Role of the WHO IVD Prequalification Programme in Light of National Regulatory Authority Approval

UN Prequalification of Medicines, Diagnostics and Vaccines 6th Consultative Stakeholder Meeting

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Goals of Talk

- Describe how a National Regulatory Authority regulates IVDs, using FDA as an example

- Understand issues that NRA approval does not necessarily address for IVD use in resource-limited settings
Bringing an IVD to Market in the US: General Approach

QUALITY
- Test design
- Manufacturing process
- Manufacturing facility

TEST
- Reliable, robust test
- Public health benefit

QUALITY

???
Bringing an IVD to Market in the US: Regulatory Framework

- **Laws/Acts**
  - Federal Food, Drug, and Cosmetic Act of 1938
  - Medical Device Amendments of 1976
  - FDA Modernization Act of 1997
  - Medical Device User Fee and Modernization Act of 2002
  - FDA Amendments Act of 2007

- **Regulations**
  - Code of Federal Regulations (CFR), Title 21, Subchapter H, Part 800: Medical Devices
  - 21 CFR Part 50: Protection of Human Subjects

- **Guidance documents**
Bringing an IVD to Market in the US: Device Classification

- **Risk-based regulatory approach**
  - Class I (low risk)
  - Class II (moderate risk)
  - Class III (high risk)
- **Data-driven marketing approvals**
- **Device regulatory controls include:**
  - Quality Management System, including design controls
  - Premarket submission review
  - Labeling
  - Registration of manufacturer and listing of marketed devices
  - Vigilance - passive surveillance for all; active for a subset of devices
FDA Approval of IVDs: HIV Detection

- IVDs used for the detection of HIV infection are Class III devices
- Require submission of a premarket approval application (PMA)
  - Filed by a sponsor to obtain FDA approval to market a device
  - 21 CFR 814
PMA: Required Elements (814.20)

- Name and address of the applicant
- Table of contents
- Summary section
  - Indications for use
    - Why a patient would use a certain test, target population, target disease/condition, for use by healthcare professional or lay user, etc.
  - Intended use
    - Description of what the manufacturer intended to measure with a certain test (manufacturer’s objective intent)
  - Device description
  - Marketing history
  - Summary of studies
  - Conclusions drawn from studies
PMA: Required Elements cont.

A complete description of:
- The device, including pictorial representations
- Each of the functional components
- The properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition
- The principles of operation of the device
- The methods, facilities, and controls used in the manufacture, processing, packing, storage, and where appropriate, installation of the device.
  - See also 21 CFR 820 - Quality System Regulations
    - Design controls
    - Manufacturing controls
PMA: Required Elements cont.

Technical sections containing data and information in sufficient detail to permit FDA to determine whether to approve the application

- Results of non-clinical (analytical) laboratory studies (what are the capabilities of the device?)
- Results of clinical investigations involving human subjects (how will the device be expected to perform in the real world?)
  - Studies on US populations
PMA: Required Elements cont.

- Bibliography of all published reports
- Copies of all proposed labeling for the device
- Environmental assessment
- Financial disclosure
- Additional information specified in 814.20
- Manufacturing site inspection
  - To meet requirements set out in Quality System Regulations (21 CFR 820)
  - Biennial post-approval inspections
Evaluation of Manufacturing Facilities: Quality System Inspection Technique
Decision-Making Process

• Review committee consisting of product and clinical experts, statistician, reviewers for facility issues and bio research monitoring (to ensure quality of clinical data)

• 180-day review clock, communicating issues to sponsor throughout the review time
Data to Support Approval of an HIV IVD

- **Clinical studies**
  - Known positives and prospective studies in low risk and high risk populations
  - Studies for each matrix claimed
  - Multiple geographically distinct sites
  - Multiple independent kit lots

- **Analytical studies**
  - Seroconversion panels, dilution panels, low titer panels
  - Interfering substances, unrelated medical conditions
  - Non-B subtypes
  - Reproducibility studies
  - Stability studies (shelf-life, shipping)
  - Etc.
Changes to the IVD

Guidance for Industry and FDA Staff

Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process

Document Issued on: December 11, 2008

This document supersedes “Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process” dated March 9, 2007.

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm
FDA Clearance of IVDs: Malaria Detection

• IVDs used for the detection of malaria are Class II devices

• Require submission of a pre-market notification: 510(k)
  - Filed by a sponsor to obtain FDA clearance to market a device
  - “Substantially equivalent” to a predicate device (previously cleared by FDA or marketed prior to 1976)
Pre-market Requirements for Malaria Diagnostics

• Submission of 510(k) pre-market notification application
  - Intended use, description of device, analytical studies, clinical studies, software/instrumentation, identification of risks, labeling, etc.
  - Manufacturing site inspection not required pre-market (expectation that Quality System is in place)

• Decision-making process
  - Review team consisting of product and clinical experts, statistician; bioresearch monitoring to ensure quality of clinical data - only when "for cause"
  - 90-day review clock, with interactive review, max. 3 deficiency letters issued
NRA vs. WHO IVD Prequalification

