World Health Organization
Prequalification of Medicines

JOINT WHO/UNAIDS INFORMAL CONSULTATION WITH
PHARMACEUTICAL COMPANIES

Forecasting Global ARV Demand 2010-2012 and Improving access to adult and pediatric treatment

WHO Headquarters, D Building, Room 46025- Geneva, Switzerland

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Update on the Prequalification of Medicines Programme

In this presentation:

- Overview, background and introduction to prequalification
- Update
  - Assessments
  - Inspections
  - Technical assistance
  - Capacity building
- Quality control laboratories
- Challenges and achievements
Update on the Prequalification of Medicines Programme

- Started in March 2001 as a Pilot Project: Focus on HIV/AIDS
- Partners included WHO, UNICEF, UNFPA, UNAIDS and supported by World bank
- Quickly expanded to include Tuberculosis, Malaria, RPHP, Influenza and others
- Funded mainly by donors at that time
- Now, Bill and Melinda Gates Foundation and UNITAID

Why prequalification of medicines?
- Report on QA systems of procurement agencies
- High disease burden
- Access to quality medicines
HIV/AIDS

Figure 1: Deaths per 100,000 population in the period 1982 to 1993. [Link to image]

In most African countries, less than 10% of people have access to ARV treatment. [Link to WHO data]

World Health Organization
Prequalification of Medicines

- Vision
- Mission

Good quality medicines for everyone.

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.

- Through
  - evaluation and inspections
  - Building national capacity for sustainable manufacturing and monitoring of quality medicines.
Prequalification of Medicines

Program Manager

Admin Support

Head: Inspections
Inspector
Inspector

Head: Dossier assessments
Assessor
Assessor

Liaison

Quality Control

Technical Assistance
Q10. When and where in the prequalification process will inspections be done?
The diagram below presents a simplified presentation of the steps in the prequalification process and where inspections will take place.
Innovator products
- Accepted, if approved by stringent regulatory authorities
- Based on availability of assessment reports, WHO Certificate of Pharmaceutical Product (CPP), batch certificate
- Continuous update on product changes after prequalification
- Confidence in scientific expertise of well-established RAs

FDA tentative approvals linked to PEPFAR
- Included in WHO PQ List
- Confidentiality agreement with US FDA in place

EU Article 58
- For products exclusively to be used outside EU

Canadian Access to medicines scheme
- WHO cooperation with the above mentioned
- Confidentiality agreement in preparation

Prequalification of Multisource (generic) Finished Pharmaceutical Products approved by Stringent Regulatory Authorities
- Assessment report (waived for anti-TB or antimalarial medicines with 30 years of therapeutic experience - including 15 years in ICH region)
- 5 years of continuous manufacturing experience
- Last Annual Product Report
Prequalification assessment

Multisource products

**Assessment**

- **Quality**: information on starting materials and finished product, (API details, specifications, stability data, formulation, manufacturing method, packaging, labelling etc.)
- **Interchangeability with reference product** (efficacy and safety): Report of bio-equivalence, biovaiwer or clinical study demonstrating interchangeability with reference product
- **Inspection** of manufacturers and CROs
- **Laboratory analysis** in case of need

**Monitoring** after prequalification
Assessors participating in PQ assessment (all visits in 2001-2008, share of the WHO regions)

In total 603 participations
In this presentation:

- Background and Introduction
- Inspections activities
- APIs
- FPPs
- CROs
Prequalification of Medicines

Inspections

- Done by teams of inspectors
- WHO inspector plus appointed from DRA (PICS member)
- Invite local inspector (DRA)
- Some cases observers and technical advisors
- Technical assistance (independent, no conflict of interest)
## Inspection of API manufacturers

### Guide to Manufacturer Risk Classification

<table>
<thead>
<tr>
<th>PRODUCT TYPE / ACTIVITY</th>
<th>RELATIVE RISK CATEGORY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRITICAL</td>
</tr>
<tr>
<td><strong>Finished Products:</strong></td>
<td></td>
</tr>
<tr>
<td>Sterile finished products</td>
<td>X</td>
</tr>
<tr>
<td>Non-sterile finished products</td>
<td></td>
</tr>
<tr>
<td><strong>APIs:</strong></td>
<td></td>
</tr>
<tr>
<td>Sterile APIs</td>
<td>X</td>
</tr>
<tr>
<td>Nonsterile APIs where there is a special risk (e.g. isomerism, polymorphism, special risk of harmful impurities, etc)</td>
<td>X</td>
</tr>
<tr>
<td>Other nonsterile APIs</td>
<td></td>
</tr>
<tr>
<td><strong>QC Laboratories</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CROs</strong></td>
<td></td>
</tr>
</tbody>
</table>
Inspection of API manufacturers

