Session 6:
WHO Prequalification Programme

Key Process Steps

WHO: Medicines

UNFPA: Condoms and IUDs

World Health Organization

UNFPA

PATH
A catalyst for global health

Session adapted from the WHO training workshop on prequalification and the WHO technical briefing seminar on prequalification

Kyiv, October 2005, and
Geneva, September 2003, respectively

Basic Principles and Benefits of the Prequalification Programme

- Voluntary (currently)
- Legitimate
- Widely discussed
- Transparent
- Efficient: Open to both innovator drugs and multi/source generic manufacturers
- Supports manufacturers in capacity development efforts

Principle Actors in Prequalification

- Medicines

  Assessors and Inspectors of National Drug Regulatory Agencies of PIC/S and ICH member countries
  (see handout for PIC/S and ICH definitions)

- Condoms and IUDs

  UNFPA staff supported by independent technical experts

Behind the Scenes: Developing Prequalification Processes

- "Draft" general procedure for product prequalification is prepared by WHO
- "Draft" Procedure circulated for comments to partners, experts, and posted on the WHO website
- Procedure revised as required
- Procedure submitted to WHO Expert Committee for Specifications for Pharmaceutical Preparations for review and adoption
- Procedure then noted by the Executive Board and World Health Assembly followed by publication in TRS and WHO website: http://mednet3.who.int/prequal

WHO Prequalification of Medicines

Key steps:

1. Publication of invitation for expression of interest (EOI)
2. Submission of dossiers
3. Initial screening of dossiers
4. Dossier assessment
5. Site inspection
6. Report on findings and recommendations
7. Publication of evaluation results
8. Sampling and testing
9. Reevaluation and reinspection
10. De-listing

UNFPA Prequalification of Condoms and IUDs

Key steps:

1. Publication of invitation for EOI
2. Submission of documents
3. Screening of documents
4. Site inspection
5. Sampling and Testing
6. Report and outcome
7. Reevaluation
8. De-Listing

“Innovator Medicines”

- Medicines that are approved or registered by countries with a stringent regulatory agency (EU, USA, Japan, and others).
- Patents are still in force, and generic equivalents are not legally available.
- Key difference in prequalification process:

  -Focus on review of existing approvals

Generic Medicines

- Medicines where patents have expired
- Other manufacturers can produce and sell these products
- Key difference in prequalification process:

  -Focus on detailed technical review of Active Pharmaceutical Ingredients (APIs), production, history, and quality assurance of finished product

Medical Devices

- Can be an instrument, apparatus, implement, machine, implant, in vitro reagent, or other similar or related article
- Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, in humans or other animals
- Does not achieve its primary intended purposes through chemical action within or on the body of humans or other animals
- Is not dependent upon being metabolized for the achievement of any of its primary intended purposes

Current Problems Noted by Prequalification

- Lack of information regarding API, validation, specifications, bioequivalence
- Some NRAs apply different standards from those recommended by WHO yet products not meeting WHO standards are registered and used in countries
- Not all substances and products have pharmacopoeial monographs
- Dilemma (new and generics): What standards to apply for essential medicines where there is no innovator product?

Current Problems Noted by Prequalification

Manufacturing site inspection problems:

- Manufacturers not ready to demonstrate current Good Manufacturing Practice (cGMP) compliance
- Inspections reveal non-compliance with cGMP *e.g. antibiotics, hormones, and other products manufactured in the same site*
- Lack of and incomplete validation
- Lack of understanding cGMP principles
- “Double standards” – local vs. international market
- Some NRAs issue CPP even as the manufacturers do not comply with requirements

Advocating for Prequalification
Small Group Exercise

Instructions (also on handout):

- Work in groups of four to six people
- Identify the key decision-makers whose support would be required to implement the WHO and UNFPA Prequalification Programmes
- Identify what the key advocacy messages could be to promote prequalification systems to stakeholders or national regulatory agency staff
- Present a short role-play to demonstrate how you would conduct an advocacy session

WHO Prequalification for Manufacturers of Medicines

Source: WHO and UNFPA, adapted by PATH

Key Steps

Step 1. Publication of expression of interest (EOI)

- Published widely
- Open and transparent
- Specifies products required
- Identifies where to find WHO guidelines for compiling a product dossier

Step 2. Submission of dossiers

- Innovator products:
  - WHO type Certificate of Pharmaceutical Product (CPP)
  - Assessment report by the national regulatory authority (NRA)
  - Batch certificate
  - Other documentation?

