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# Prequalification of Medicines

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Health Systems and Services (HSS)


# Web site updated constantly – www.who.int/prequal

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## 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.

New SPCs and WHOPARs published

3 new WHO Public Inspection Reports published

Update to List of Quality Control Laboratories

2 new ARV products prequalified

**All News**

**QUICK LINKS**

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# Prequalification of Medicines Programme

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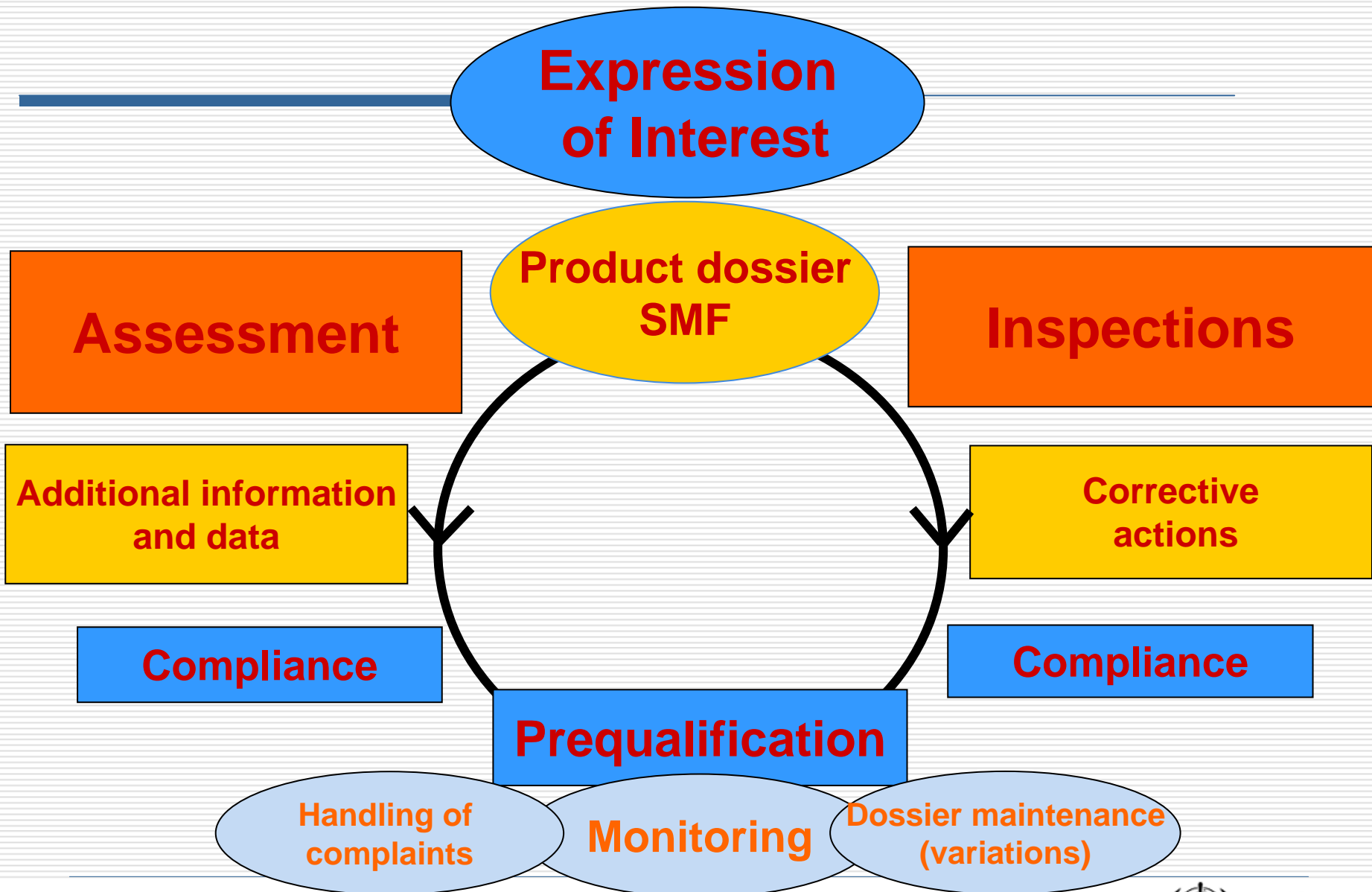
- ❑ The UN Prequalification Programme is ensuring that medicines procured with international funds are of assessed and inspected **quality, efficacy and safety**.
- ❑ The Prequalification Programme is **an action plan** for expanding access to priority essential medicines in the following areas:
  - HIV/AIDS
  - Tuberculosis
  - Malaria
  - Reproductive Health
  - Selected products for other diseases such as oseltamivir and Zinc sulphate
- ❑ A UN Prequalification Program of **Quality Control Laboratories** exists to facilitate the quality control of the prequalified products.

