# WHO Prequalification of Diagnostics, quality assurance, and procurement

**Advanced Course on TB Diagnostics**
**8-12 July 2013, Montreal**

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World Health Organization

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- **Overview of WHO Prequalification of Diagnostics**
- Other WHO approval mechanisms
- Product selection
- Procurement of diagnostics and related items
- Quality management systems

# Regulation of diagnostics (IVDs)

- Regulation, specifically for diagnostics, is often poorly implemented and/or enforced
- Different categories of IVDs regulated with differing stringency depending on the **risk related** to their use within the regulator's jurisdiction
  - IVDs for HIV screening/diagnosis attract greatest stringency
  - Perception of risk is different in different settings, e.g. malaria
- Procurement policies of global partners drive supply of quality assured products
  - often acting as de facto regulatory control

# Who sets international standards?

| Organization | |
|---|---|
| International Organization for Standardization (ISO) | Certification of ISO compliance is made by an independent (inspectorate) agency. |
| Global Harmonization Task Force (GHTF) | Comprised of national regulators & industry.<br>Issues guidance on specific topics related to medical devices including IVDs. |
| International Medical Device Regulators Forum (IMDRF) - replaced GHTF | Comprised of national regulators.<br>Maintains GHTF guidance documents. |
| Clinical and Laboratory Standards Institute (CLSI) | Issues guidance documents specific for testing processes. |

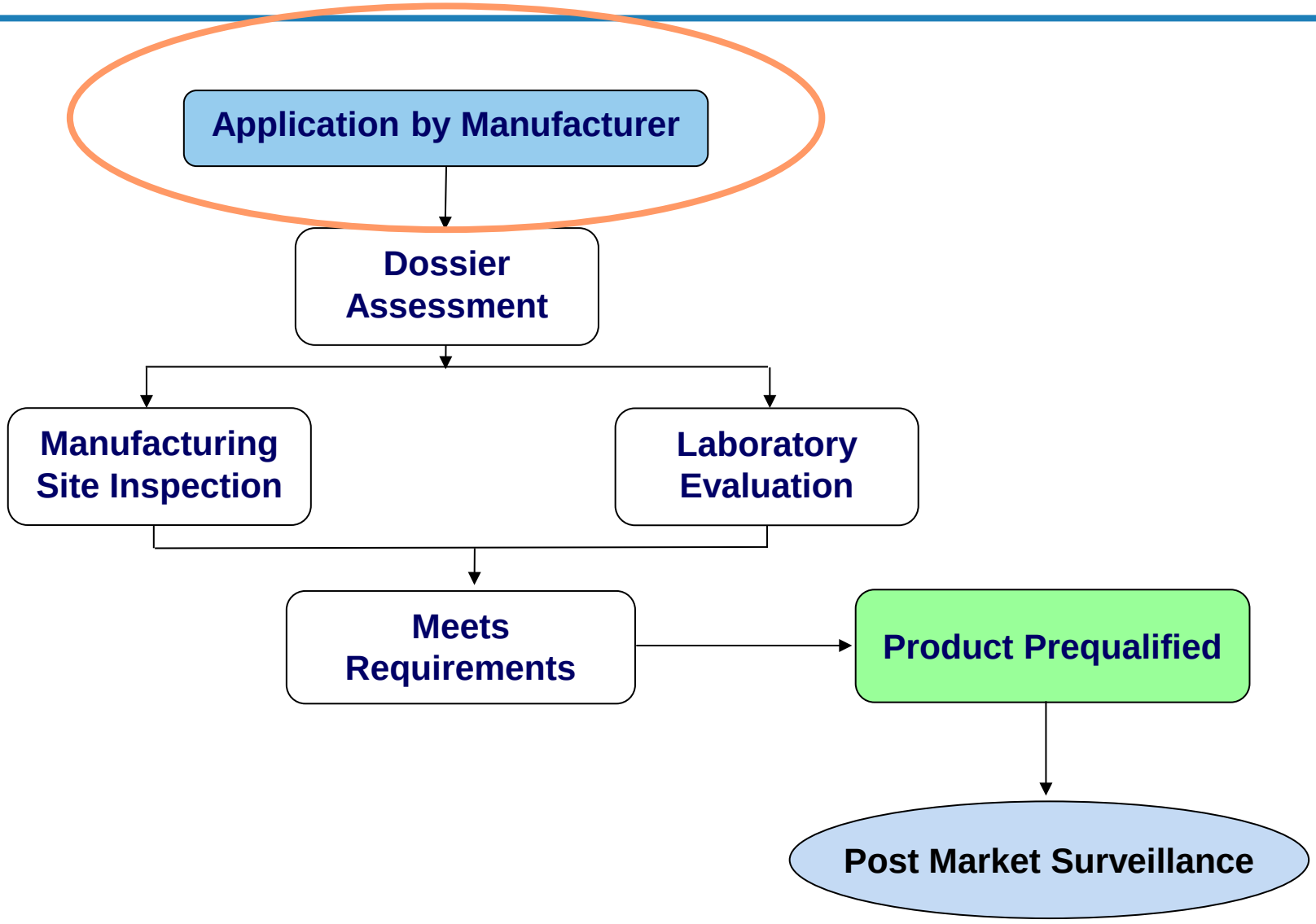
# Role of WHO

- To provide normative guidance to WHO Member States on when and how to use IVDs to guide clinical decision-making
  - 2013 WHO consolidated ART guidelines, e.g. CD4 for ART initiation, VL for ART monitoring
- To provide recommendations on quality and performance of IVDs through the WHO Prequalification of Diagnostics programme, assessed according to international standards
- To increase in-country capacity to effectively regulate & to monitor quality of diagnostics in their market

# Aim of WHO Prequalification of Diagnostics

- To promote and facilitate access to safe & appropriate diagnostic technologies of good quality in an equitable manner
  - Through adoption of GHTF/IMDRF guidance and ISO requirements
- Customers
  - WHO Member States
  - UN agencies
  - Funding and procurement agencies

# Prequalification of Diagnostics



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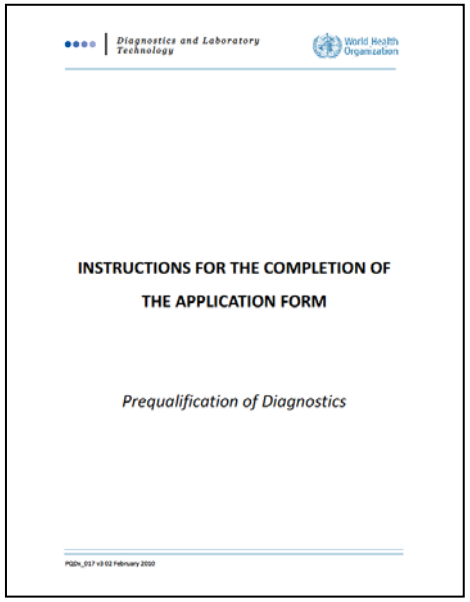
# Application: prioritization criteria

| Current prioritization criterion | Comment |
|---|---|
| Already listed on WHO/UN procurement scheme and procured by UN organizations in significant levels | Ensure continuity of supply and quality of products procured |
| Assist diagnosis of infection with HIV-1/HIV-2, or malaria | Focus on priority disease areas – historically highest procurement |
| Rapid test format (or for use at point-of-care) | Bringing testing closer to the community |
| Original product manufacturers | Ensure known supply chain; no duplication of effort, best possible prices. But re-branders are a large proportion of suppliers. |
| Few other prequalified products exist in the product category such as CD4, viral load | Focus on unmet market / procurement needs |