Parameters considered:

- Polymorphism
- Solubility in water
- Route of Synthesis
- Solvents used
- Impurities
- Sterile API
- Fermentation
- Toxicity
- Activity/potency
- Particle size
- Other properties to be considered
- Site compliance information (WHO/EDQM/Other)
WHO GMP for APIs – ICH Q7

II. QUALITY MANAGEMENT
III. PERSONNEL
IV. BUILDINGS AND FACILITIES
V. PROCESS EQUIPMENT
VI. DOCUMENTATION AND RECORDS
VII. MATERIALS MANAGEMENT

VIII. PRODUCTION AND IN-PROCESS CONTROLS
IX. PACKAGING AND IDENTIFICATION LABELING OF APIs AND INTERMEDIATES
X. STORAGE AND DISTRIBUTION
XI. LABORATORY CONTROLS
XII. VALIDATION

XIII. CHANGE CONTROL
XIV. REJECTION AND RE-USE OF MATERIALS
XV. COMPLAINTS AND RECALLS
XVI. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)
XVII. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS
### Inspection of API manufacturers

#### 2008

<table>
<thead>
<tr>
<th>Disease</th>
<th>Observations</th>
<th>Major</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>43</td>
<td>4</td>
<td>India</td>
</tr>
<tr>
<td>HIV/ Mal</td>
<td>11</td>
<td></td>
<td>India</td>
</tr>
<tr>
<td>Mal</td>
<td>22</td>
<td></td>
<td>China</td>
</tr>
<tr>
<td>Mal</td>
<td>27</td>
<td></td>
<td>China</td>
</tr>
<tr>
<td>Mal</td>
<td>33</td>
<td>2</td>
<td>India</td>
</tr>
<tr>
<td>TB</td>
<td>20</td>
<td>6</td>
<td>India</td>
</tr>
<tr>
<td>TB</td>
<td>Investigation</td>
<td></td>
<td>India</td>
</tr>
<tr>
<td>TB</td>
<td>19</td>
<td></td>
<td>India</td>
</tr>
<tr>
<td>HIV</td>
<td>Investigation(38)</td>
<td>10</td>
<td>India</td>
</tr>
<tr>
<td>HIV</td>
<td>28</td>
<td></td>
<td>India</td>
</tr>
<tr>
<td>HIV</td>
<td>Investigation</td>
<td></td>
<td>China</td>
</tr>
<tr>
<td>Mal</td>
<td>11</td>
<td></td>
<td>China</td>
</tr>
</tbody>
</table>
Number of inspections per year

Site locations: Countries inspected
Inspection of API manufacturers

![Graph showing inspections and observations over years](image-url)
Inspection of API manufacturers

2007 - 2009. Inspections (disease areas) and number of observations

Areas of non-compliance

Ave (total) obs per site
Ave (Major)

Ave (Major)

Major deficiencies

TB
HIV/AIDS
MAL

Cross contamination
Batch records
SOPs
Material Management
Cleaning
Labeling
Inspection of FPP manufacturers

To get started (FPP manufacturer):

- Product dossier submitted
- Listed as a manufacturer in a product dossier
- Assessment in progress
- Risk assessment
- Submit a SMF
- Announce inspection
- Provide tentative inspection plan
- Inspect, prepare inspection report – corrective action
Inspection of FPP manufacturers

Manufacturers: Normally over 4 days

- Covers all aspects of GMP
  - Quality management, Quality assurance, Premises, Equipment, Documentation, Validation, Materials, Personnel
  - Utilities (e.g. HVAC, water) . . .

- Also data verification (dossier) including stability data, validation (process), development batches and bio batches

- Quality control laboratory – specifications, reference standards, methods of analysis, validation and qualification
### Qualification and validation

**In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.**

4.1 In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.

4.2 The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.

4.3 Qualification and validation should establish and provide documentary evidence that:

(a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification or DQ);

4.3 (defined in Annex 15 – not included here)

### India

Validation and Process validation

### China

Validation of manufacturing processes included

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**WHO** | **PICS** | **India** | **China**
---|---|---|---
Qualification and validation | 4. | Validation and Process validation | 20

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**WHO** | **PICS** | **India** | **China**
---|---|---|---
In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled. | 4. | Validation and Process validation | 20