# Prequalification of Medicinal Products: Objectives

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- Propose a list of **prequalified products and manufacturers** meeting international norms and standards, for which the quality, efficacy and safety have been assessed and inspected and any changes (variations) controlled
- Ensure that **international norms and standards** are applied at all the steps of the Prequalification Programme.
- Make sure the list is **maintained**, in terms of control of variations, re-evaluation and QC testing.
- Help the national drug regulatory authorities to build capacity in **assessment, inspection and control**, meeting international norms and standards.
- Develop the **local possibilities** of production and clinical studies by offering customized technical assistance.

# Medicines Prequalification Process



# Prequalification of Priority Essential Medicines (1)

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**Assessment** of the product dossier i.e. quality specifications, pharmaceutical development, stability, bioequivalence...

☐ Copenhagen assessment week

- 15 to 20 assessors during 5 days at least once every two months
- Every dossier is assessed by two assessors including one senior assessor
- An assessment report is issued
- Letter summarizing the findings and asking for clarification and additional data if necessary; sent first by e-mail to the applicant followed by surface mail

☐ **Handling of variations of prequalified products**

- Done in house on a continuous basis

# Prequalification of Priority Essential Medicines (2)

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Inspections of manufacturers of

- 1 - **Finished Products (FPP)**
- 2 - **Active Pharmaceutical Ingredient (API)** and also
- 3 - **Contract Research Organizations (CRO)**, which carry out clinical/bioequivalence studies)

Team of inspectors

- **WHO representative** (qualified GMP inspector)
- **Inspector from well-established inspectorate**
- **National inspectors** invited to be part of the team as observers but have no decision-making power (different GMP standards, potential conflict of interest)
- **Inspector of potential target countries** (or other countries in need) as observer, for capacity building purposes.

# Assessments & Inspections

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- Key numbers for 2008
  - 40 products prequalified (21 in 2007),
  - 92 dossiers submitted (90 in 2007)
  - 732 assessment reports (463 in 2007)
  - 52 inspections (45 in 2007)
  
- For each prequalified product there were:
  - ◆ 5-15 assessment reports
  - ◆ At least 1 inspection
  - ◆ 2 years median time to get prequalified

# List of WHO Prequalified Medicinal Products

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- ☐ Currently prequalified products (10 March 2009):
- ☐ **171** for treatment of **HIV/AIDS** and related diseases
- ☐ **20** for treatment of **tuberculosis** (12 prequalified in 2007-08)
- ☐ **15** for treatment of **malaria** (10 prequalified in 2007-08)
- ☐ Total **206**

# Product dossiers accepted for assessment

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	<u>2005</u>	<u>2006</u>	<u>2007</u>	<b><u>2008</u></b>
HIV	67	42	25	<b>42</b>
TB	17	9	17	<b>12</b>
Malaria	3	5	7	<b>9</b>
Repr Health	-	-	10	<b>4</b>

# Currently under assessment in WHO Prequalification Programme

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As of 10 March 2009 :

- ▣ **60** products for treatment of HIV/AIDS and related diseases
- ▣ **35** products for treatment of tuberculosis
- ▣ **19** products for treatment of malaria
- ▣ **14** reproductive health products
- ▣ Total **114**

# Transparency – dossier status information on the web

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Quality Control Laboratories

Training material, workshops and meetings

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assessment in progress     
 additional data to be provided by the manufacturer     
 dossier part acceptable

Product (INNs)	Strength	Unit	Dosage Form	Quality part	Efficacy/Safety part
abacavir	20 mg/ml	solution, oral			
abacavir	20 mg/ml	solution, oral			
abacavir	60 mg	tablet			
abacavir + lamivudine	60/30 mg	tablet			
abacavir + lamivudine + zidovudine	60/30/60 mg	tablet			
aminosalicylate sodium	60 %	granule			
amodiaquine + artesunate	153.1/50 mg	tablet			
amodiaquine + artesunate	306.2/100 mg	tablet			
amodiaquine + artesunate	50/153 mg	tablet			
amodiaquine + artesunate	50/153 mg	tablet			

# Inspections - statistics in 2008 vs 2007

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- **A total of 62 (46 in 2007) inspections were carried out in 2008:**
  - 27 (26) inspections of the manufacturing sites of finished product manufacturers
  - 11 (6) inspections of the manufacturing sites of active pharmaceutical ingredients (APIs)
  - 14 (13) inspections of contract research organizations (CROs)
  - 10 (1) Quality control laboratories
  
- In 2008 3-4 inspectors in-house

# Prequalification Programme: Transparency – WHOPARs, WHOPIRs and NOCs

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- These are published in response to the WHA Resolution WHA57.14 of 22 May 2004, which requested WHO:  
*"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 Assessment Report (WHOPAR)** is a summary of the quality and efficacy/safety assessments for a product at the time of prequalification and includes the Summary of Product Characteristics (SPC)
- **A WHO Public Inspection Report (WHOPIR)** provides a summary of the inspection where found to be GMP compliant
- **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 research organization.