# Application: requirements

Relevant WHO documents:

1. Prequalification of diagnostics application form
2. Instructions for the completion of the application form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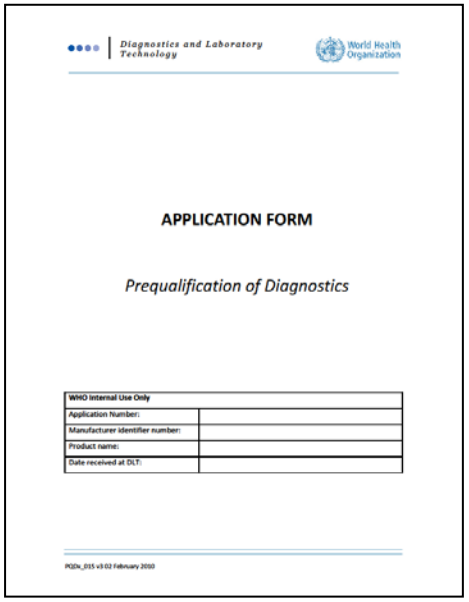
INSTRUCTIONS FOR THE COMPLETION OF THE APPLICATION FORM

*Prequalification of Diagnostics*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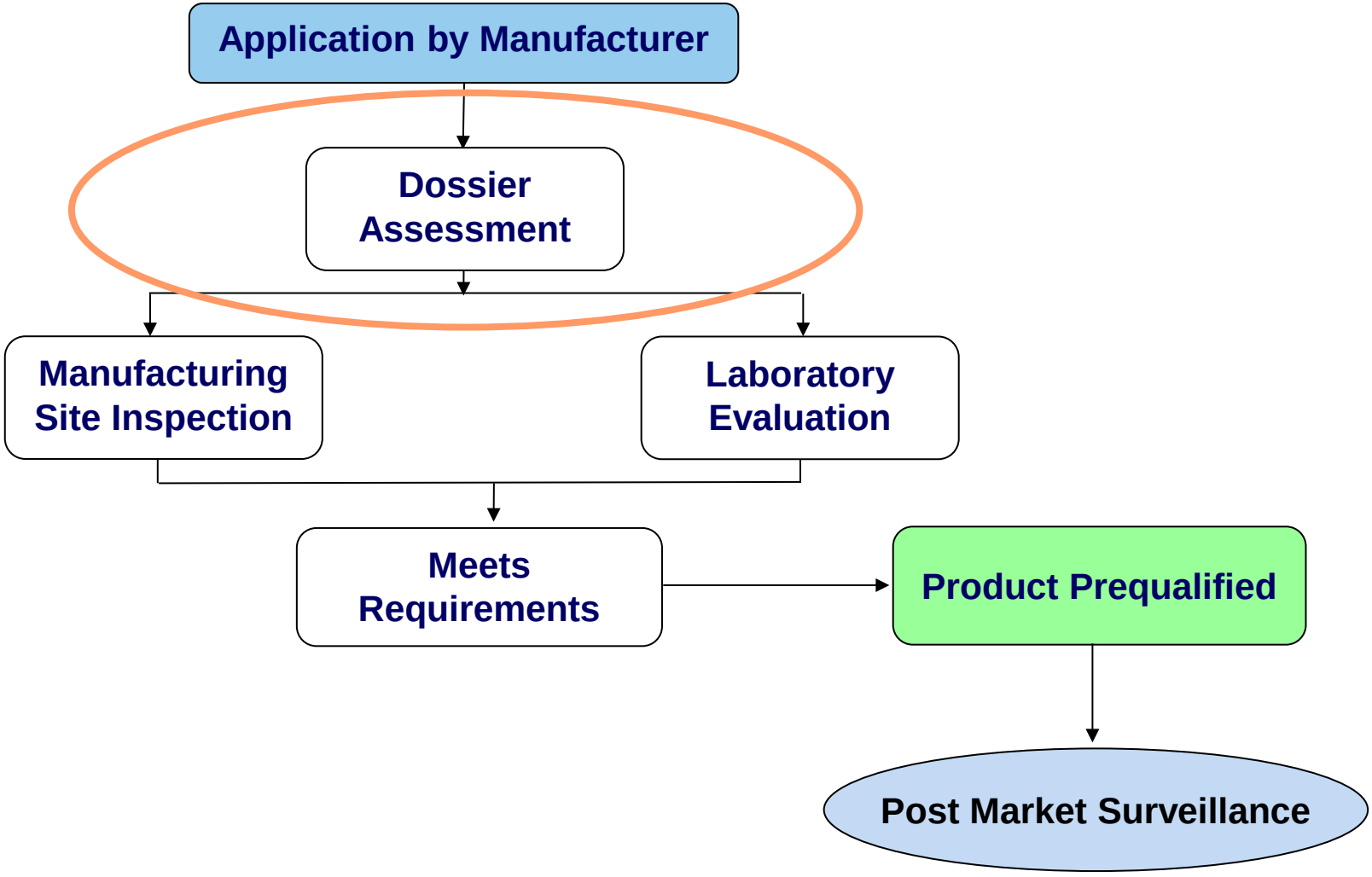
APPLICATION FORM

*Prequalification of Diagnostics*

| WHO Internal Use Only | |
|---|---|
| Application Number: | |
| Manufacturer identifier number: | |
| Product name: | |
| Date received at DLT: | |

- Common issues
  - Poor information and/or wording in the instructions for use (IFU)
    - GHTF/SG1/N43:2005 Labelling for Medical Devices criteria is applied
  - Differences between regulatory versions often unclear, e.g. different QC lot release procedures, different labelling/packaging, etc.

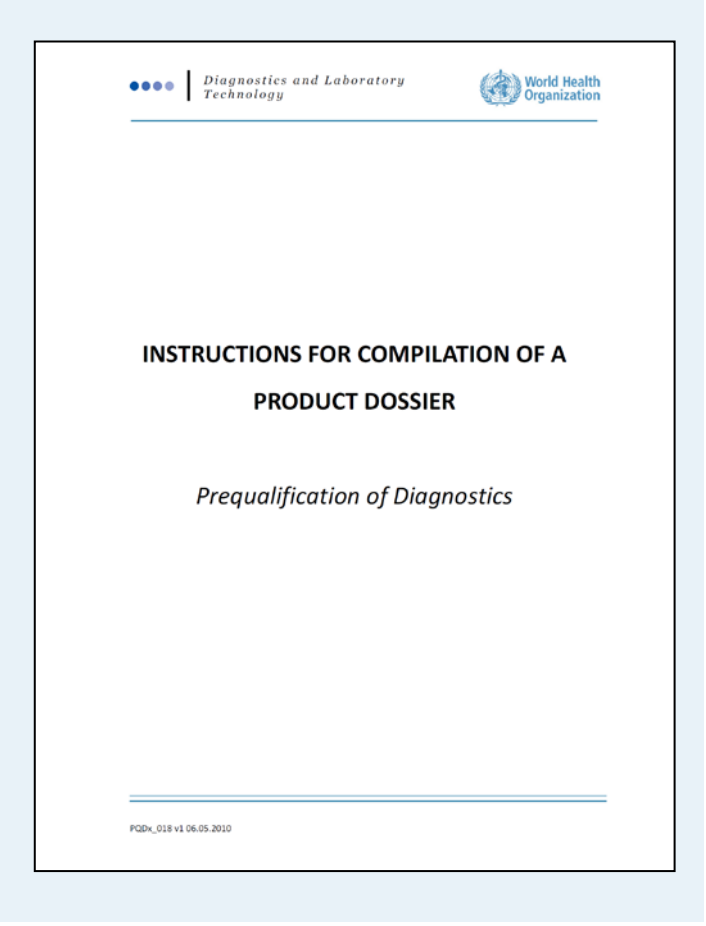
# Prequalification of Diagnostics



# Dossier: requirements

- Dossier must demonstrate that the IVD conforms to the Essential Principles of Safety and Performance of Medical Devices (GHTF/SG1/N41R9:2005)

