WHO Prequalification of Diagnostics

Inspections of Sites of Manufacture
(September 2010 – September 2013)

How and Why?
WHO PQDx Inspections
Are all inspections equal?

New York Times - 1 September 2013

‘Fast and Flawed Inspections of Factories Abroad'

“The auditors are put under greater pressure on speed, and they’re not able to keep up with what’s really going on in……"”

“If it’s a check-the-box inspection, you better have the right boxes to look at…”

“You can never visit facilities often enough to make sure they stay compliant — you’ll never have enough inspectors to do that. What really keeps factories compliant is when workers have a voice and they can speak out when something isn’t right.”’
The EU’s System for regulating medical devices

Now is the time for radical change….
BMJ 2012;345:e7126

'The CE mark certifies that a product meets certain • manufacturing standards and is safe when used as designed. There is no requirement to show benefit or efficacy, and the safety certification does not have to be based on clinical data’.
‘.. notified bodies are private companies that enter into • contracts with manufacturers’.
‘In short, the system is fragmented, privatised, and largely • opaque; safety is dealt with in an unsatisfactory way and efficacy not at all.'
'The notified bodies lie at the heart of the problems with the current system,

 vary widely in quality and diligence,

 lack the capacity to challenge or test the (clinical) data against expert advice.

 their contractual position (with manufacturers) represents a conflict of interest.

 The EU recognises that the current system cannot survive unmodified.....
 ......However, the basic structure and relationships will remain the same.'
USFDA PMA/510k – suitable for all UN Member States?

US-centric tests:
- suitable for US expertise and US population
- clinical evaluation in US
- risk mitigation for resource-limited environments usually limited
- product may be made in US but destined only for outside US do not come under USFDA oversight

WHO PQ programme has found examples of problematic • 510k practices and interpretation of what 510k clearance means
- one not compliant as equivalence not demonstrated – rectified by USFDA; since
- outsourcing of 510k submission Mx do not understand content and do not hold a copy
Prequalification Dx inspections – activities

42 sites visited: September 2010 – September 2013
30 Sites of manufacture of diagnostics inspections
   6 Re-inspections
2 Male Circumcision Devices inspections
Both had ISO 13485 certification; one product prequalified after re-inspection; second product re-inspection scheduled

2 Advisory visits
Initiative of PQDx programme; timely intervention - R&D phase with early stage manufacturing

2 Inspection of sub contractors
However, is responsibility of legal manufacturer

Plus Communication with manufacturers
One on one with manufacturers; workshops; assistance while onsite performing inspection
WHO inspections – what and who

WHO IVD inspections programme has global outlook

- Inspect QMS (ISO 13485, other standards)

AND IMPORTANTLY

- dossier submission data – to confirm is true
- specific product - production line, QC and lot release, focus on outsourcing (sub-contractors)
- end user issues - IFU, stability (transport, in use, to expiry dates), user training, complaints reporting mechanisms etc
- potential for increased productionSCALE up

WITH appropriately qualified and independent inspection team
An Inspection Team

WHO Lead Inspector

3 Invited Inspectors

1 Observer - MSF (CEO)
Qualified Inspectors

**Sourced from**

- Regulatory agencies e.g. ANSM (negotiating with FDA, TGA)
- IVD experts from Public Institutions e.g. PEI, ITM, Australian Public Health, University of Antwerp, Health Canada
- QMS/Production Consultants e.g. currently work for Notified Bodies; formerly TGA, SANAS, FDA, industry; some work also for other agencies e.g. MSF, UNICEF.
- Current pool of 18 inspectors – includes IVD specialists
Countries with Stringent Regulatory Authorities (SRAs) – why go to inspect?

Our experience in the EU, Japan, USA, Canada

- Agency certifications not always reliable
  - USA: company with 510K – subsequently re-investigated by FDA
  - Canada: product ‘new’ as new antigens – Health Canada (and NB) now notified

- Level 5 nonconformities found in areas of
  - managing outsourcing; responsibilities of legal manufacturer
  - unable to confirm performance claims through evidence onsite
  - in use stability, transportation stability (environmental conditions-heat, humidity)
  - end user applicability of IFUs / training materials / skills / language
  - customer feedback mechanisms, recall/advisory notices, complaints
  - Lot release QC
What is a Level 5 (critical) nonconformity in inspection?

Level 5 nonconformity (Ref IMDRF – formerly ‘critical’ NC) must be rectified before PQ granted.

- significant deception/falsification of data and claims regarding the quality and performance of the product e.g. actual site of all of manufacture, batch release data falsified, performance claims misleading or false etc.
- likely to result in a hazardous and injurious situation to the user
- serious noncompliance with international best practice and standards, or with the customer's requirements e.g. leads to high probability of inaccurate test result; ‘systemic’ failure
- A deficiency which has produced, or leads to a significant risk of producing a product which repeatedly fails to fulfill design and performance requirements.
Examples of Level 5 Nonconformities

1. Quality control laboratory without effective quality management system - evidenced by a poorly performing elements of the quality management system e.g. inappropriately qualified staff, poor documentation, poorly controlled reference materials etc.