- Multi-source products:
  - Dossier with required data as in the WHO Manual, *Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: WHO/DMP/RGS/98.5*

- Dossier requirements:
  1. Details of the product
  2. Regulatory status in other countries
  3. Active pharmaceutical ingredient(s) (API)
     - 3.1 Properties of the API
     - 3.2 Sites of manufacture
     - 3.3 Route(s) of synthesis
     - 3.4 Specifications
       - API described in a pharmacopoeia
       - API not described in a pharmacopoeia
     - 3.5 Container closure system
     - 3.6 Stability testing
  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 and other packaging requirements
     - 4.8. Stability testing
     - 4.9. Container labeling
     - 4.10 Product information
     - 4.11 Patient information and package inserts
     - 4.12 Justification for any differences to the product in the country issuing the submitted WHO-type certificate
     - 4.13 Interchangeability (bioequivalence studies)
     - 4.14 Summary of pharmacology, toxicology, and efficacy of the product

Step 3. Initial screening of dossiers

- Screen for completeness
- Inform supplier
- Listed for a possible site inspection

Step 4. Assessment of dossiers

- Team of experts (pharmaceutical development, bioequivalence, etc.) from NRA
- Standard: WHO Manual and guidelines *Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: WHO/DMP/RGS/98.5)*
- Outcome of the evaluation communicated to supplier

Step 5. Site inspection

- According to WHO current good manufacturing practices (cGMP)
- Inspection team:
  - Appointed inspector: technically qualified, preferably from NRA
  - Local or national inspectorate
  - WHO representative

Step 6. Report on findings and recommendations

- Reports on dossier evaluation and site inspection
- Communicated to supplier and manufacturer
- If not compliant, additional information to be submitted is identified

Step 7. Publication of evaluation results

- Meet standards: added to prequalified suppliers' list
- Outcome communicated to manufacturer and NRA
- WHO Public Assessment Report published on WHO website
- WHO Public Inspection Report published on WHO website

Step 8. Sampling and testing

- Samples submitted with product dossier
- Random samples of products supplied after prequalification and inspections-batch verification
- Failure: Investigation and communication to manufacturer

Step 9. Reevaluation and reinspection

- At regular intervals (minimum every three years), unless changes are made to product by supplier and/or manufacturer
- Other instances: misconduct, suspension of supply, complaints
  - Complaints investigated
  - Written report and action to be taken identified
  - NRA involvement

Step 10. De-listing

UNFPA Prequalification for Manufacturers of Condoms and IUDs

Key Steps

1. **Publication of expression of interest (EOI)**

2. **Submission of documents**
   - Current national registration
   - Licensing certification
   - Certification of current good manufacturing practice (cGMP) compliance
   - Certificate of quality assurance (QA) manufacturing processes (ISO 9001-2 specific for medical devices)
   - Certificate of compliance with WHO/UNAIDS, Population Council, other specifications as required
   - Manufacturer's declaration of product compliance with specifications

3. **Evaluation of documents**

4. **Site inspection**
   - Production capacity and supply chain
   - Quality management system
   - Equipment and raw materials technology
   - Product quality records
   - External certification/documentation
   - Process control and QA sampling plans
   - Laboratory test equipment and procedures

5. **Sampling and testing**
   - Random samples of finished product tested to specification requirements

6. **Report and outcome**
   - Reports on evaluation and site inspection
   - Communicated to supplier and/or manufacturer
   - Any additional information required is identified

7. **Reevaluation**

8. **De-Listing (?)**

Handouts

It is recommended that participants refer to these handouts during the presentation.