| Key Components |
| --- |
| Product description |
| Design and manufacturing information |
| Product performance specifications & associated validation and verification studies |
| Labelling |
| Commercial history |
| Regulatory history |
| Quality management system |



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# Dossier: submission

- Analytical studies
  - Different specimen types, e.g. venous vs. capillary whole blood
  - Accuracy and trueness of measurement
  - Precision of measurement
    - Repeatability and reproducibility
  - Analytical sensitivity
  - Analytical specificity
    - Interfering substances, concomitant infections
  - Measuring range, validation of assay cut-off
  - Stability
    - Shipping stability, claimed shelf life, in-use stability,

# Dossier: submission

- Clinical evidence to validate performance claims (STARD)
  - One clinical evaluation* performed by Manufacturer
  - One clinical evaluation* performed independently
    - Must clearly relate to the product undergoing prequalification (same name, same product code, same regulatory version)

| Performance characteristics |
|---|
| Clinical (diagnostic sensitivity) including seroconversion sensitivity |
| Clinical (diagnostic) specificity |
| Positive and negative predictive values (high/low prevalence) |
| Specimens from different clinical stages |
| Specimens of geographical distribution (consider the setting of intended use) |
| Genotypic differences |

*For IVDs that are List A of Annex II of Directive 98/79/EC, the EC Common Technical Specifications (CTS) for IVDs 2009 are used as a guide

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:039:0034:0049:EN:PDF

# Useful ISO references

| Relevant ISO standards | |
|---|---|
| ISO 13485:2003 | Medical devices - Quality management systems - Requirements for regulatory purposes |
| ISO/TR 10013:2001 | Guidelines for quality management system documentation |
| ISO 14971:2007 | Medical devices - Application of risk management to medical devices |
| ISO 17511:2003 | In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials |
| ISO 14155:2003 parts I and II | Clinical investigation of medical devices for human subjects |
| ISO 23640:2011 | In vitro diagnostic medical devices - Evaluation of stability of in vitro diagnostic reagents |

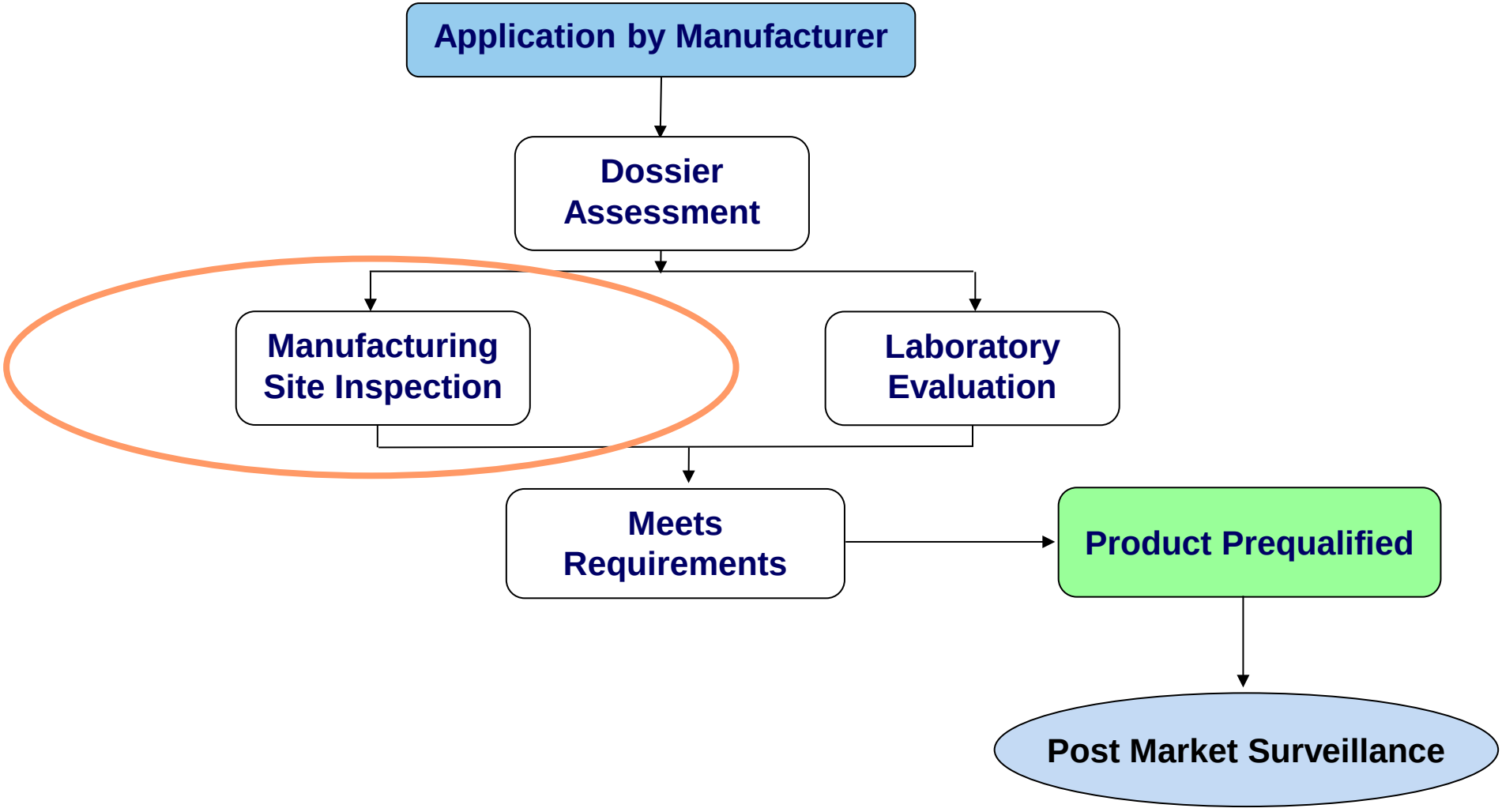
# Useful GHTF references

| Relevant GHTF guidance | |
|---|---|
| GHTF/SG1-N63:2011 | Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices |
| GHTF/SG1/N41R9:2005 | Essential Principles of Safety and Performance of Medical Devices |
| GHTF/SG1/N70:2011 | Labelling for Medical Devices |
| GHTF/SG2-N54R8:2006 | Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices |
| GHTF/SG2-N57R8:2006 | Medical Devices Post Market Surveillance: Content of Field Safety Notices |