2. Batch release records with content not at an internationally recognized standard, consistently incomplete or found to be fraudulent; lack of independent quality assurance oversight.

3. Lack of comprehensive identification and traceability from raw materials through production to lots released for sale.

4. Change control/validation grossly inadequate.

5. Multiple examples of fraudulent practice.

*Problem:* test not ‘state of the art’ – can be new or have been on the market for some years.
Level 5 Nonconformities – a real example

#1 lack of compliance with QMS documentation requirements as required in ISO 13485:2003.

#2: inadequate quality assurance and quality control staff to maintain an effective QMS.

#3: lack of adequate control over equipment and inadequate work environment.

#4: product quality requirements were not adequately defined and documented.

#5: inadequate procedures to ensure purchased product conformed to specified purchase requirements.

#6: inadequate documentation and procedures to ensure production was carried out under controlled conditions.

#7: inadequate processes to verify QC of lot release and that the product requirements had been met.
<table>
<thead>
<tr>
<th>Year</th>
<th>Number of inspections</th>
<th>Number of products</th>
<th>1st Re-inspections</th>
<th>2nd Re-inspections</th>
<th>Advisory Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010 (Sept-Dec)</td>
<td>8</td>
<td>14</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2011</td>
<td>10</td>
<td>20</td>
<td>3</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>2012</td>
<td>8</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>2013 (Jan-Sept)</td>
<td>4</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total: 37 months</td>
<td>30</td>
<td>59</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
## Diagnostics Inspected - PQDx Product range

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th># of Mx Total</th>
<th># of Mx 'PQ'd'</th>
<th># Mx not yet</th>
<th># prod Insp</th>
<th># prod PQ’d</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria RDT</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>11</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>HIV VL</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>10</td>
<td>8</td>
<td>2 prods (1Mx) Insp Sept13</td>
</tr>
<tr>
<td>HIV RDT</td>
<td>16</td>
<td>6</td>
<td>9</td>
<td>22</td>
<td>8</td>
<td>1 prod InspSept13</td>
</tr>
<tr>
<td>HIV EIA</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CD4</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>1 Closed</td>
</tr>
<tr>
<td>HCV EIA</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HCV RDT</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HBV EIA</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>HBV RDT</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>30</strong></td>
<td><strong>13</strong></td>
<td><strong>17</strong></td>
<td><strong>59</strong></td>
<td><strong>23</strong></td>
<td><strong>Note: Mx can have more than 1 product type.</strong></td>
</tr>
</tbody>
</table>

(1 withdrawn)
Key findings – nonconformities (NCs)

30 Dx Mx first inspections.
Canada -2, China -4, EU -8, India -5, Israel -1, Japan -1, S Korea -1, USA -7, Russia -1.

- 8 Mx had Levels 1-3 (minor) nonconformities only (EU_2; USA_6)
- 5 Mx had Level 4 (major) nonconformities (EU_3; Jap_1; USA_1)

-----------------------

- 17 Mx had Level 5 nonconformities (rectification required prior to PQ) Canada_2; China_4; EU_2; India_5; Israel_1; S Korea_1; Russia_1; USA_1.

  30% - 5/17 – within SRAs (GHTF - US, HC, TGA, EU and Japan)
  70% - 12/17 - less regulated environments

-----------------------

- Resource utilization: 2 Mx re-inspection after 1 yr – Level 5 nonconformities persisted in both, 1 Mx with 2\textsuperscript{nd} re-inspection (1xLevel 5 NC persisting – soon resolved)
'The (inspection agency) audit reports were considered to be very superficial, appearing to use stock phrases (non-specific) to very briefly describe scope and activities. On each inspection occasion, a single low level nonconformity was found. As this was in significant contrast to the findings of the current WHO inspection as outlined in this report, the ISO 13485 certification was considered to be invalid.'

Note: manufacturers are often surprised by outcome as their trust in the ‘experts’ has been misplaced
Correlation with WHO and other agencies

29/30 Manufacturers had ISO 13485 certification
(One Mx did not, and was not compliant with ISO 13485)

- 38% in agreement at first inspection: 11 (withdrawn:1; still early in PQ process:1)
- 62% not in agreement at first inspection
  - 14% In agreement following WHO corrective action request: 4
  - 48% Not yet in agreement: 14
    - working towards compliance - time needed for Mx to make corrective action / re-inspection scheduling: 12
    - still early in PQ process:1; closed:1

Agencies: BSI, EVPU, ITC, LNE-GMED, LRQA, MDC, SAI, SHI, TUV RH, TUV SUD, UL, URS.
Why these discrepancies with WHO and agencies?