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**WHO** | **PICS** | **India** | **China**
---|---|---|---
The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan. | 4.2 | Validation of manufacturing processes included

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**WHO** | **PICS** | **India** | **China**
---|---|---|---
Qualification and validation should establish and provide documentary evidence that: | 4.3 | Validation of manufacturing processes included

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**WHO** | **PICS** | **India** | **China**
---|---|---|---
(a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification or DQ): | 4.3 (defined in Annex 15 – not included here) | Validation of manufacturing processes included

---

**WHO** | **PICS** | **India** | **China**
---|---|---|---
(defined in Annex 15 – not included here) | Validation of manufacturing processes included

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Inspection of FPP manufacturers

- Highest number of inspections in India
- Followed by China
- Other countries:
  - South Africa
  - USA
  - France, Switzerland,
  - Indonesia,
  - Pakistan, Egypt
Inspections of Contract Research Organizations (CROs)

- **Clinical sites**: Normally over 2 days
- **Started 2004**: Covers all aspects of GCP and GLP
  - Ethical considerations, Protocol, Volunteers etc
- **Data verification**: Identified misrepresentation of data
- **Clinical part**
  - Clinic, Pharmacy and related areas, data verification
- **Bio-analytical part**
  - Laboratory and data verification
- **Statistical analysis**

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Annex 9

Additional guidance for organizations performing in vivo bioequivalence studies

Introduction

1. Scope
2. Glossary
3. Organization and management
4. Computer systems
   Hardware
   Software
   Data management
5. Archive facilities
6. Premises
7. Clinical phase
8. Clinical laboratory
9. Personnel
10. Quality assurance
Inspections of Contract Research Organizations (CROs)

- GCP inspections performed:
  - India (largest number)
  - China
  - Canada
  - South Africa
  - United States...

- About 30 GCP inspections 2004 - 2007

- Several rejected even if assessment report accepted

- WHOPIR – positive outcomes

- NOC – negative outcomes
Inspections of Contract Research Organizations (CROs)

Examples

- Half of the CRFs "missing"
- Source data destroyed accidentally by fire or "monsoon"
- Sponsor claims the data were kept by the CRO, and the CRO claims the data were kept by the sponsor
- All data and retention samples destroyed as the product "expired" – even though the submission is still under evaluation
- Two of the ECGs shown to the inspectors, bearing different subject numbers and initials, were found to be identical.
- Other ECGs bearing different subject numbers and initials appear to have been recorded from a single subject. Out of 95 ECGs copied by the inspectors, 43 appear to have been recorded from the same and single subject during a single session.
CRO - Example reintegration

CROs
Inspections - statistics in 2008 vs 2007

- A total of 52 inspections were carried out in 2008: (45 in 2007) excluding QC labs
  - 27 (26) FPP manufacturers
  - 11 (6) active pharmaceutical ingredient (API) manufacturers
  - 14 (13) contract research organizations (CROs)

In 2008 three inspectors in-house (plus manager)
Three AIDS medicines will be removed from prequalification list this week

04 AUGUST 2004 | GENEVA -- As part of the continuous effort to rigorously monitor the quality of medicines, the World Health Organization (WHO) is carrying out systematic inspections of contract research organizations which have done bioequivalence studies for prequalified medicines, starting with products for priority diseases.

During the most recent inspection a contracted laboratory which had done bioequivalence studies for three AIDS medicines has been found non-compliant with international standards of good clinical and laboratory practices. As a result, the three antiretrovirals, which are manufactured by Ranbaxy, will be removed from the list until such a time as Ranbaxy can submit data of new studies providing unequivocal evidence of the products' bioequivalence with the originator medicines.
Technical assistance...
Technical assistances organized by WHO PQP 2006-2008

- Provision of expert consultants to
  - Manufacturers
  - Quality control laboratories
  - Regulators

- Assistance focuses on
  - GMP, GCP or GLP compliance
  - Regulatory guidance

- Assistance is separated from the assessment / inspections and may be followed by specific trainings
Capacity building

- Assessors - Copenhagen
- Assessors – rotational post
- Inspectors – local DRA
- Inspectors – recipient country

Indirect – local manufacturer and CRO
Training workshops ...