# Useful CSLI references

| Relevant CSLI Standards | |
|---|---|
| EP07-02 | Interfering testing in clinical chemistry, 2nd edition |
| EP25-A | Evaluation of Stability of IVDs |
| EP5-A2 | Evaluation of Precision Performance of Quantitative Measurement Methods, 2nd edition |

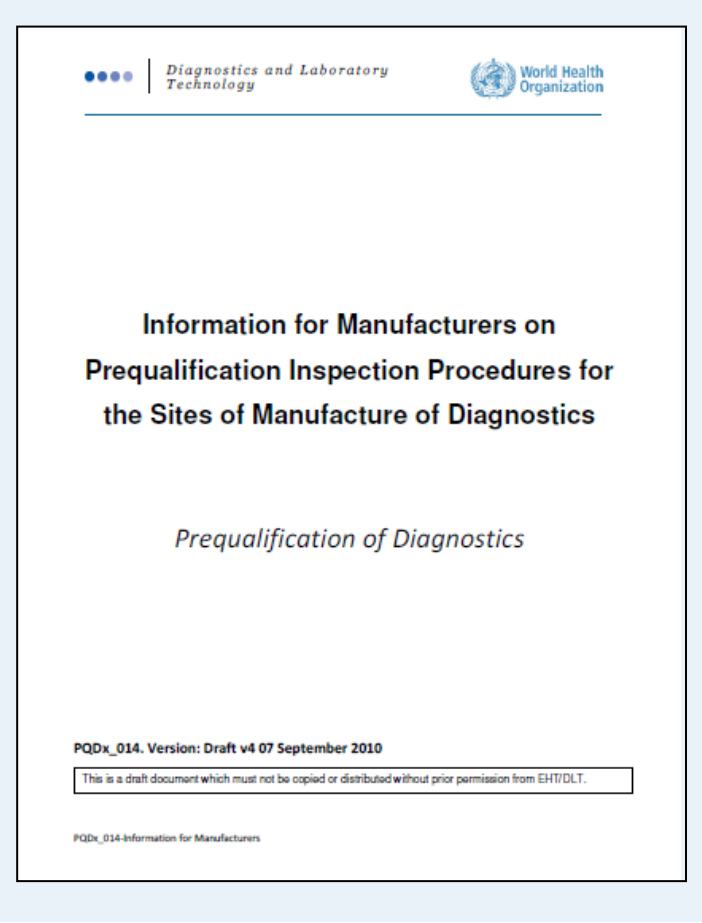
# Prequalification of Diagnostics



# Inspection: requirements

- The manufacturer must demonstrate that the IVD is produced under a functional quality management system e.g. conforms to ISO 13485:2003

| Key Components |
| --- |
| **Quality management system** including documentation requirements |
| **Management responsibility** including customer focus, quality policy |
| **Resource management** including human resources, work environment |
| **Product realization** including production and service provision, control of monitoring and measuring devices |
| **Measurement, analysis and improvement** including control of nonconforming product, improvement |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Information for Manufacturers on Prequalification Inspection Procedures for the Sites of Manufacture of Diagnostics

*Prequalification of Diagnostics*

PQDx_014. Version: Draft v4 07 September 2010

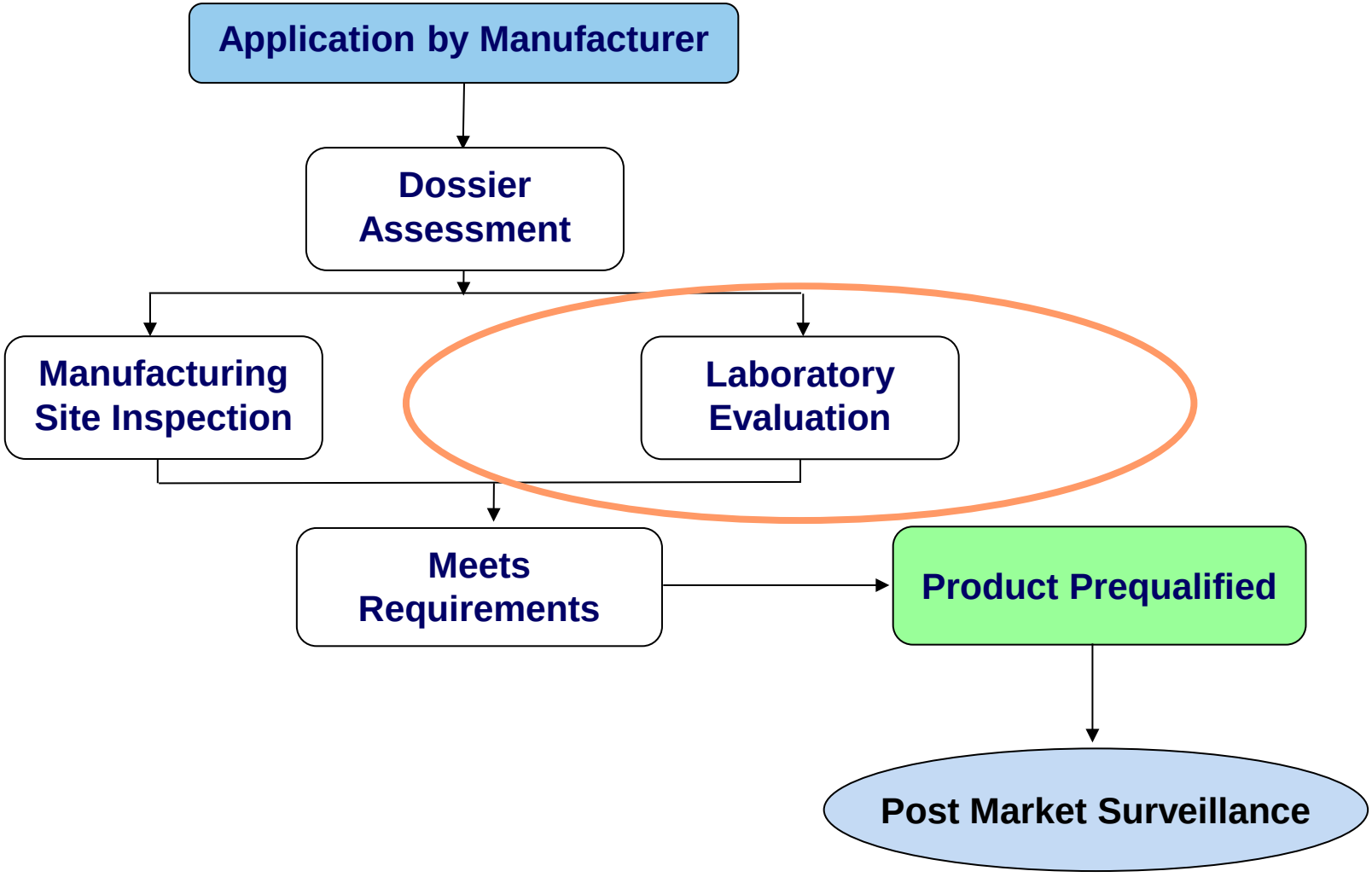
This is a draft document which must not be copied or distributed without prior permission from EHT/DLT.

