Programme update
WHO Prequalification of Diagnostics

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World Health Organization
Contents

- Overview and importance of PQ Dx
- Recent progress
- Facing the challenges
- Future plans
Aim of Prequalification of Diagnostics

- To promote and facilitate access to safe and appropriate diagnostic technologies of good quality in an equitable manner.

- To increase **in-country capacity** to effectively **regulate** and to **monitor** quality in-market.

*Quality diagnostics improve the health of people in low- and middle-income countries.*
Large number of HIV & malaria tests procured

Source: WHO and UNICEF annual procurement data from WHO (GSM) and UNICEF Supply Division. Shows numbers of tests procured from 2005 through to 2010.
The need for PQ Dx

- Changing global market for diagnostics for priority diseases: HIV, TB, malaria
- Production of many diagnostics has moved to countries with less stringent regulations
- Of 193 WHO Member States, fewer than one-third have a regulatory system in place for diagnostics

In response:
A rigorous process to identify diagnostics that meet quality standards, of which product testing is one component
The impact of WHO PQ Dx

- Often the only agency that ensures the quality of diagnostics for priority diseases in LMIC at reduced cost
- Simplifying fair procurement and supply chain management at country level
- Promoting innovation targeted at resource-limited settings
- Improving manufacturers' capacity to produce quality diagnostics of public health importance
- Improving capacity at country level to regulate and monitor the quality of diagnostics on their market
Overview and importance of PQ Dx

Recent progress

Facing the challenges

Future plans
Strong progress was made in 2010

● Strong progress since first dossiers received in June 2010
  – PQ Dx procedures in place & aligned with new international standards
  – Regularly updated status of PQ applications on the web pages
  – Robust PQ Dx pipeline

● Speeding up process without sacrificing quality
  – "Batching" of priority applications for steady dossier throughput;
  – Manufacturing site inspections combined where possible
  – Potential for fast-track procedure reviewed

● Balanced approach to ensure a variety of products
  – Initial focus on HIV and malaria rapid tests
  – Now also HCV tests, HIV viral load, CD4 technologies

● First product prequalified (SD Bioline Malaria Ag P.f) in Dec 2010; more products for 2011
The PQ Dx process

- Submission of application form (*review within 15 days*)
- Signed letter of agreement and fee payment
- Review of product and performance (*screen within 30 days, full review and report approx. 150 days*)
- Assessment of manufacturer’s quality management system (*inspection and report 120 days + scheduling*)
- Laboratory evaluation of operational and performance characteristics of the product by WCC (120 days)
- If a product meets the prequalification requirements, then it can become eligible for inclusion in UN procurement tenders

(1) Target (DLT working days)  (2) WHO Collaborating Centre. WHO Global Malaria Programme coordinated malaria product testing
## PQ Dx applications received

<table>
<thead>
<tr>
<th>Analyte</th>
<th>EIA</th>
<th>Rapid Tests</th>
<th>CD4 Technologies</th>
<th>Virological Technologies</th>
<th>Other</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>HIV</td>
<td>7</td>
<td>37</td>
<td>6</td>
<td>9</td>
<td>4</td>
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<tr>
<td>HIV/HCV</td>
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<td>HCV</td>
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<td>HBV</td>
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<td>N/A</td>
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<tr>
<td>Malaria</td>
<td>2</td>
<td>29</td>
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<tr>
<td>Other</td>
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<td></td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>25</td>
<td>83</td>
<td>6</td>
<td>9</td>
<td>5</td>
<td>128</td>
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</tbody>
</table>

Status as of 28 March 2011, based on analysis of PQ tracking document
Country of manufacture of products submitted

Where are products manufactured?
(applications by country and % of total, total n=132)