- **Different objectives:** certification relates to QMS only – not looking for effective implementation, accuracy of performance claims etc – *(WHO focus)*
- **Not incisive:** Agency reports had minimal findings. *(WHO inspectors review agency reports – WHO found nonconformities in all areas including basic documentation, production and QC)*
- **Inadequate team and time:**
  - NB/certifying agency inspections are often subcontracted/local with skill level and independence of the auditors unclear *(WHO highly skilled team and independent)*
  - Inspections often very brief sometimes 1-2 inspector days only *(WHO varies 4-16 inspector days)*
- **Contractual arrangement:** between agencies and manufacturer – *(WHO is independent)*
- **CE-mark:** HIV 'stringent' and malaria 'self-declared'.
Lot testing of HIV CE marked IVDs

Re: CE marked products – HIV ('stringent') and malaria ('self-declared').

- Inspections revealed great variability in batch release procedures of HIV kits by notified bodies
  
  **Option 1:** kits sent to third party laboratory e.g. PEI
  
  **Option 2:** manufacturer supplied with panel of 4-5 strongly positive and known results (EIA S/CO results)
  
  **Option 3:** manufacturer creates own panel and sends report to notified body for batch release.

The last two options apply to the majority HIV rapids thus far inspected and indicates the need for high reliance on the competency and ethics of the manufacturer with batch release.
Lots submitted for lab evaluation

Re: Kits submitted for laboratory evaluations: examples of findings onsite

- Two lot numbers submitted to WHO but found onsite the batch records for only one lot i.e. manufacturer had made fraudulent claim.
- No evidence that lot submitted for malaria testing (2008 – Round 1) and Round 2) had been made onsite.
- Multiple changes to malaria product after submission for testing without notification by manufacturer

In addition

- Small lots specifically made for submission for testing is most common finding.
- Long time period between original performance testing and current production output, especially malaria products
From this preliminary data

- No correlation with findings by WHO and identity of NBs or certifying agencies
- Best predictor of QMS compliance for some Mx may be ‘reputation’; for other manufacturers appears to be ‘random’

Comments

- Inspected a wide range of Mx - now have advantage of benchmarking
- Working with local NRAs to build local expertise
- Abbreviated inspections for 15/30 (50%) of inspections; based on experience, inspections even more risk-based in future
- Manufacturers are encouraged to demand more from their certifying/inspection agencies
Advisory visits for Mx and readiness for PQ

- Initiative of WHO PQDx
- With R&D teams, early stage manufacturing
- For innovative or new products
- Advisers with expertise in WHOPQ, QMS, product type, R&D and manufacturing interface
- Expedite entry and progression through PQ process
Advisory visits and 'innovative products'

Experience thus far at advisory visits (and from some inspections) shows gaps between current compliance status, meeting end user needs and international best practice.

Visits can also help with due diligence reporting requirements of funding agencies – skilled team

Discussion regarding the IVD…..

- Meet user's needs in current format? Risk considered (production and use)? Stability studies appropriate? Verification and validation studies? Ruggedness of IVD? Content of IFU?
Challenges for inspections - communication

Major challenge for inspections (and WHO PQ programme)

Question 1:

- How many products are prequalified? How long is the list of products of good quality?

Questions 2 and 3: need to be asked

- What poor-quality issues are being found that preclude prequalification in the near future?
- When will manufacturers be able to fix these problems?
Practical Challenges for inspections

- **Scheduling** - abbreviated inspections implemented (50%) but several sites with regulatory approvals / certification found to be very poorly performing

- **Outsourcing of Mx (OEM)** - legal manufacturer must be inspected, but production often occurs in another country (increasingly China) with poor sub-contractor/key supplier control being high risk

- Managing manufacturers with **deceptive practices**

- **Re-inspections** are required for sites with Level 5 nonconformities – resources

- **Assistance** to very poorly performing manufacturers that may already have significant market share - resources

- PQDx for **other IVDs** e.g. hepatitis, syphilis, NTDs, NCDs,
Inspections: what went well, what next

Need to
- Close out / postpone poorly performing applicants early in process; determine consequences for fabrication of information
- Limit re-inspections to 'prioritized' manufacturers only
- Cover more product types
- Increase communication/workshops/advisory visits – reach more manufacturers

Continue to
- Collaborate with stringent NRAs, NBs and other agencies
- Work with local National Regulatory Authorities (NRAs)
- WHO oversight but use external experts; detailed reports (not 'tick box') and continue with onsite then final report format
- Provide advisory visits, including for innovative products
- Use inspections to assist manufacturers towards PQ compliance
WHO inspections – take home message

- **Opportunity for improvement** in the global market regarding ISO 13485 certification, SRAs, and countries with regulation in development.

- Many problems revealed but **making progress** in improving quality of diagnostics already in the market. Many manufacturers and other stakeholders see ‘added value’ and quality improvement as a result of PQ.

- **Assist innovative products** with public health benefit to reach the market and be of assured quality.

- **Future inspections?**
  - Majority of compliant Mx so far were CD4, VL, HIV and from SRA.
  - These manufacturers will now require less oversight with new products
  - Expert Review Panel (ERP) is an option for products in high demand for public health benefit but not yet reaching PQ compliance.
  - In future, focus may be on rapid and other tests from less regulated environments

- **Experience to date suggests that on site inspections will continue to meet the challenges and rewards in the pursuit of quality of diagnostics.**
Quality has some associated costs.....

Balance this with test design and with procurement and pricing...
Questions ?