PQDx_014-Information for Manufacturers

# Inspection: requirements

- Product-specific audit to confirm dossier submission is true
- QC and lot release
  - QC lot release panels must be challenging enough to detect failure, trends, drift
  - Independent and adequately staffed QA/QC department
  - Deviation reporting procedures observed
- WHO related/end user issues
  - Instructions for use
  - Stability (transport, in-use, expiry dates)
  - Training
  - Management of suppliers and agents/distributors
  - Complaints reporting mechanisms

# Prequalification of Diagnostics



# HIV serology laboratory evaluation

| Performance characteristics | Specimens |
|---|---|
| Sensitivity<br>Specificity | WHO specimen reference panel of clinical specimens |
| Inter-reader variability | WHO specimen reference panel of clinical specimens |
| Invalid rate | WHO specimen reference panel of clinical specimens |
| Lot to lot variability | 2-fold dilutions of clinical specimens |
| Seroconversion sensitivity | Commercial seroconversion panels |
| Analytical sensitivity | Commercial mixed titer panel<br>Commercial HIV-1 p24 antigen panel |

# Performance acceptance criteria - serology

| EIA (Laboratory) | RDT (Point of Care or Laboratory) |
|---|---|
| **HIV serology** | |
| Sensitivity: 100%<br>Specificity: ≥ 98% | Sensitivity ≥ 99%<br>Specificity ≥ 98%<br>Inter-reader variability ≤5%<br>Invalid rate ≤5% |
| **HCV serology** | |
| Sensitivity: 100%<br>Specificity: ≥ 98% | Sensitivity ≥ 98%<br>Specificity ≥ 97%<br>Inter-reader variability ≤5%<br>Invalid rate ≤5% |
| **HBsAg serology** | |
| Sensitivity: 100%<br>Specificity: ≥ 98% | Sensitivity 100%<br>Specificity ≥ 98%<br>Inter-reader variability ≤5%<br>Invalid rate ≤5% |

# Performance acceptance criteria- CD4

| Laboratory (conventional instruments) | Point-of-care (dedicated cytometers) |
|---|---|
| **Intra-assay variability (CoV) same specimen, same instrument, same day** | |
| <15% at 200 cells/µl<br><10% at 350 and at 500 cells/µl | <20% at 200 cells/µl<br><15% at 350 and at 500 cells/µl |
| **Inter-instrument variability (CoV) same specimen, same day, different instruments** | |
| <15% at 200 cells/µl<br><10% at 350 and at 500 cells/µl | <20% at 200 cells/µl<br><15% at 350 and at 500 cells/µl |
| **Inter-assay variability (CoV) same specimen, same instrument, different days** | |
| <15% at 200 cells/µl<br><10% at 350 and at 500 cells/µl | <20% at 200 cells/µl<br><15% at 350 and at 500 cells/µl |
| **Carryover** | |
| <2% | N/A |

Note: differences between venous vs. capillary whole blood should be characterised

Taken from draft meeting report of WHO technical advisory group meeting on performance and quality criteria of POC CD4 technologies, May 2013

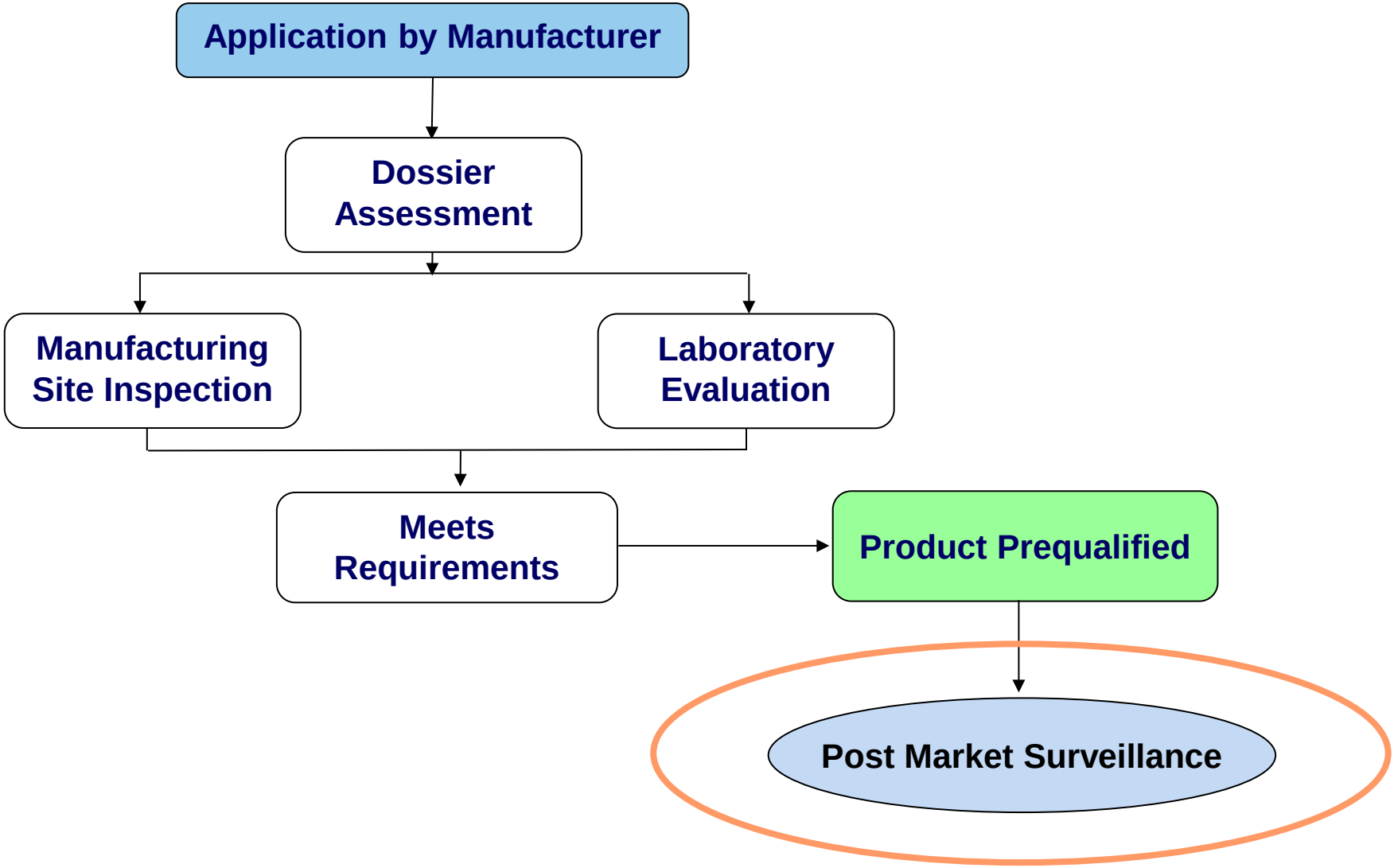
# Performance acceptance criteria- CD4

| Point-of-care technologies |
| --- |
| **Accuracy, if quantitative, compared to the reference method** |
| Standard deviation of 40 cells at <200 cells/µl<br>Standard deviation of 50 cells at 200 - 500 cells/µl<br>Standard deviation of 75 cells at >500 cells/µl |
| **Misclassification, if qualitative, compared to the reference method** |
| Sensitivity ≥90%<br>Specificity ≥90% |