- **Guideline on Submission of Documentation for Prequalification of Multi-source (Generic) Finished Pharmaceutical Products (FPPs) Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis**
  Available online at:
  http://healthtech.who.int/pq/info_applicants/Guidelines/GuideGenericSubmitDocFPPs_08_2005_WoAnnexes.pdf

- **Guide on Submission of Documentation for Prequalification of innovator Finished Pharmaceutical Products (FPPs) used in the treatment of HIV/AIDS, malaria and tuberculosis and approved by Drug Regulatory Authorities (DRAs) in the International Conference on Harmonization (ICH) region and associated countries, including among others the EU, Japan and USA**
  Available online at:
  http://healthtech.who.int/pq/info_applicants/Guidelines/GuideSubmittingDocFPPs_DRA_ICH_08_2005.pdf

Advocating for Use of the WHO Prequalification Programme
Discussion in Small Groups

Instructions to participants:

1. Work in groups of four to six people.
2. Identify the key decision-makers whose support would be required to implement the WHO and UNFPA prequalification systems. Do not provide specific names, just the generic titles and types of positions (e.g., Director, Ministry of Health Procurement Department).
3. Identify what the key advocacy messages could be used to promote prequalification systems to stakeholders or national regulatory agency staff.
4. Each group should identify the top priority group or decision-maker to advocate to and present a short role-play (skit or mini-theater) to demonstrate how you would conduct an advocacy session for the top priority group or decision-maker selected.

Discussion questions:

1. Who are the key decision-makers whose support would be required to implement the WHO Prequalification Programme in your country?

2. What would be the most important advocacy messages that you could use to convince stakeholders to use the WHO Prequalification Programme?

Brainstorm of key decision-makers:

Brainstorm of key messages:

Advocating for Use of the WHO Prequalification Programme
Answer Key

1. Who are the key decision-makers whose support would be required to implement the WHO Prequalification Programme in your country?

   Note: There are several different groups that would be involved to different degrees in the acceptance and implementation of the WHO Prequalification Programme.

   - National legislature - to support and implement a national procurement policy that allows use of prequalification in procurement regulations
   - National regulatory authority (NRA) - to provide technical support to prequalification process and participate in site inspections
   - Directors of government procurement agencies – to support using the system when procuring health care goods
   - Directors of national health care programs – whose programs would benefit from access to WHO prequalified products
   - National Bureau of Standards
   - National Quality Control Laboratory
   - Budget Committee
   - Others?

2. What would be the most important advocacy messages that you could use to convince stakeholders to use the WHO Prequalification Programme?

   Key advocacy messages:
   Technical robustness of WHO Prequalification Programme:
   Use of the WHO Prequalification Programme reduces the risk of poor quality product entering the health care system through the application of a thorough and structured process that imposes specific technical requirements and is implemented by qualified technical experts. Examples of some of the key process steps that help ensure product quality include:
   - Requirements for current good manufacturing practices (cGMP) certification
   - Requirements for licensing and registration with the NRA
   - Use of technical experts in product dossier assessment
   - Technical review of raw materials used
   - Technical review of product specifications
   - Technical review of packaging requirements
   - Use of technical experts in site inspection
   - Inspection of manufacturing premises, procedures and equipment
   - Technical review of quality assurance (QA) sampling plan and quality control testing procedures
   - Testing of product samples
   - Use of qualified testing laboratories to test product samples
   - Transparency of evaluation process
   - Others?

Limited local capacity:

a. National Regulatory Agencies

Among NRAs there are varying degrees of capacity and resources available for implementing the standard regulatory requirements necessary for ensuring only products of acceptable quality enter the health care system. Use of the WHO prequalification helps ensure that in such situations where NRA resources are limited, there is a sound and proven technical process for obtaining acceptable quality products.

b. Procurement agencies

Some procurement units and agencies also have limited resources and staff may not be trained in implementing proper procurement procedures that help ensure product quality, such as including appropriate product technical specifications and testing requirements in relevant procurement documents. Again, use of the WHO prequalification system in such situations helps ensure that proper tests are done to make certain the manufacturer produces a good quality product. Procurement agencies still have additional responsibilities to ensure product quality that are outside those areas addressed by the WHO/UNFPA prequalification systems.

Cost:

Acceptance and use of the WHO Prequalification Programme can help health care programs save funds by avoiding duplicative testing of products that have been WHO-prequalified.

Quantifying the cost of product failure to personal health and the health care system can help convince stakeholders of the need to invest in good QA systems including the WHO Prequalification Programme.

Other advocacy messages?

Optional or "homework" exercise: Quality Considerations in Evaluating and Selecting a Product

Case Study

In January 2007, the Family Planning and Welfare unit of the Ministry of Health of Pretonia (FPW/P—a fictitious name) received funding from the Government of Pretonia to finance its procurement of the oral contraceptive (OC) tablet ethinyl estradiol and levonorgestrel for the 2008–2013 program years.