- In Brazil, China, Ghana, India, Indonesia, Iran, Jordan, Morocco, Nicaragua, Pakistan, Tanzania …

- More than 500 participants - staff of regulatory authorities and pharmaceutical manufacturers

- Topics:
  - Development of dossiers for submission
  - Assessment of bioequivalence (interchangeability) of medicines
  - Pharmaceutical Development of Paediatric Formulations
  - GMP, Quality and Bioequivalence of malaria ATC products
  - GMP, Quality and Bioequivalence of RHPs
  - Pharmaceutical Development of Paediatric Formulations
Topics of training workshops
2006-2008

- Prequalification advocacy: 8
- Prequalification requirements: 10
- Good manufacturing practice: 5
- Quality control: 3
- Bioequivalence/BCS and GCP: 3
- Assessment of medicines: 3
- Pharmaceutical development: 4
- PQ general: 2

Legend:
- Prequalification advocacy
- Prequalification requirements
- Good manufacturing practice
- Quality control
- Bioequivalence/BCS and GCP
- Assessment of medicines
- Pharmaceutical development
- PQ general
Participants in trainings organized or supported by PQP

- **2007**
  - Others: 57
  - QCL staff: 103
  - Regulators: 198
  - Manufacturers: 165

- **2008**
  - Others: 68
  - QCL staff: 5
  - Regulators: 301
  - Manufacturers: 263

*Others, QCL staff, Regulators, Manufacturers*
Quality control laboratories...

Prequalified QCLs:
- South Africa, RIIP+CENQAM (2005)
- Algeria, LNCPP (2005)
- South Africa, Adcock Ingram (2007)
- Morocco, LNCM (2008)
- Kenya, NQCL (2008)
- India, Vimta Labs (2008)
- France, CHMP (2008)
- Vietnam, NIDQC (2008)
- Kenya, MEDS (2009)
- Singapore, HSA (2009)
- Singapore, TÜV (2009)
Inspections

![Graph showing total inspections and pre-audits from 2004 to Sep-09.]

- **2004**: 1 Pre-audit, 1 Inspection
- **2005**: 3 Pre-audits, 3 Inspections
- **2006**: 6 Pre-audits, 1 Inspection
- **2007**: 6 Pre-audits, 1 Inspection
- **2008**: 4 Pre-audits, 6 Inspections
- **Sep-09**: 1 Pre-audit, 3 Inspections
Sampling and testing projects in 2008

- **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 antituberculosis medicines (2009)**
  - Eastern Europe - Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, Uzbekistan
  - First- and second-line anti-TB medicines to be collected close to patients
  - 291 samples collected, testing is ongoing

- **General Outcome:**
  - Low failure rates (1.8%) - generally of good quality - no serious failures
  - More than half of the samples were of WHO-prequalified products
Challenges and achievements...

Prequalified priority essential medicines
(July 2009)

- HIV/AIDS: 80
- Tuberculosis: 164
- Malaria: 12
- Reproductive health: 10
- Influenza: 1

Combination
Mono-component
Countries where prequalified medicines are manufactured (July 2009)

- India: 194
- France: 16
- South Africa: 12
- Germany: 11
- Switzerland: 11
- USA: 11
- Canada: 9
- Spain: 9
- Netherlands: 8
- China: 6
- Morocco: 3
- UK: 3
## List of WHO Prequalified Medicinal Products

**5 December 2009**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>251</td>
<td>HIV/AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Tuberculosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Malaria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Reproductive health</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total **300**
Prequalification Programme: Transparency - WHOPIRs and NOCs

- These are published in response to the WHA Resolution WHA57.14 of 22 May 2004, which requested WHO, among other actions:
  - "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;"

- Public Reports
  - WHOPAR
  - WHOPIR

- A Notice of Concern (NOC) is a letter reflecting areas of concern where the non-compliances require urgent attention . . .
Some PQ Outcomes . . .

- Performance monitored - timelines - Donors (Gates, UNITAID)
- Return on investment (170:1 – PWC)
- Positive and negative outcomes published
- Sampling and testing programmes
- Complaints investigated
- Variations monitored
- Ongoing inspections and investigations
- Harmonization, cooperation (e.g. FDA)
- Suspension and withdrawals
- Improved assurance of quality
- Improved access to medicines
Also . . .