Note: overestimation could be permitted, but underestimation will affect decision to initiate ART

Taken from draft meeting report of WHO technical advisory group meeting on performance and quality criteria of POC CD4 technologies, May 2013

# Prequalification of Diagnostics



# Post-market surveillance

- WHO complaint form for end users to report issues
  - some problems may relate to the manufacture or design of the devices, other problems may be user-related
- Manufacturers obliged to perform PMS and to respond to complaints
  - GHTF/SG2-N54R8:2006
    - Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices
  - GHTF/SG2-N57R8:2006
    - Medical Devices Post Market Surveillance: Content of Field Safety Notices

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# Other WHO approval mechanisms: TB

- Strategic and Technical Advisory Group for Tuberculosis (STAG-TB)
  - gives technical advice to WHO on proposed recommendations such as endorsement for certain categories of TB diagnostics
- An Expert Group will meet to assess evidence for adoption or otherwise of a product for an intended use
  - E.g. WHO Expert Group on automated nucleic acid amplification technology for simultaneous and rapid detection of tuberculosis and rifampicin resistance: Xpert MTB/Rif system *and* WHO Expert Group on commercial serodiagnostic tests for diagnosis of tuberculosis

# STAG-TB Recommendations

- The Expert Group reviews performance evaluation data (both published and unpublished), often as a systematic review, according to the GRADE criteria (strong/ conditional recommendations, high/low quality evidence)
  - http://www.gradeworkinggroup.org/index.htm
- The meeting report of the Expert Group is presented to the STAG-TB for their consideration
- This approach does not assess the quality management system used to manufacture the diagnostic i.e. no inspection or dossier assessment
  - Has been used for product categories that are currently poorly regulated compared to HIV

# WHO endorsement: TB diagnostics

- WHO endorsement of Xpert MTB/RIF assay on the GenXpert platform
  - For automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance
- FIND, collaborated with the University of Medicine and Dentistry of New Jersey and the manufacturer (Cehphid, Inc.) to develop and validate the assay
  - FIND coordinated the analytical studies, clinical validation studies, and field demonstration studies submitted to the Expert Group, other published and unpublished data was also reviewed

# WHO endorsement: TB diagnostics

- The WHO evidence synthesis process confirmed a solid evidence base to support widespread use of Xpert MTB-RIF for detection of TB and rifampicin resistance as replacement or add-on
- Recently, STAG-TB updated these recommendations for other intended uses
- Tip - WHO Guideline Review Committee
  - low quality evidence ≠ strong recommendation

# Differences between WHO endorsement and WHO prequalification

- Unique and previously unmet need was fulfilled by the rapid introduction of Xpert MTB/RIF
  - Better to bring quickly to market and iron out implementation issues later
  - Initially, high cost has prohibited quicker roll-out, but recent reduced pricing
- HIV market is more established, with more interested parties
  - Numerous RDT manufacturers
  - But fewer POC CD4 and viral load manufacturers
- WHO guidelines already prescribe use of CD and VL

# Differences between WHO endorsement and WHO prequalification

- Endorsement relies on review of published literature and clinical trials, with no inspection of quality management system
- Prequalification relies on the regulatory approach adopted by GHTF/IMDRF (through national regulatory authorities)
- Similar issues for HIV and for TB products that are specifically developed for low and middle income countries
  - Poor/ad-hoc/inadequate regulatory review prior to market entry by national authorities
  - Best approach?  Probably not one size fits all
  - Evolve as more suppliers enter the market (streamline)

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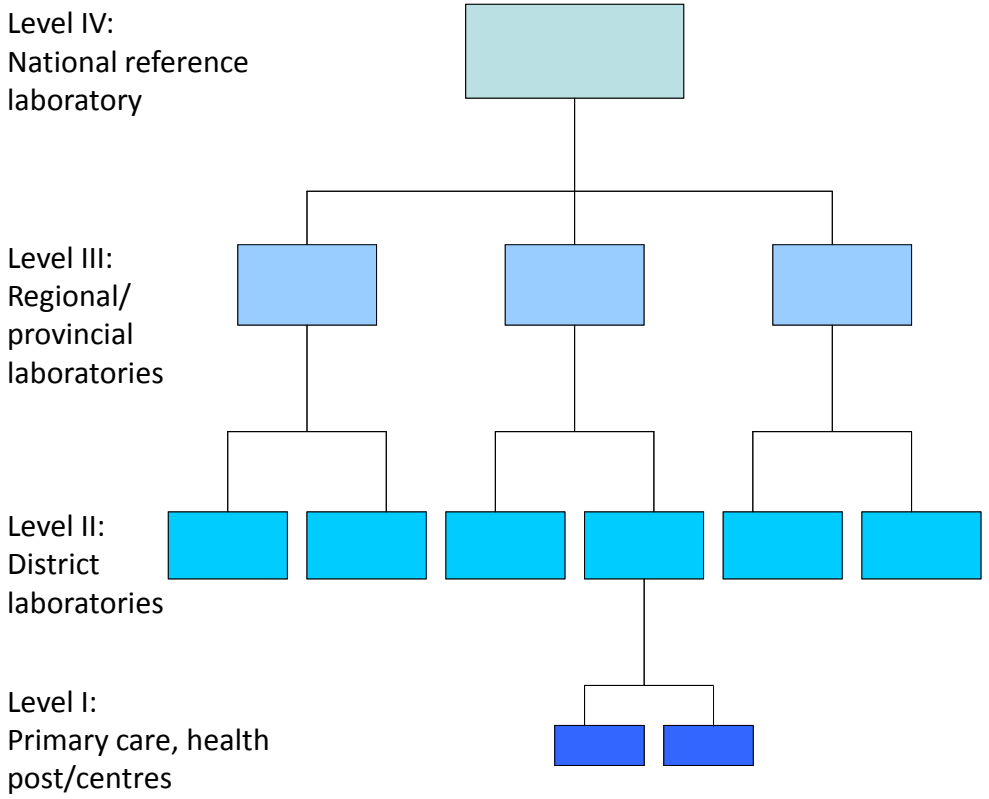
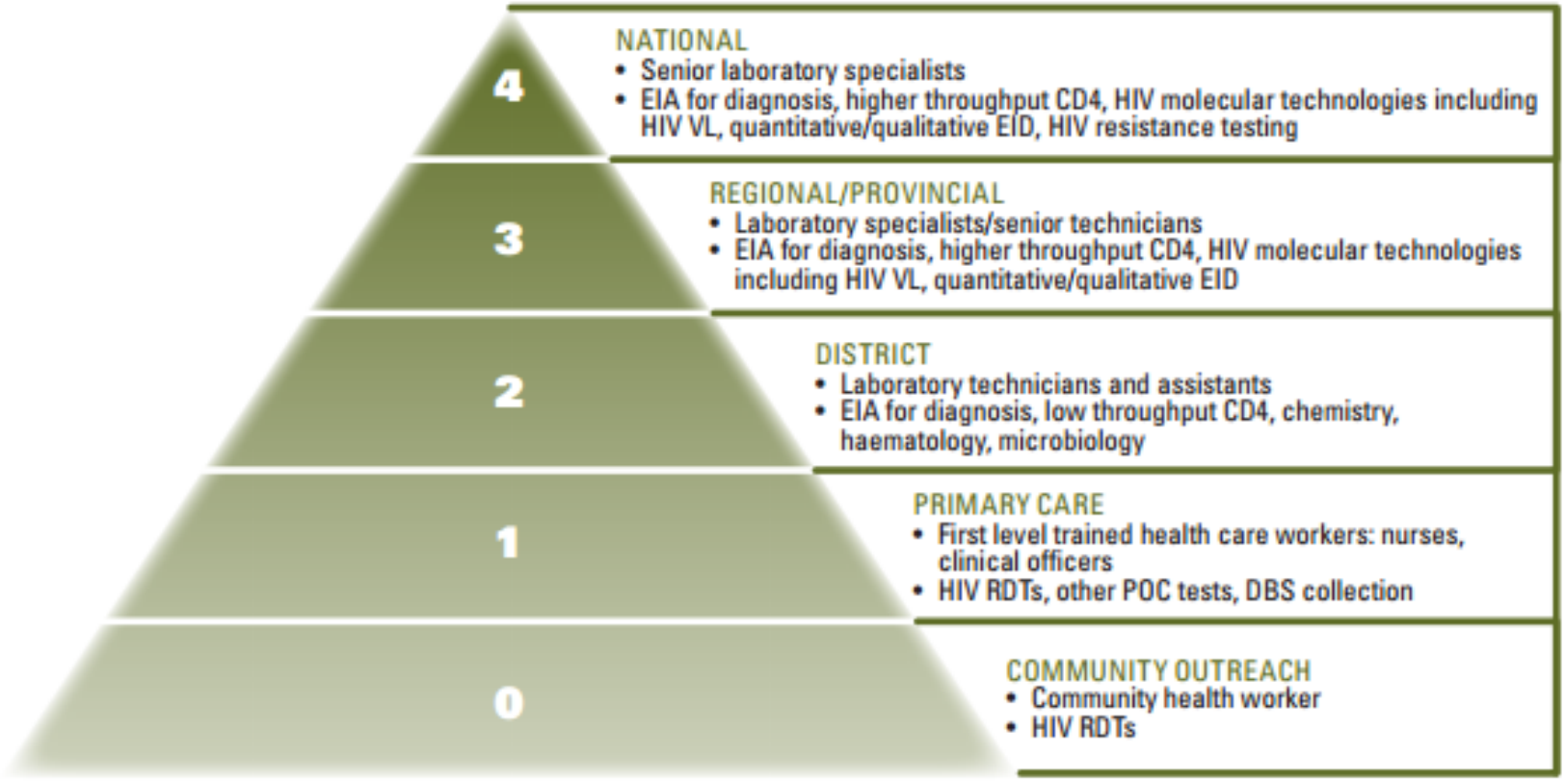
# Product selection and deployment