In May 2007, FPW/P released an international bid for the OC requirement for the 2008 annual program requirements only. (Note: In 2008, FPW/P will release another invitation to bid for 2009 program requirements that will reflect new Government of Pretonia quality assurance (QA) requirements—that beginning in 2009 all ethinyl estradiol and levonorgestrel contraceptive tablets procured under government financing must be WHO prequalified).

A few of the key requirements for the 2007 procurement activity regarding product quality (included in the invitation to bid) are listed below.

Oral contraceptive tablets

1. Composition
   Oral contraceptive tablets in accordance with the following specifications: Twenty-eight day cycle package consisting of 21 ethinyl estradiol and levonorgestrel tablets and seven ferrous fumarate tablets

   Contraceptive tablets: each tablet shall contain 30 micrograms ethinyl estradiol and 150 micrograms levonorgestrel

   Spacing tablets: each tablet shall contain 75 mg ferrous fumate

2. Registration
   Oral contraceptives offered under this purchase requirement must be registered in Pretona and approved by the National Regulatory Authority (NRA) of Pretona by February 15, 2008 to support program delivery requirements.

3. Certificate of Licensing status
   Oral contraceptives offered under these purchase requirements shall be licensed for marketing by the drug regulatory authority of the country of origin. Prior to award, the successful offerer shall provide a "Statement of Licensing Status of Pharmaceutical Products" as provided under the World Health Organization (WHO) Certification Scheme.

4. Certificate of Pharmaceutical Product
   The supplier must be able to provide certification issued by the NRA in the country of manufacture that the oral contraceptives offered under this purchase requirement are approved for use in the exporting country and the manufacturer's facility is inspected regularly and meets current good manufacturing practice (cGMP) requirements according to WHO recommended current good

manufacturing practices. Such certification is found in the WHO Certification Scheme document "Certificate of a Pharmaceutical Product."

1. Other information on product quality
   Any other certification or information that documents the overall quality of the product being offered should be submitted by the manufacturer for evaluation.

Responses were received from three manufacturers: two generic manufacturers (one local and one international) and one international brand name manufacturer on August 1, 2007.

Abaco Generics – local manufacturer of generics in Pretonia
Bersdin Generics – international manufacturer of generics
Cardos International – international brand name manufacturer
(Note: all fictitious names)

The FPW/P has evaluated the bid responses and a summary of these responses is presented in the table below.

Evaluation of 2007 bid responses

Requirements	Abaco Generics	Bersdin Generics	Cardos International	Comments
1. Composition	Compliant	Compliant	Compliant	
2. Registration Status in Pretonia	Registered	Registered	Not registered	Cardos registration submitted June 15, 2007; authorization expected Feb. 15, 2008
3. Certificate of Licensing	Provided	Provided	Provided	Pretonia is not a PIC/S member country
4. Certificate of Pharmaceutical Product	Provided	Provided	Provided	Abaco document notes several past product recalls
5. Additional information on product quality	Produced in a non-PIC/S country	Produced and licensed in a PIC/S country	Produced and licensed in PIC/S country	

The prices for all products were within a competitive range, so the recommendation to the Cabinet of Ministers is to be based on product quality and availability. A contract award release date of October 1, 2007 is anticipated to allow the manufacturer sufficient lead time to produce and ship the product to support a March 1, 2008 initial delivery.

1. Based on the above information, and limiting your selection criteria to product quality and availability, what product would you recommend to the Cabinet of Ministers for procurement for 2008 and why?

2. For the 2008 Invitation to Bid (to support the 2009 program needs), what changes should be made to the QA requirements of the bidding documents to reflect the new national requirement to procure only WHO prequalified product?

3. What challenges might you anticipate Abaco Generics, whose manufacturing facility is located in a non-PIC/S country, could face in applying and receiving WHO prequalification in order to qualify for the 2008 FPW/P Invitation to Bid?

4. What challenges do you think the other manufacturers in similar situations as Bersdin (a generic manufacturer in a PIC/S country) and Cardos (a brand name manufacturer in a PIC/S country) might face in obtaining WHO prequalification?

5. What measures can be taken to support Abaco in applying for and obtaining WHO prequalification of its oral contraceptive tablet?