- South Korea: 18%
- USA: 15%
- China: 14%
- India: 24%
- France: 7%
- Germany: 4%
- South Africa: 1%
- Japan: 4%
- Hong Kong: 1%
- Canada: 2%
- Russia: 2%
- Israel: 2%
- UK: 3%
- Turkey: 3%
- South Korea: 18%
- USA: 15%
- China: 14%
- India: 24%
- France: 7%
- Germany: 4%
- South Africa: 1%
- Japan: 4%
- Hong Kong: 1%
- Canada: 2%
- Russia: 2%
- Israel: 2%
- UK: 3%
- Turkey: 3%

Based on analysis of PQ Tracking document 30 March 2011

- Four countries account for >70% of all products submitted for PQ Dx
- PQ required for products even from countries with stringent regulatory authorities
Applications:
- First wave of priority applications (24)
  - April - May 2010
- Second wave of priority applications (27)
  - Oct - Nov 2010

Dossiers:
- 29 dossiers received (11 pending)
  - 13 HIV
  - 5 CD4
  - 9 malaria
  - 1 VL
  - 1 HCV
- 29 dossiers screened
  - All required amendments
- 13 dossiers under full assessment
  - 9 completed, 4 under review

Prioritized applications, by type:
- 20 HIV rapid (41%)
- 12 malaria rapid (25%)
- 6 CD4+ (13%)
- 6 HIV VL (13%)
- 3 HIV/HCV rapid (6%)
- 1 other (2%)
A pool of assessors and inspectors is in place

- In 2010, the pool of external experts supporting PQ Dx was expanded to:
  - Facilitate timely review of dossiers
  - Ensure sufficient capacity for manufacturing site inspections

- Dossier assessor pool now 13

- External inspector pool expanded to 14, with 7 more potential inspectors identified (in discussion)
PQ Dx progress: lab evaluations & site inspections

- Inspections of manufacturing sites and lab evaluations are being aligned with dossier assessment.

- Manufacturing site inspections are ongoing
  - Inspections for 16 products conducted
  - 6 additional inspections confirmed
  - Scheduling for 8 products in preparation

- Lab evaluations completed for many malaria products (data from GMP); scheduled for HIV-related products.
PQ Dx progress reflects a range of product types

Prequalification in progress: selected PQ Dx activities

- New dossiers requested
- Dossiers received & screened
- Dossiers under full review
- New inspections scheduled
- Inspections performed
- Inspection reports with manufacturer

- HIV rapids
- Malaria
- CD4
- HCV
- HIV virological tech
- HIV ELISA

Status as of 24 March 2011
CD4 technologies, HIV tests & VL technologies
Pilot countries

- Strengthen regulatory capacity

- Strengthen post-market surveillance of diagnostics
Pilot country achievements

- Burkina Faso, Côte d'Ivoire, South Africa, Tanzania
  - country missions completed
  - SWOT analysis conducted
  - Key partners in countries identified
  - Country action plan
    - Tanzania: completed
    - Burkina Faso & South Africa: under development
    - Côte d'Ivoire & PR China postponed (alternative countries lined up)

- Staff of NRA and NRL participated in capacity building activities
Communication - Advocacy Events

- Manufacturers
  - Several interactions with individual manufacturers & manufacturers associations

- Regulatory Authorities
  - AFFSAPS, FDA, PHAC, PEI, GHTF

- UN Agencies
  - UNDP PSM Workshop, Copenhagen, May 2010
  - Interagency Pharmaceutical Coordination group meetings

- Others
  - Global Fund, procurement agencies, implementers
Tools for stakeholders

- List of prequalified products
  - Information on each product includes product code and manufacturing site

- Updated information on PQ status for individual products
  - List of PQ applications received & status in PQ process
  - Frequently asked Questions
  - diagnostics@who.int

- Communication with stakeholders
  - PQ Dx Update (newsletter) issued quarterly with progress report and hints
Contents

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Key challenges

- Delays due to alignment with new international standards
- Establishing fast-tracking procedures: Regulatory versions of products submitted to WHO differ from those approved by stringent regulatory authorities
- Existing backlog of PQ Dx applications: 1 new hire, batch approach to resolve it
- Poor quality of dossiers & manufacturing sites: Capacity and time required for manufacturers to respond
- Voluntary applications from manufacturers: Outreach to manufacturers
- Comparative data requires testing in a batch: Requires that all products are complete and commercialized (CD4 technologies, Viral load)
- More regular communication to key stakeholders: Communication plan
Progress also depends on manufacturers