- ERP on behalf of Global Fund
- Prequalification of Neglected Tropical diseases
- Procedure for Prequalification of APIs
  - Already adopted, not yet implemented
- Requalification procedure adopted
  - under implementation
- Joint inspection programme with harmonization, recognition, exchange of information to be published soon
- Inspection information (letter) and trends
Estimated number of people receiving antiretroviral therapy, people needing antiretroviral therapy and percentage coverage in low- and middle-income countries according to region, December 2003 to December 2007

<table>
<thead>
<tr>
<th>Geographical region</th>
<th>Estimated number of people receiving antiretroviral therapy, December 2007 (range)</th>
<th>Estimated number of people needing antiretroviral therapy, 2007 (range)</th>
<th>Antiretroviral therapy coverage, December 2007 (range)</th>
<th>Estimated number of people needing antiretroviral therapy, December 2006 (range)</th>
<th>Antiretroviral therapy coverage, December 2006 (range)</th>
<th>Estimated number of people receiving antiretroviral therapy, December 2005 (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>2,120,000[1,625,000–2,315,000]</td>
<td>7,000,000[6,250,000–7,900,000]</td>
<td>30% [27%–34%]</td>
<td>1,375,000[1,280,000–1,470,000]</td>
<td>6,700,000[5,900,000–7,600,000]</td>
<td>21% [18%–23%] [75,000,000–125,000]</td>
</tr>
<tr>
<td>Eastern and southern Africa</td>
<td>1,690,000 [1,560,000–1,820,000]</td>
<td>5,300,000[4,700,000–6,000,000]</td>
<td>32% [28%–38%]</td>
<td>1,115,000[1,050,000–1,180,000]</td>
<td>5,100,000[4,400,000–5,700,000]</td>
<td>22% [20%–25%] [56,000,000–94,000]</td>
</tr>
<tr>
<td>Western and central Africa</td>
<td>430,000[370,000–490,000]</td>
<td>1,700,000[1,400,000–2,100,000]</td>
<td>25% [20%–31%]</td>
<td>260,000[230,000–290,000]</td>
<td>1,600,000[1,400,000–2,100,000]</td>
<td>16% [12%–19%] [19,000,000–31,000]</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>380,000[350,000–430,000]</td>
<td>630,000[550,000–770,000]</td>
<td>62% [51%–70%]</td>
<td>345,000[305,000–385,000]</td>
<td>600,000[510,000–740,000]</td>
<td>58% [47%–68%] [160,000–260,000]</td>
</tr>
<tr>
<td>Latin America</td>
<td>360,000[320,000–400,000]</td>
<td>590,000[490,000–700,000]</td>
<td>64% [51%–73%]</td>
<td>325,000[290,000–360,000]</td>
<td>530,000[450,000–670,000]</td>
<td>61% [49%–72%] [156,000–255,000]</td>
</tr>
<tr>
<td>The Caribbean</td>
<td>30,000[25,000–35,000]</td>
<td>70,000[60,000–80,000]</td>
<td>43% [38%–50%]</td>
<td>20,000[15,000–25,000]</td>
<td>85,000[50,000–75,000]</td>
<td>31% [27%–40%] [3,000–5,000]</td>
</tr>
<tr>
<td>East, South and South-East Asia</td>
<td>420,000[375,000–465,000]</td>
<td>1,700,000[1,300,000–2,100,000]</td>
<td>25% [20%–32%]</td>
<td>260,000[225,000–335,000]</td>
<td>1,600,000[1,220,000–2,060,000]</td>
<td>18% [14%–23%] [82,000–88,000]</td>
</tr>
<tr>
<td>Europe and Central Asia</td>
<td>54,000[51,000–57,000]</td>
<td>320,000[240,000–440,000]</td>
<td>17% [12%–22%]</td>
<td>35,000[33,000–37,000]</td>
<td>260,000[180,000–380,000]</td>
<td>13% [9%–19%] [11,000–19,000]</td>
</tr>
<tr>
<td>North Africa and the Middle East</td>
<td>7,000[6,000–8,000]</td>
<td>100,000[70,000–135,000]</td>
<td>7% [5%–10%]</td>
<td>5,000[4,000–6,000]</td>
<td>97,000[66,000–130,000]</td>
<td>5% [4%–8%] [750,1,550]</td>
</tr>
<tr>
<td>Total</td>
<td>2,990,000[2,700,000–3,200,000]</td>
<td>9,700,000[8,700,000–11,000,000]</td>
<td>31% [27%–34%]</td>
<td>2,040,000[1,850,000–2,230,000]</td>
<td>9,300,000[8,200,000–10,600,000]</td>
<td>22% [19%–25%] [300,000–500,000]</td>
</tr>
</tbody>
</table>

Note: some numbers do not add up due to rounding.

For an explanation of the methods used, see explanatory notes to Annex 1.

Data on children – when available – are included.

The coverage estimate is based on the estimated numbers of people receiving and needing antiretroviral therapy.

Also good news

2003: 400,000
2007: 2,990,000


World Health Organization
Thank you for your attention