6. What advantages will the 2009 national requirement to procure only WHO-prequalified products provide to the FPW/P?

Quality Considerations in Evaluating and Selecting a Product Case Study

Answer Key

1. Based on the above information, and limiting your selection criteria to product quality and availability, what product would you recommend to the Cabinet of Ministers for procurement for 2008 and why?

   Issues:

   - *Recommendation of the international brand name product (Cardos) would be risky since the product is not expected to be registered by the NRA until February15 and first program delivery is required for March 1, 2008.*
   - *While both generic manufacturers (Abaco and Bersdin) submitted information indicating their product meets technical requirements, the Abaco documentation indicates there have been quality problems previously as evidenced by the product recalls. There may be a higher level of risk in the quality of product supplied by Abaco given this prior history.*
   - *WHO Certification Scheme documents. Since there currently are no WHO prequalified Ethinyl estradiol and levonorgestrel OC tablets the FPW/P used the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce in its documentation requirements. This scheme is an international voluntary agreement designed to enable countries with limited national regulatory capacity to obtain partial assurance from exporting countries about the safety, quality, and efficacy of pharmaceuticals they plan to import. It is an inexpensive way for procurement personnel to obtain product quality information. However, the reliability of the certificates issued under the WHO scheme largely depends on the reliability and capability of the exporting country's NRA.*
   - *Bersdin's manufacturing facility is in a PIC/S country while Abaco's manufacturing facility is located in a non-PIC/S country (Pretonia). Traditionally PIC/S country NRAs are considered more stringent in applying and monitoring quality assurance standards.*
   - *Abaco is a local manufacturer and there may be local pressure to procure from and support local industry.*

2. For the 2008 Invitation to Bid (to support the 2009 program needs), what changes should be made to the QA requirements of the bidding documents to reflect the new national requirement to procure only WHO prequalified product?

   Issues:

   - *The technical specifications of the bidding documents should be amended to include the requirement for certification that the offered product has been prequalified by WHO under the WHO Prequalification Programme.*
   - *The above requirement would supersede the requirements for documents under the WHO Certification Scheme.*

3. What challenges might you anticipate Abaco Generics, whose manufacturing facility is located in a non-PIC/S country, could face in applying and receiving WHO prequalification in order to qualify for the 2008 FPW/P Invitation to Bid?

   Issues:
   - *Possible lack of understanding on Abaco's part of the benefits of WHO-prequalification could prevent them from applying.*
   - *Given Pretonia is a non-PIC/s country, the scale of upgrades required to comply with WHO prequalification requirements may be more significant than that required for a manufacturer in a PIC/S member country.*
   - *Possible limited financial resources to implement any upgrades required to comply with WHO prequalification requirements.*
   - *Other?*

4. What challenges do you think the other manufacturers in similar situations as Bersdin (a generic manufacturer in a PIC/S country) and Cardos (a brand name manufacturer in a PIC/S country) might face in obtaining WHO prequalification?

   Issues:

   Generic manufacturers in PIC/S countries:
   - *Possible lack of understanding of the benefits of WHO prequalification could prevent them from applying.*
   - *Possible limited financial resources to implement any upgrades required to comply with WHO prequalification requirements.*
   - *Given their presence in a PIC/S country the scale of upgrade required would be less significant than that of a manufacturer in a non-PIC/S country.*

   Brand name manufacturers in PIC/s countries:
   - *Challenges are likely to be minimal. Traditionally international brand name manufacturers have adequate financial resources to address any upgrade requirements, which would be expected to be minimal given manufacturing presence in a PIC/S country.*

5. What measures can be taken to support Abaco in applying for and obtaining WHO prequalification of its oral contraceptive tablet?

   Issues:
   - *Provide Abaco with information on the financial and market benefits of WHO prequalification*
   - *Provide Abaco with information on the technical assistance offered by WHO which is designed to help manufacturers understand and comply with WHO prequalification requirements.*
   - *Other?*

6. What advantages will the 2009 national requirement to procure only WHO-prequalified products provide to the FPW/P?

- *In countries with variable or limited NRA quality assurance capacity helps ensure products being procured will be of good quality.*
- *Where public sector procurement agencies have limited technical capacity or experience in incorporating and implementing procurement quality assurance procedures, helps ensure products being procured will be of good quality.*
- *Can shorten the procurement cycle time line by eliminating the time required to conduct an independent QA prequalification process or a post qualification process.*
- *Other?*