# Transparency – Inspection outcomes on the web



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Home - Notices of Concern

## Notices of Concern

As of 1 June 2008, the WHO Prequalification of Medicines Programme will publish Notices of Concern (NOC) after inspections have been conducted at manufacturers of prequalified medicines and research organizations involved. A NOC will be published when the nature of deficiencies identified during a manufacturer inspection indicate a significant failure of the quality management system, resulting in inadequate assurance of product quality.

### What is a Notice of Concern (NOC) ?

A Notice of Concern is a letter issued by the WHO Prequalification of Medicines Programme, after an inspection was performed at a site where observations were made that result in concern regarding compliance of the site with specified standards such as Good Manufacturing Practices or Good Clinical Practices. A NOC will not disclose commercially confidential information.

A NOC is issued to remind a manufacturer or research organization of their obligations to quality assurance and to inform suppliers and procurement agencies of potential risks associated with a given product or manufacturer. A NOC is not cause for public concern. If WHO identifies a public health risk, appropriate additional steps will be taken to advise the public.

### What does a NOC contain ?

A NOC states observations made during an inspection that are considered to be "critical" or "major" non-compliances or deficiencies.

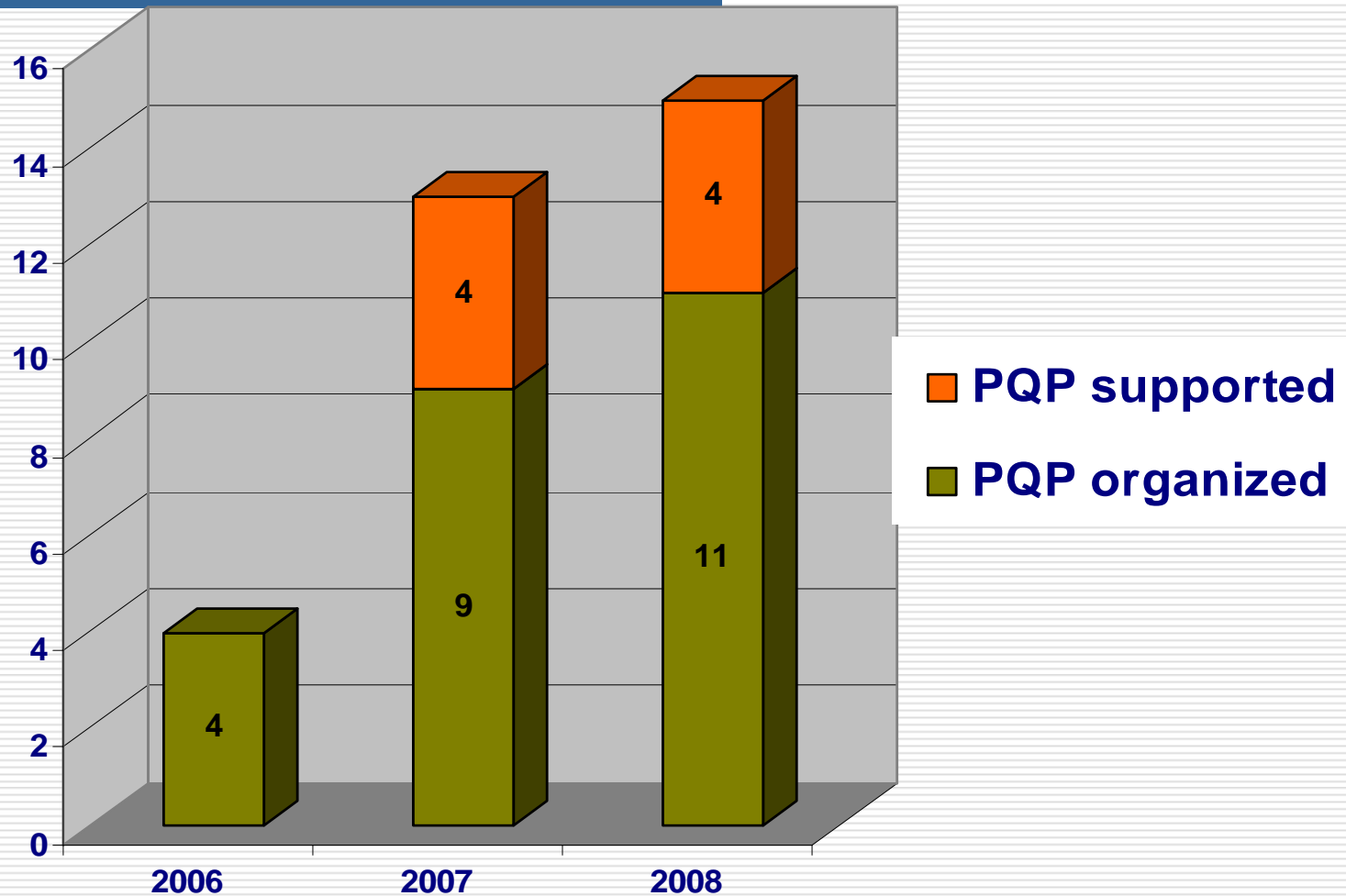
Critical Deficiency – a deficiency which has produced, or leads to a significant risk of producing a product which is harmful to the human patient.