- Which technology and where
  - Based on performance & operational characteristics
  - Trade-offs may need to be made
- Different technologies for different levels of the health systems
  - Depending on the needs (through-put) and available resources (financial/human)



# Product selection and deployment cont'd

**FIGURE 1. THE TIERED, INTEGRATED LABORATORY NETWORK, WITH EXAMPLES OF STAFF TYPICALLY FOUND AND TESTS THAT COULD BE PERFORMED AT EACH LEVEL**




**WHO Expert Meeting Report on Short, Medium, and Longer Term HIV Product Development Priorities in HIV-Related Diagnostics, 6-7 June 212**

# Product selection and deployment cont'd

- Select testing strategy for an intended use/purpose
- Use list of prequalified and/or registered diagnostics
- Validation of national testing algorithms by populating a strategies with specific products
  - Streamlines procurement, bigger impact of QA and training efforts
- If product is well validated, repeating of diagnostic accuracy studies at national level, beyond regulatory assessment, is usually not required/cost-effective
- Instead, focus on implementation research studies

# Product selection and deployment cont'd

- At programme level – planning, coordinating partners
- Assess testing facilities available and their needs
  - Required through-put required at the testing facility
    - High/low patient volume facilities, high/low throughput technologies
  - Opening hours of facility
  - Number of staff
  - Other services required during the same visit to facility
- Are more people likely to visit a facility, if POC technologies become available?

# Product selection and deployment cont'd

- Key aspects of diagnostics
  - Performance characteristics
    - Serology (sensitivity, specificity, lot-to-lot variability, inter-reader variability) CD4 /VL/EID (repeatability, reproducibility, LoD, accuracy)
  - Operational characteristics
    - Specimen type and volume required
    - Specimen preparation and precision required
    - Stability of specimen once collected into device/cartridge
    - Time to result
    - Random access capability
- Other factors
  - Storage/stability of reagents, life span of instrument, data capture, quality control

# Operational characteristics

- Characteristics of the technology (equipment/instrument)
  - Including through-put, time to result, parameters available, power source, portability
- Characteristics of the reagents
  - Including stability/shelf life for storage and in-use stability
- Specimen preparation
  - Including specimen type & volume, number of steps, precision of measurement, specimen stability after application to device

# Operational characteristics cont'd

- Quality assurance
  - Including internal QC (software and instrument), external QC specimens, compatibility with known EQA schemes
- Regulatory, cost & other operational aspects
  - Including national registration, cost of instrument and/or reagents, connectivity & data management, maintenance, training, technical support

# Information sources

- WHO Prequalification of Diagnostics Public Reports for each individual product
  - http://www.who.int/diagnostics_laboratory/evaluations/PQ_list/en/index.html
- WHO composite comparative report of performance and operational characteristics – *coming soon for CD4*
  - http://www.who.int/diagnostics_laboratory/publications/evaluations/en/index.html
- Methodology developed by Lehe et al., 2012, Evaluating operational specifications of point-of-care diagnostic tests: a standardised scorecard

# Ensuring readiness of the testing services

- Re-organising service delivery
  - Clinic design and workflow
  - Clinic operations, including longer operating hours
  - Additional staffing required
    - Task shifting away from laboratory staff to nurses/ART initiators, etc.
- National programmes will need to re-budget, re-plan procurement, re-allocate resources and staff, re-train new cadres of staff

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# Procurement of diagnostics

- General guidance for procurement officers who are unfamiliar with diagnostics
- http://www.who.int/diagnostics_laboratory/procurement/en/

# Procurement of diagnostics

- Planning phase
  - Needs assessment
  - Procurement planning
  - Quantification
- Implementation phase
  - Technical and commercial specifications
  - Bidding (solicitation, evaluation, award)
- Monitoring and evaluation phase
  - Supplier evaluation
  - Post-market surveillance

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# QMS: challenges to quality of testing

- Test procedure not observed
  - Specimen not taken correctly (fingerprick, serum/plasma, OF)
  - Incorrect buffer volumes added
  - Incorrect specimen transfer pipette used
  - Precision pipettes not available when required
  - Recommended reading times not observed
  - Recommended endpoint stability not observed
- Why?
  - Busy health services
  - Untrained or poorly trained users
  - Short cuts are easier!

