

- 4.9 Container labelling
- 4.10 Product information
- 4.11 Patient information and package inserts
- 4.12 Justification for any differences to the product in the country or countries issuing the submitted WHO-type certificate(s)
- 4.13 **Interchangeability** (bioequivalence studies)
- 4.14 Summary of pharmacology, toxicology and efficacy of the product
**General procedure: Prequalification**

**Steps of the Procedure**

1. Invitation for EOI
   - Wide publication
   - Open, transparent
   - Specify products required

2. Guidelines for product dossier compilation and requirements available
   - Multi-source products
   - Innovator products
General procedure: Prequalification

3. Receiving of dossiers
4. Screening of dossiers
   - Screen for completeness
   - Inform supplier
   - Listed for a possible site inspection

5. Dossier evaluation
   - Team of experts (quality, pharmaceutical development, bioequivalence etc)
   - From national regulatory authorities
   - Standard: Including, but not limited to WHO Manual and guidelines
     "Marketing Authorization of Pharmaceutical Products with special Reference to Multisource (Generic) Products: a Manual for a Drug Regulatory Authority, WHO/DMP/RGS/98.5"
   - Outcome of the evaluation communicated to supplier
6. Site inspection
   - WHO GMP
   - Inspection team:
     - Appointed inspector
     - Experience, qualification, preferably from DRA
     - Local, national inspectorate
     - WHO representative

7. Report and outcome
   - Reports on dossier evaluation and site inspection
   - Communicated to supplier/manufacturer
   - Compliance? Additional information to be submitted?
Pilot project

Access to HIV/AIDS Drugs and Diagnostics of Acceptable Quality

- Difficulties and problems
- Assessment – from ABC to XYZ
  - API source, impurities, lack of stability data ... lack or defective bioequivalence data
- Manufacturing site inspections
  - Manufacturers not ready
  - Upgrading of facilities to comply with WHO GMP
  - DRAs issued CPP – yet non-compliance
  - Inspections reveal non-compliance, e.g. antibiotics (penicillin), hormones and other products manufactured in the same site
  - No validation
  - Time needed to respond to report
  - “double standards” – local vs. international market
Pilot project

Access to HIV/AIDS Drugs and Diagnostics of Acceptable Quality

- Expanded
  - Tuberculosis products: First line as well as second line treatment
  - 119 Product dossiers
  - Several inspections in various countries
  - List of products and manufacturers not yet published – SERIOUS QUALITY PROBLEMS

- Malaria
  - 27 Product dossiers, mainly artemesinin and combination products
  - List of product(s) published in August 2003
  - HOW TO ASSESS?
    - Some neither originators nor generics
Pilot project

Expansion to cover other important areas?

- Prequalification of QC laboratories
  - Standards and procedure ready
  - Two laboratories assessed, one approved

- Prequalification of procurement agencies
  - Standards and procedure ready
  - Model Quality Assurance System created, under finalization
Procurement, Quality and Sourcing Project

Prequalification project

Current status:

- **Good news**
  - Relatively large number of ARV products and suppliers indicated
  - Many potential suppliers appreciating feedback and willing to improve
  - Unique knowledge obtained about generic ARVs and other products, including TB products
  - “Quality” generic products do exist

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