# Training activities in 2008

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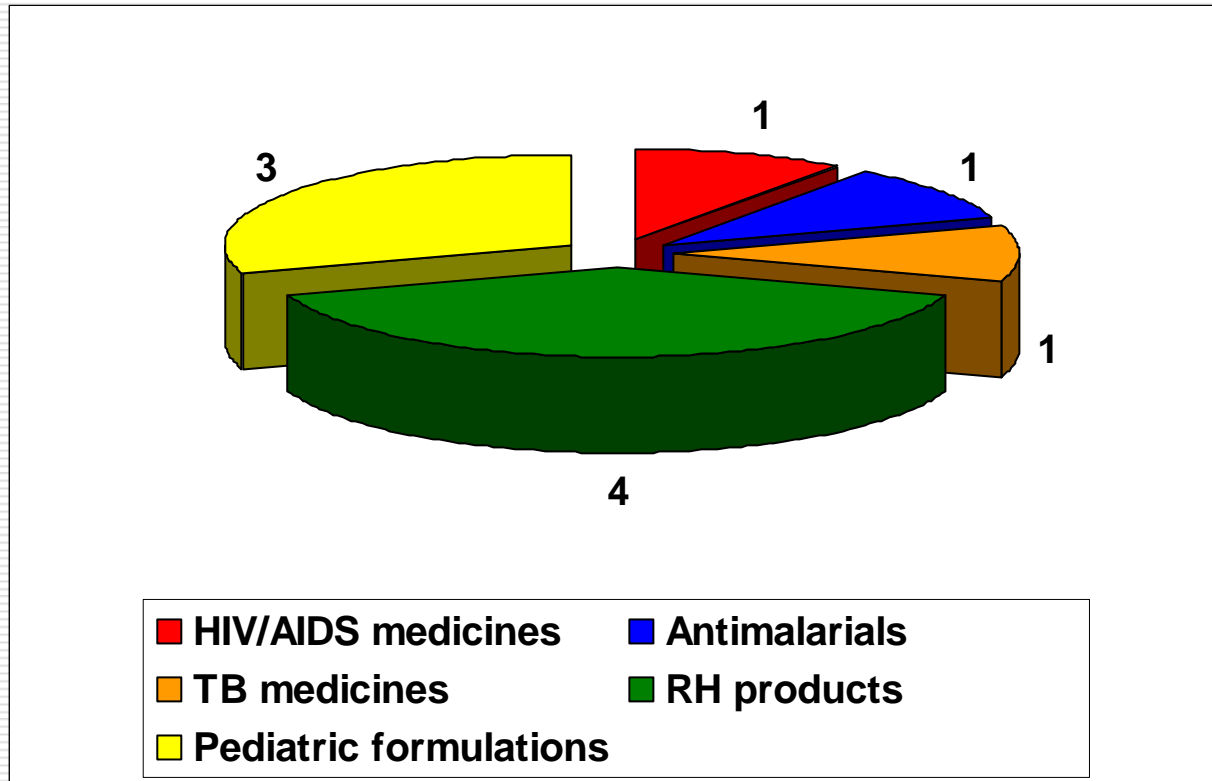
- **In total 11 training courses organized and 4 co-organized**
- **In Brazil, China, Ghana, India, Indonesia, Iran, Jordan, Morocco, Nicaragua, Pakistan, Tanzania ...**
- **More than 500 participants - staff of regulatory authorities and pharmaceutical manufacturers**
- **Topics:**
  - Compilation of dossiers for submission
  - Assessment of bioequivalence (interchangeability) of medicines
  - Pharmaceutical Development of Paediatric Formulations
  - GMP, Quality and Bioequivalence of malaria ACT products
  - GMP, Quality and Bioequivalence of Reproductive Health products