# QMS: challenges to quality of testing

- SEAD study in South African HIV VCT sites
- Overall process compliance for 27 distinct testing 'steps' was 3.4%
  - rural better than urban, high through-put better than low throughput
- Median test incubation time was 5 minutes
  - Alere Determine HIV-1/2 should incubate for 15 minutes
- Absence of test buffer in 35% testing events

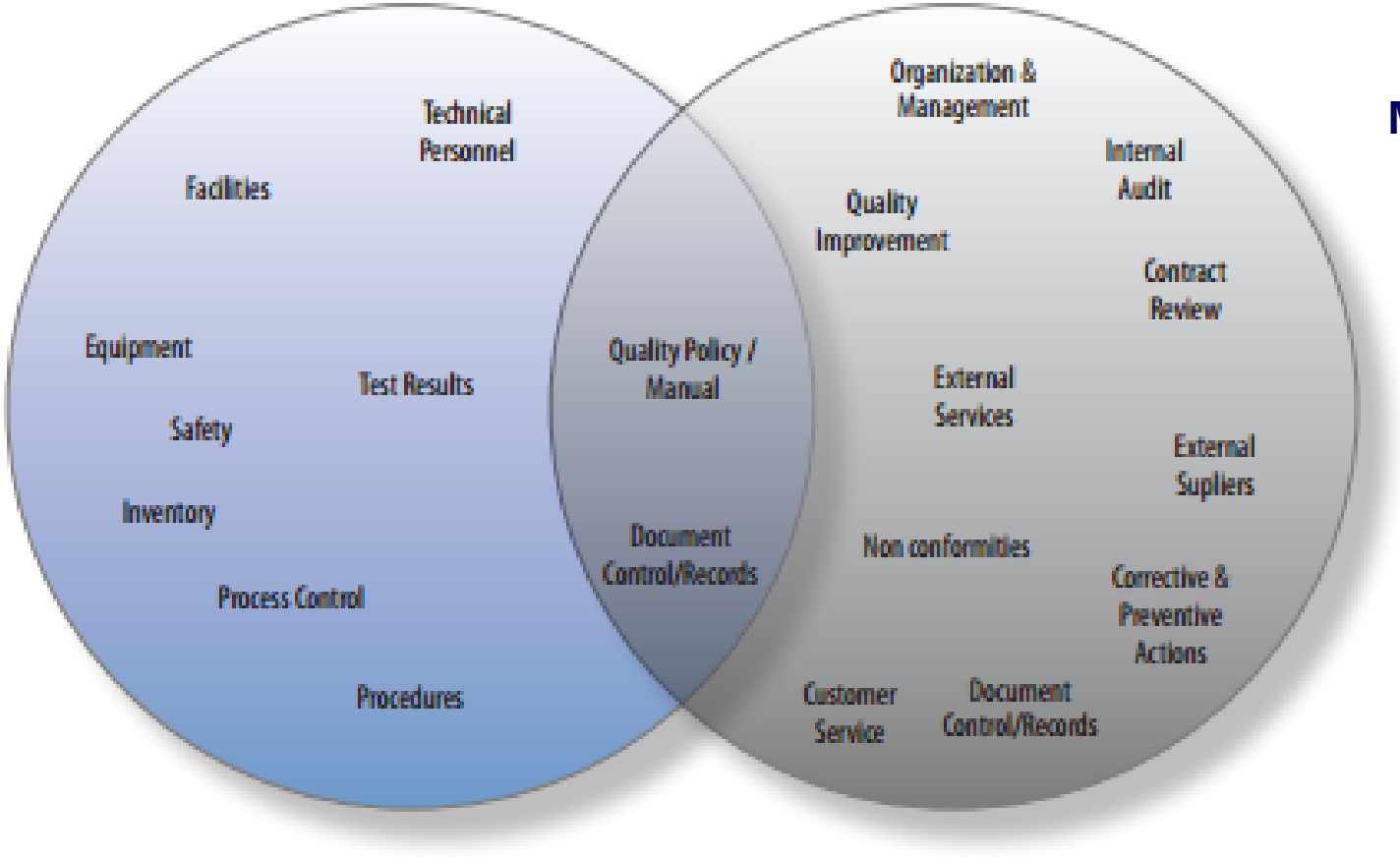
# Quality management systems

- A systematic approach to ensuring quality of testing:
  - Facilities and safety
  - Organization
  - Personnel
  - Equipment
  - Purchasing and inventory
  - Process control (including QC)
  - Information management
  - Document and records
  - Customer service
  - Assessment (including EQAS/PT)
  - Occurrence management/process improvement

# Quality management systems

Figure 1. Management and technical components of a quality system (Adapted from ISO 15189 Medical Laboratories - Particular requirements for quality and competence, International Standards Organization, 2007; and CLSI GP26 Application of a quality management system model for laboratory services management.)

**Operators**




**Managers**



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# QMS: Quality control

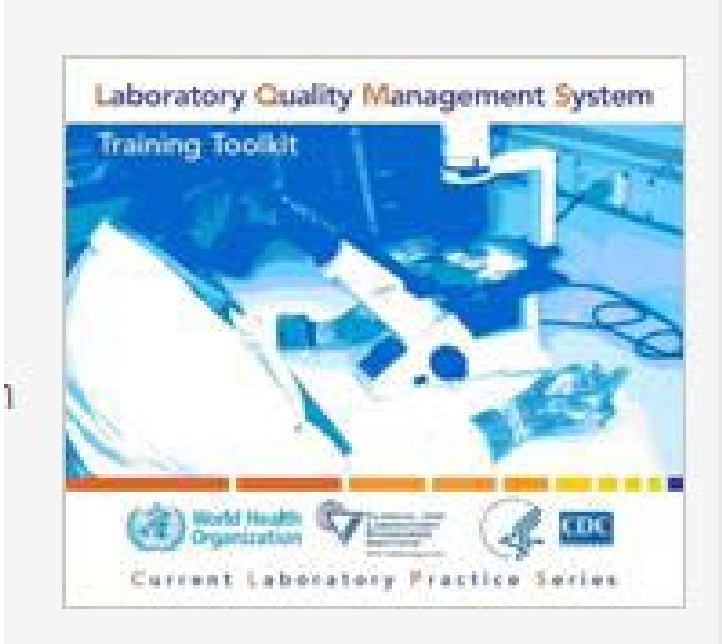
- A process to ensure the test procedure has worked
  - i.e. use of control materials to monitor the accuracy and precision of all process associated with the analytic phase of testing
- Many diagnostics claim built-in QC, such as control line
- For both quantitative or qualitative measurement
  - Ensure properties of QC material are well characterised
    - Must be challenging for performance of the assay i.e. low reactive QC specimen
  - Set acceptable control limits
  - Ensure F/U when acceptance criteria is not met

# QMS: External quality assessment

- A programme that assesses and compares the performance of laboratories/testing sites by demonstrating the reliability and accuracy of testing results
- EQA may include proficiency testing (otherwise known as an EQA scheme), or on-site visits to assess the laboratory practices and procedures, or a combination of the above
  - Adapted from: *ISO 17043 Conformity assessment – General requirements for proficiency testing.*

# QMS: training tools

- Laboratory Quality Management System Training Toolkit, developed by WHO, CDC, CLSI
  - http://www.who.int/ihr/training/laboratory_quality/en/
- GLI Stepwise process towards TB laboratory accreditation
  - http://www.gliquality.org/



# Contact us

WHO Diagnostics & Laboratory Technology website

http://www.who.int/diagnostics_laboratory/en/

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