- 11-13 October 2010

**WHO Technical Working Group on Product Dossier Assessment for Prequalification of Diagnostics**

- Comparison of Prequalification criteria to NRA criteria for HIV and malaria IVDs
Conclusion from Meeting

NRA IVD Assessment

WHO IVD Prequalification

CONSTANTS

VARIABLES

VARIABLES

VARIABLES
\[
R = \rho^l e^{-\frac{1}{2} \rho} H(\rho)
\]
\[
R' = \left(\frac{l}{\rho} - \frac{1}{2}\right) R + \rho^l e^{-\frac{1}{2} \rho} H'
\]

\[
\frac{1}{\rho^2} \frac{(\rho^2 R')'}{\rho^l e^{-\frac{1}{2} \rho}} = \left(\frac{l}{\rho^2} - \frac{1}{\rho}\right) H + \left(\frac{l}{\rho} - \frac{1}{2}\right) \left[\left(\frac{l}{\rho} - \frac{1}{2}\right) H + H'\right]
\]
\[
+ \left(\frac{l + 2}{\rho} - \frac{1}{2}\right) H' + H''
\]
\[
= \left[\frac{l(l + 1)}{\rho^2} - \frac{l + 1}{\rho} + \frac{1}{4}\right] H + \left[\frac{2l + 2}{\rho} - 1\right] H' + H''
\]
Constants?
Design and Manufacturing

- Product description
- Product design
- Design overview
- Formulation and composition
- Biological safety
- Documentation of design changes
- Manufacturing process
- Overview of manufacture
- Site of manufacture
- Key suppliers
Constants?
Product Performance

- Analytical studies*
- Specimen types
- Analytical performance characteristics
- Accuracy of measurement
- Analytical sensitivity
- Analytical specificity
- Metrological traceability of calibrators and control material values
- Measuring range of assay
- Validation of assay cutoff
- Software verification and validation
Constants?

Other

- Commercial history (countries of supply)
- Quality Management System
  - Quality manual
  - Quality management system documents
- Inspection
\[
R = \rho^l e^{-\frac{1}{2} \rho} H(\rho)
\]
\[
R' = \left( \frac{l}{\rho} - \frac{1}{2} \right) R + \rho^l e^{-\frac{1}{2} \rho} H'
\]

**VARIABLES**

\[
\frac{1}{\rho^2} \left( \rho^2 R' \right)' = \left( \frac{l}{\rho^2} - \frac{1}{\rho} \right) H + \left( \frac{l}{\rho} - \frac{1}{2} \right) \left( \frac{l}{\rho} - \frac{1}{2} \right) H' + H''
\]

\[
+ \left( \frac{l}{\rho} - \frac{1}{2} \right) H' + H''
\]

\[
= \left[ \frac{l(l+1)}{\rho^2} - \frac{l+1}{\rho} + \frac{1}{4} \right] H + \left[ \frac{2l+2}{\rho} - 1 \right] H' + H''
\]
Variables

- What does FDA approval/clearance of an IVD address?
  - Safety and effectiveness for marketing in the US
  - Test performance in predominantly US populations
  - Consistency of manufacturing at specific manufacturing sites
  - Test design for US users
  - Test design for US testing environments
Variables
Test Performance

- Testing in US populations
  - Population/region differences in test performance
  - Sensitivity/specificity/predictive values may vary by country/region/disease prevalence
  - Confounding factors (co-infections, environmental, other)
Variables
Manufacturing Site

- Manufacturing facility evaluated with product
- Same controls in place at manufacturing site not approved with product?
- Potential for significant impact on product performance
- Product design
Variables
Product Design

- **US approved/cleared test designed for US operators and US conditions**
  - Storage requirements (temperature/humidity) and stability
  - Instructions for use
  - Trained personnel

- **Resource-limited settings**
  - Temperature and humidity outside of validated range
  - Lack of trained personnel
  - Lack of special storage conditions
  - Unreliable power sources
  - Need for studies to demonstrate test shelf-life, shipping stability, etc.
Variables
Product Design, cont.

• “Regulatory versions” of products
  - Manufacturers produce different versions of the same test for use in different markets
    • Manufacturing site
    • Product quality
    • Different NRA degree of oversight
  - May lead to assumption that all tests by that name are the same
**Variables**

**Risk**

- Risk/benefit consideration may differ from region to region
- Nevertheless, it is critical for:
  - Performance parameters to be well characterized
  - Performance to be consistent from lot to lot
  - Labeling to be truthful
SUMMARY

• Review of IVDs is critical to assure their safety and effectiveness and to support their role in maintaining public health.

• There are elements of that evaluation by an NRA that may be taken into account by WHO for its IVD prequalification (constants).

• However, there are also critical elements that do not necessarily transfer (variables), and should be taken into account to assure maximum public health benefit in specific settings.