# Trainings organized or supported by PQP



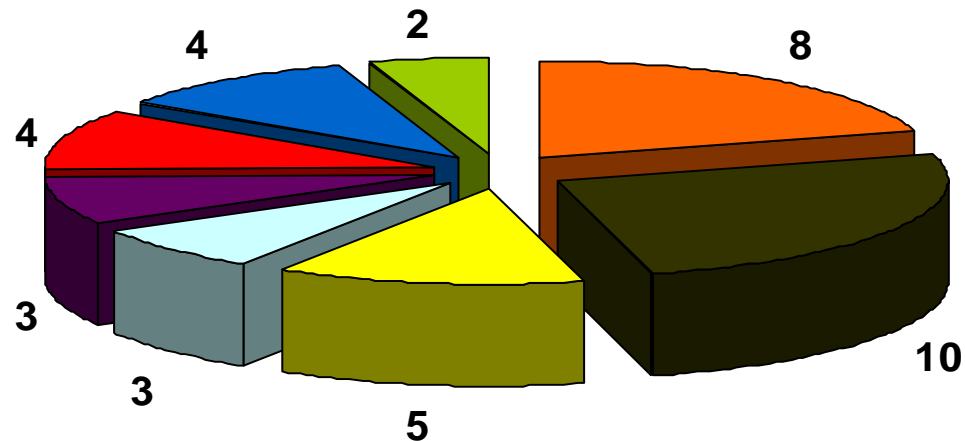
# Training workshops focusing on specific categories of medicines

2006-2008



# Topics of training workshops

2006-2008



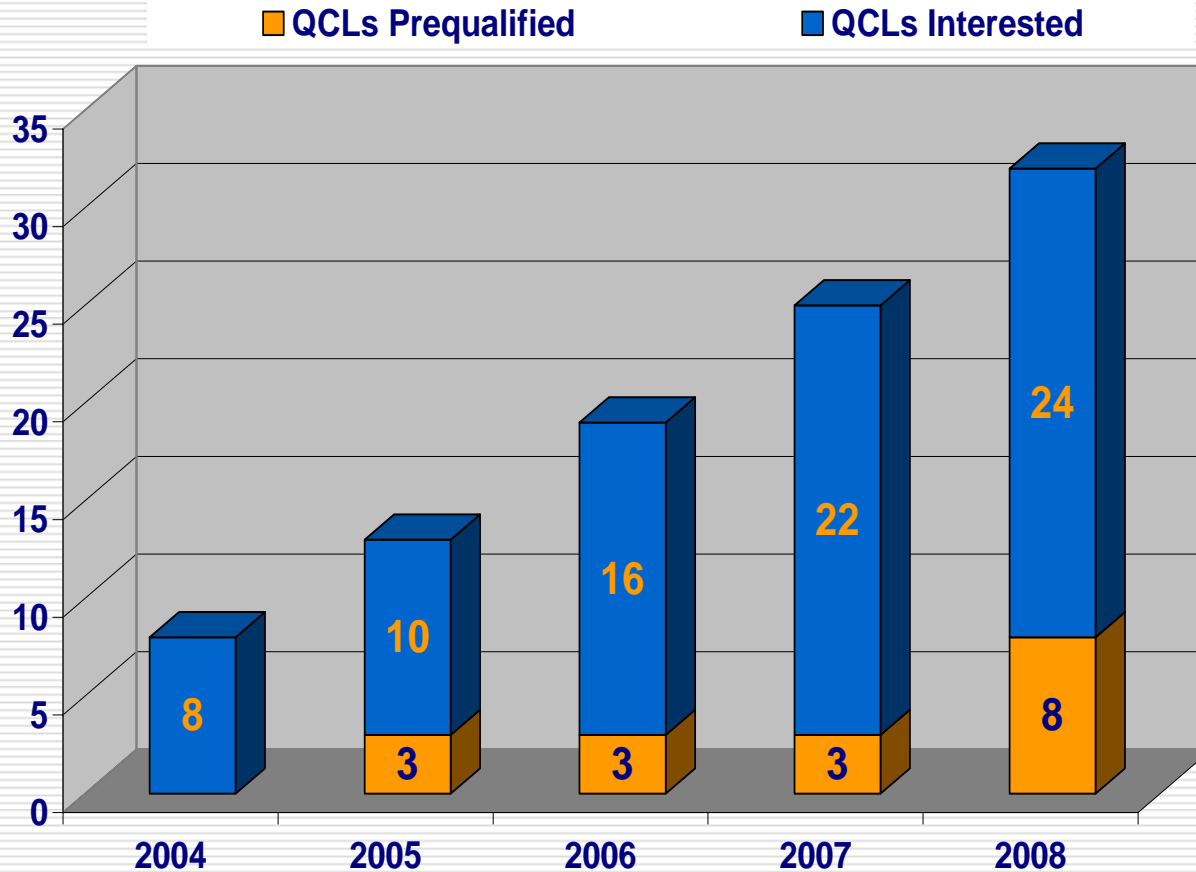
- Prequalification advocacy
- Prequalification requirements
- Good manufacturing practice
- Quality control
- Bioequivalence/BCS and GCP
- Assessment of dossiers
- Pharmaceutical development
- PQ general

