US Regulation of In Vitro Diagnostic Devices (IVDs)

SoGAT- Clinical Diagnostic
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Highlights

• Regulatory process

• Device requirements

• Review challenges
FDA’s Mission

Ensure that devices on the market are safe and effective

Get safe and effective devices to market as quickly as possible
Risk-Based Regulation of IVDs

- **Class I: common, low risk devices**
  - *e.g., vitamin A deficiency test*
  - General Controls
  - Most exempt from premarket submission

- **Class II: moderate risk**
  - *e.g. prognosis, monitoring in already diagnosed cancer patients*
  - Special Controls
  - Premarket Notification [510(k)]

- **Class III: most complex, highest risk**
  - *e.g. cancer diagnosis or screening*
  - Safety, effectiveness, supported by valid scientific evidence
  - Premarket Approval [PMA]

(Substantial Equivalence)
Safe & Effective vs Pred.
510(k) sect. of the Act

(Evidence of Safety and Effectiveness)
Impact on patient
Controlled clinical trials
Device stands on its own
General & Special Controls

• General Controls
  – Register and List
  – Follow cGMP
    • Design Control
  – Report device failures
  – System for remedying device failures

• Special Controls
  – Premarket notification
  – Guidelines/guidance
  – Performance standards
  – Tracking requirements
  – Postmarket surveillance
Key Elements of a Submission

- Intended use/indications for use
- Device description
- Analytical validation
- Clinical validity/clinical utility
- Instrument and software validation, if applicable
- Labeling (package insert)
- Manufacturing, design controls, quality system requirements (QSRs/cGMP) (For PMA)
Major Review Issues

• Analytical performance
  – How reliably and correctly test measures analyte

• Clinical performance
  – How reliably test measures clinical condition

• Labeling
  – Intended use, directions for use, warnings, limitations, interpretation of results, performance summary
Challenges for the Review

• Lack of “gold standards”/performance standards
• Cutting edge new technology - multiplex, bioinformatics, nanotechnology
  – Paucity of standard methods and materials
• New biological/clinical knowledge
  – Changes in practice of medicine
• Overt and latent bias
• Issues of traceability
IVDs and Standards

• Determination of analytical sensitivity
• Viral load/NAT detection vs. infectivity
• Determination of IU vs. SI
Lack of Standards/Ref. Materials

• Microbiology
  – TB (NAT and infectivity)
  – Malaria, WNV. Parasites (Chagas, Trypanosomiasis)
  – CMV, EBV, VZV, HSV

• Chemistry
  – Glucose
  – Troponin

• Immunology
  – PSA/AFP (for low level)
  – Other specific cancer, allergen, autoimmune marker
  – Copy number
Current Tentative Solutions

• Analytical calibration related to infective units
• Clinical performance referred to a cleared device
• Clinical performance related to clinical truth (clinical trial outcome)
• Use of consensus of literature
• Composite reference + other lab tests/clinical history
• Use of recognized reference panels (CDC)
• Generation of Standards by accredited organization
Quest for Standards

- Standards already in documentation
  - Founding member of NCCLS (CLSI)
  - QSReg (21 CFR 820) (~ISO 13485/9100)
- Traceability-Commutability-Robustness
- Working with NIST
Handling the Challenges

• Regulatory trail is well lit - Literature, Guidance

• Broad menu of flexible regulatory tools
  - Pre-IDE
  - IDE
  - 510(k)
  - PMA
  - Exempt
  - de novo
  - Real time
  - Expedited

• Review not outcome oriented

• Mandate to be least burdensome

• New scientific resources/programs

• Evidence, risk, and knowledge base

Eye on Public Health
Transparency

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k062694

B. Purpose for Submission:
New device

C. Measurand:
70 gene expression profile

D. Type of Test:
Expression microarray
Test service performed in a single laboratory in Agendia’s Amsterdam

E. Applicant:
Agendia BV

F. Proprietary and Established Names:
MammaPrint®

G. Regulatory Information:
1. Regulation section:
www.fda.gov/cdrh/oivd
www.fda.gov/cdrh/devadvice

• Guidance
  – Documents/Recommendations

• Regulation
  – Device Requirements

• Databases
  – 510(k)/PMA/GGP/CLIA

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Supplementary Information
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FDA Guidance Documents

- Factor V Leiden DNA Mutation Detection Systems – March 2004
  [Link](http://www.fda.gov/cdrh/oivd/guidance/1236.html)

- Instrumentation for Clinical Multiplex Test Systems – Class II Special Controls Guidance Document – March 2005
  [Link](http://www.fda.gov/cdrh/oivd/guidance/1546.html)

- Drug-Diagnostic Co-Development Concept Paper – April 2005
  [Link](http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf)

  [Link](http://www.fda.gov/cdrh/oivd/guidance/1563.html)

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