Most manufacturers request an extension to submit dossier
- Extension for 37 products (90%)
- Average extension requested was 31 working days (range: 7-140 days)

All dossiers required amendments

Observed variability in quality management systems at the manufacturing sites
- Often more time required to resolve non-conformities noted in the inspection report

Dossier submission extension requested

- Yes: 90%
- No: 10%

Status as of 24 Mar 2011, based on analysis of PQ tracking document
DLT is committed to process improvement

- Increased staff & pool of assessors and inspectors
- Experience gained allows for increased efficiency
- Process tracking to identify areas to streamline
- Fast-tracking procedure in development in collaboration with stringent regulatory authorities (SRAs)
- Are we focussing on the right priorities?
Progress tracking shows reduced processing time

PQ Dx progress tracking: application and dossier assessment

Batch 1, n=24

- LoA invitation
- LoA and payment attestation
- Dossier invitation
- Dossier preparation (incl. extension)
- Dossier admin. processing
- Dossier screen for completeness
- Resolution of issues flagged in screening
- Revised dossier processing

Batch 2, n=28

Where Day 0 = Date of decision to prioritize. * average reflects those in progress
Status as of 30 Mar 2011, based on analysis of PQ tracking document
**Dossier review will be accelerated (fast tracking)**

- Potential to fast track

<table>
<thead>
<tr>
<th>Section of WHO Product Dossier</th>
<th>FDA PMA</th>
<th>FDA 510(K)</th>
<th>EU CE Mark</th>
<th>HC Class IV</th>
<th>HC Class III</th>
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<tr>
<td>5.1. Regulatory versions of this product</td>
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<td>5.2. Product description incl. variants and accessories</td>
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<td>5.3. Essential Principles (EP) checklist</td>
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<td>5.4 Risk analysis and control summary</td>
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<td>6.1. Product design</td>
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<td>6.2. Manufacturing process</td>
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<td>7.1. Analytical studies</td>
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<td>7.2 Stability (claimed shelf-life, in-use, shipping)</td>
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<td>7.3. Software verification and validation</td>
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<td>7.4. Clinical evidence (sensitivity and specificity)</td>
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<td>8.1. Labels</td>
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<td>8.2. Instructions for use</td>
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<td>9.2. Adverse events and field safety corrective actions</td>
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<td>10. Regulatory History</td>
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<td>11.1. Quality manual</td>
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<td>11.2. Quality management system documents</td>
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<td>11.3 Quality management system certificate</td>
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A draft conceptual framework for prioritization is in development.

The aim is to focus prequalification efforts on diagnostics that will optimize impact.

*Draft conceptual framework*

- **Public Health Priorities**
  - Burden of disease
  - Public health benefit of diagnostics: WHO guidelines and recommendations
  - International commitment

- **Priority Product Categories**
  - Prequalified diagnostics per category
  - Procurement volumes (demand)
  - Market impact, infrastructure needs & fit with health system

- **Product-Specific Issues**
  - Innovativeness of product
  - Original manufacturer
  - Performance
  - QMS & reg. status

PQDx
Contents

- Overview and importance of PQ Dx
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The way forward: 2011-2012

- Continue to prequalify additional products
- Improve manufacturers' preparedness for dossier submission & inspections
- Implement "Fast Tracking" procedures
- Finalize and implement the prioritization framework for PQ Dx
- Extend PQ Dx applications for new products of public health value
- Conduct survey of manufacturers & update business plan
- Build further on synergies with other PQ programmes
- Build capacity for regulation and post-market surveillance of diagnostics in countries
Contact us

- Help shape PQ Dx by letting us know what your PQ Dx needs are
  - Which diseases?
  - Which specific products?
  - Suggestions for improvement

- Email diagnostics@who.int


Thank You