# Prequalification of **Quality Control Laboratories** (QCL)

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- So far mainly for AFRO region, now wider scope
- 6 QCL **prequalified** in 2008
  - Adcock, South Africa – 01/2008
  - National QCL, Kenya – 07/2008
  - National QCL, Morocco – 07/2008
  - Vimta Labs, India – 07/2008
  - CHMP, France – 10/2008
  - National institute of Drug Quality Control - NIDQC (Vietnam) -11/2008
- 10 **inspections** and **pre-audits** of QCLs performed
  - In cooperation with inspectors from South Africa, Austria, France, Poland, Singapore and Estonia
- 8 QC Labs expressed **interest in 2008**, 2 of them already prequalified

# QCL Prequalification trends



## Prequalified QCLs:

- South Africa, RIIP+CENQAM (2005)
- Algeria, LNCPP (2005)
- South Africa, Adcock Ingram (2008)
- Morocco, LNCM (2008)
- Kenya, NQCL (2008)
- India, Vimta Labs (2008)
- France, CHMP (2008)
- Vietnam, NIDQC (2008)

# Sampling and testing projects in 2008

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## ■ **Quality survey of antimalarials (ACTs and sulfadoxine-pyrimethamine)**

- Cooperation with NDRAs in Cameroon, Ethiopia, Ghana, Kenya, Madagascar, Nigeria, Senegal, Tanzania, Uganda
- 936 samples collected and screened by Minilab, 299 selected for full testing in laboratory (testing ongoing)
- Assessment of quality of product information (Labelling and PIL)

## ■ **Quality monitoring of products funded by UNITAID**

- Pilot phase (paediatric and second-line antiretrovirals) in cooperation with NDRAs in Kenya, Tanzania, Uganda, Zambia
- 378 samples collected and tested in laboratory (testing ongoing)
- Assessment of quality of product information (Labelling and PIL)

## ■ **Quality survey of anti-TB medicines in Eastern Europe**

- Cooperation with NDRAs in Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, Uzbekistan; Focused on Rifampicin, Isoniazid, Rifampicin/Isoniazid, Ofloxacin, Kanamycin (360 samples planned)

# Technical Assistance - Policy

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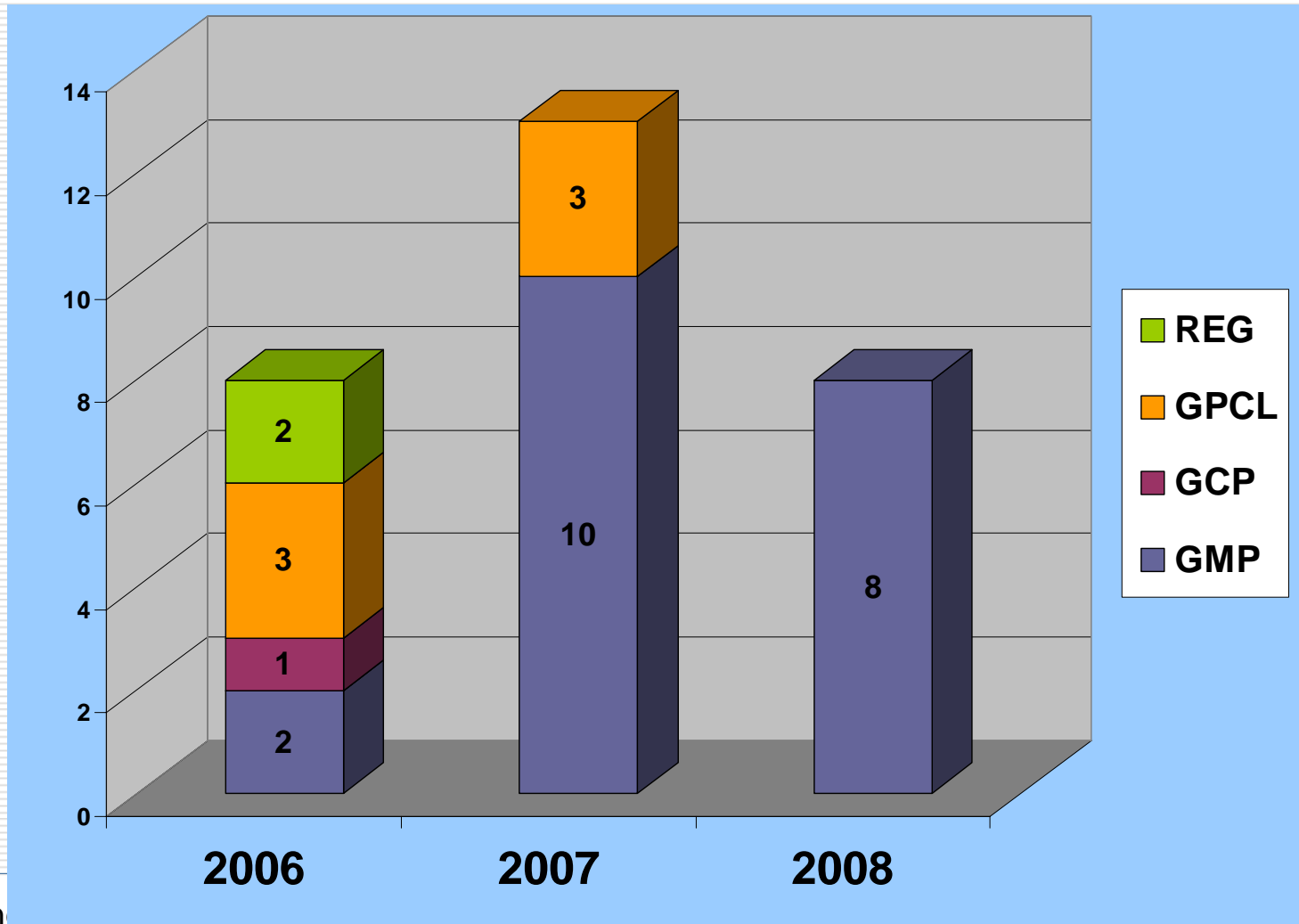
## **Criteria (products):**

- Inclusion in the list of Expression of Interest
- High public health value
- Poorly represented on prequalified list
- Manufacturer has submitted a product dossier to the Programme (exemptions can be made if justified)

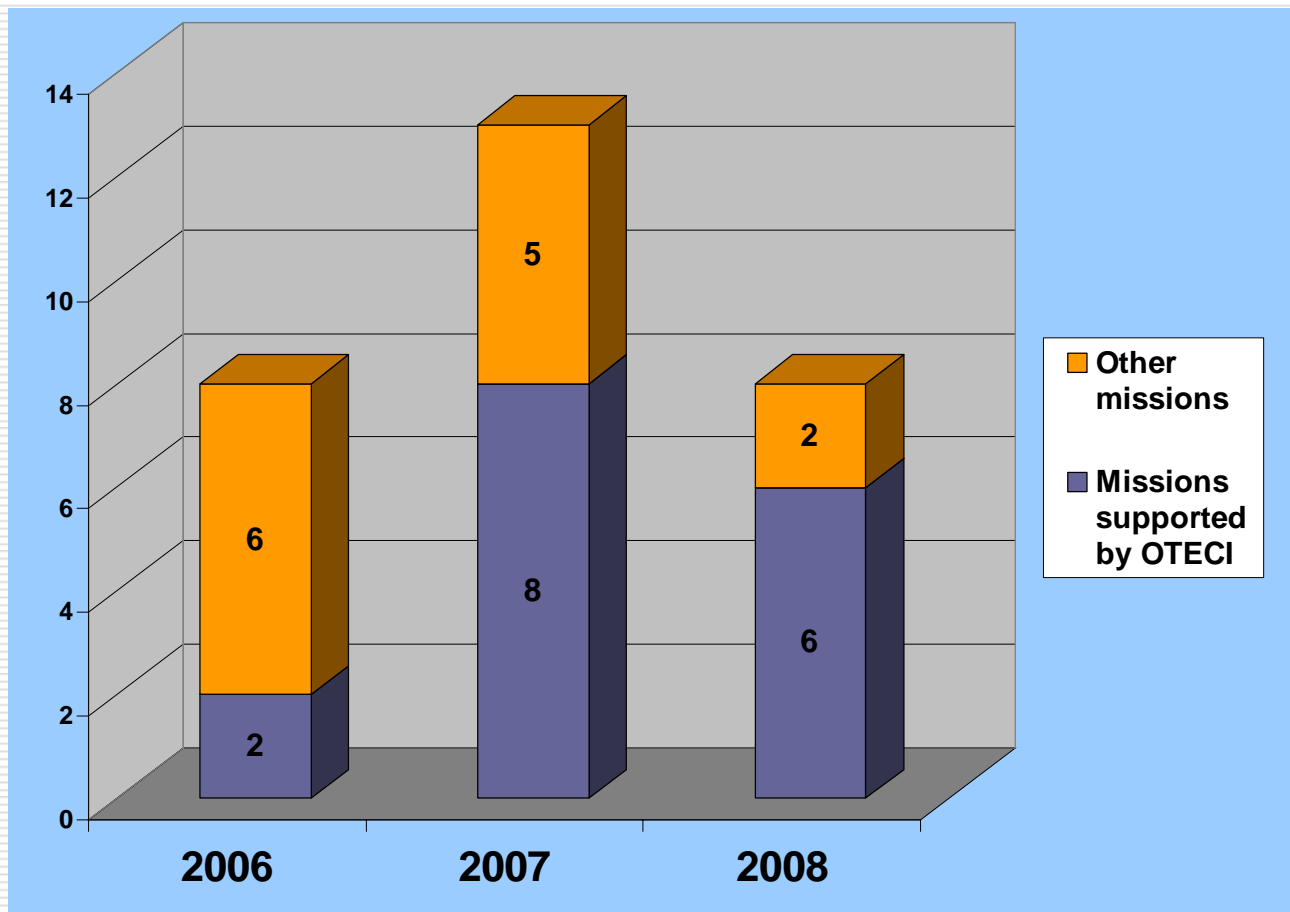
## **Criteria (experts):**

- Excellent qualifications and long standing experience in the area where expertise is required
- Absence of conflict of interest
- Independence from inspection and assessment of product dossiers submitted to the Programme

# Technical assistance – main focus of missions in 2006-2008



## Technical assistance - missions in 2006-2008 supported by OTECI or others



# Revision of PQ procedure in 2008

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## Reasons for revision

- 5 years experience from implementation
- Differences between procedure and actual practices
- Clarify responsibilities of parties

## Aims of revision

- increase transparency of PQ activities
- publish more details on prequalified products
- harmonize terminology and clarify procedures
- better define responsibilities
- confidentiality agreement with applicants

# New PQ procedure for APIs in 2009

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- Until now the **qualification of API source and manufacturer** is primarily the responsibility of the finished product manufacturer => API manufacturer may not be inspected and API dossier may not be evaluated in depth
- **API source considered "confidential" information**
- Oct 2008 WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed
  - Procedure for API Master File in Prequalification Programme
  - PQ procedure for active pharmaceutical ingredients (APIs) – new "regulatory" approach

# Problems

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- **Anti-malarials and anti-tuberculosis products – old problems but few new solutions**
  - Immature submissions – takes time to get to the maturity needed
  - Relative lack of motivation from applicants
  - Relative lack of new innovator products
  - "Generic" products with no innovator
  - ...or problem "new" products
  - GMP non-compliance (both for finished dosage form and API)
  - Quality part of the dossier – specifications, stability data etc incomplete

Safety and efficacy – poor clinical and safety data, poor quality information, poor information for users

# Challenges

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- Availability of national experts (qualified assessors and inspectors) in forthcoming years
- Increasing demand for capacity building – shift from general to more specific and technical
- Increasing demand for prequalified products of high public health value (new product groups, specific products, NTD products)
- Increasing demand for ad hoc services regarding quality
- Trust building and information exchange to avoid duplication
- Constant need to improve communication (resource needs remain underestimated)
- Meeting the increasing needs with the staff available

# Summary remarks (1)

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- The purpose of the Prequalification Programme is to list good quality, safe and effective medicinal products of public health interest in resource-limited countries.
- The products should be submitted with technical data proving the quality of API and finished product together with necessary data on safety and efficacy (good quality submissions are in demand)
- Manufacturing sites of APIs and finished products should operate according to GMP principles in order to deliver consistent quality products
- CROs should conduct studies in compliance with GCP / GLP as appropriate

## Summary remarks (2)

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- Technical assistance for promising manufacturers/products can be made available to achieve the goal and speed up the prequalification process.
- Close cooperation with international procurement and financial institutions
  - **quality as prerequisite for procurement decision**
  - **instruments to support quality production**
- Encourage manufacturers to invest in quality, and to apply for independent evaluation
- **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!

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- WHO wishes to acknowledge the assistance and help provided in 2008 by our many partners in and outside WHO, donors and many other individuals and organizations
- We are especially grateful to the staff of the National Drug Regulatory Authorities of:
- Australia, Austria, Brazil, Canada, China, Estonia, Ethiopia, France, Germany, Ghana, Hungary, Italy, Kenya, Netherlands, Poland, Singapore, South Africa, Spain, Sweden, Switzerland, Tanzania, Uganda, Ukraine, United Kingdom, and Zimbabwe...