In Vitro Diagnostics (IVDs)

Asian Harmonization Working Party Pre-Meeting
New Delhi, India, November 3-4, 2008

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U.S. Food and Drug Administration
U.S. Department of Health and Human Services
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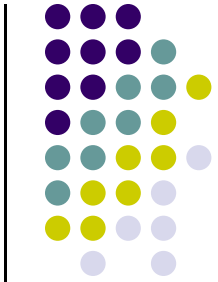
Legal Basis of Regulation
(the same as for other medical devices)

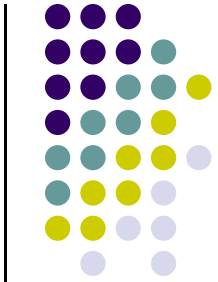


- Authority to regulate medical devices
  - Federal Food Drug and Cosmetic Act (FFDCA)
  - Medical Device Amendments 1976
  - Safe Medical Devices Act
  - Food and Drug Administration Modernization Act
  - Medical Device User Fee Modernization Act

What FDA regulates

- FDA regulates medical devices, including those "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals" (FFDCA 201(h))
- IVDs are a subset of medical devices which are "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such product are intended for use in the collection, preparation, and examination of specimens from the human body." (21 CFR 809.3)

Regulation of Medical Devices

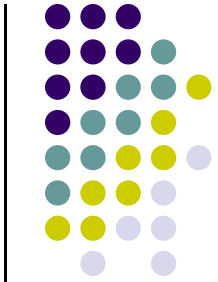


- Medical Devices Amendments added to FFDCA in 1976, requires devices to be legally marketed
  - All devices on the market in 1976 are “preamendments” and did not require premarket review prior to sale
  - Any device entering market after 1976 must follow FDA regulations in order to be marketed
  - “Legally marketed” devices = preamendments devices, FDA-cleared or approved devices, class I exempt devices

Risk-based classification

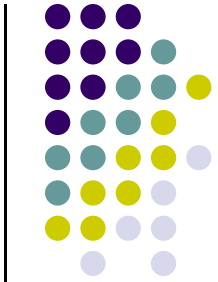
- Devices classified by FDA into
  - Class III—higher risk, present risk of injury or illness (to the patient or user)
  - Class II—moderate risk, general controls not sufficient, but can be mitigated through special controls
  - Class I—lower risk, little/no potential for unreasonable risk of injury or illness, general controls usually sufficient

General controls—all devices



- Registration and listing
  - Manufacturers must register their manufacturing facilities, and list the devices they manufacture
- Good Manufacturing Practices (GMP) and Quality System Regulation (QS reg)
  - Devices must be manufactured in a controlled manner using a defined, auditable quality system
- Prohibition against misbranding, adulteration, false or misleading claims, sales of banned devices

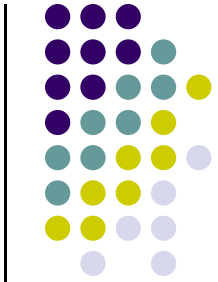
General controls (2)



- Premarket notification, unless exempt
- Maintenance of records and provision of reports to FDA
- Notification of purchasers/users/prescribers if device is faulty or fraudulent
- Repair, replacement, or refund for devices that have unreasonable risks
- Restriction on sale only to specified users

Regulatory Pathways

PreIDE process



- A mechanism for communicating early
- Informal review of sponsors' proposed intended use, validation plans, etc.
  - Based on information sponsor chooses to provide
  - Not binding on FDA or sponsor
  - Helps sponsor choose best intended use, best study design
  - Good option for new sponsors, new tests
  - Can be a single interaction or multiple cycles

IDE

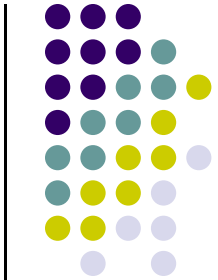
- Devices for which safety and effectiveness data is being gathered
  - Must be labeled as “investigational use only”
- Formal approval process
- Required for “significant risk” devices
- Informed consent for samples
- IRB approval of study

(Note: most IVD Studies are Non-Significant risk or Exempt studies)

510(k)

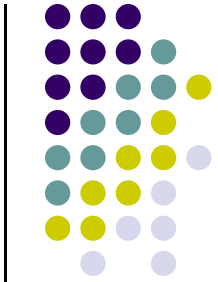
- Premarket notification = 510(k)
- 510(k) submission required
  - Some class I devices
  - Most class II devices
- FDA clearance based on “substantial equivalence” to legally marketed device
  - Requires available “predicate” or device of similar type with similar intended use
  - Review decision summaries posted publicly on web

De novo 510(k)



- Moderate risk device with no existing legally marketed predicate
- Reviewed for safety and effectiveness
- Downclassified (class I or II) upon request by sponsor
  - Special controls implemented
  - Classification published
  - De novo device now a predicate for future devices of same type with same intended use

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY/ASSAY-ONLY TEMPLATE

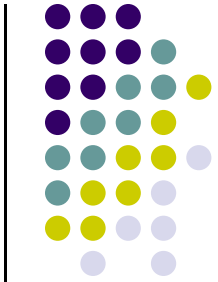


A. 510(k) Number:
B. Purpose for Submission:
C. Measurand:
D. Type of Test:
E. Applicant:
F. Proprietary and Established Names:
G. Regulatory Information:
    1. Regulation section:
    2. Classification:
    3. Product code:
    4. Panel:
H. Intended Use:
    1. Intended use(s), 2.Indications for use:
    3. Special conditions for use statement(s):
    4. Special instrument requirements:
I. Device Description:
J. Substantial Equivalence Information:
    1. Predicate device name(s):
    2. Predicate 510(k) number(s):
    3. Comparison with predicate:

K. Standard/Guidance Document Referenced (if applicable):
L. Test Principle:
M. Performance Characteristics:
    1. Analytical performance:
        a. Precision/Reproducibility:
        b. Linearity/assay reportable range:
        c. Traceability, Stability,(controls, calibrators, methods):
        d. Detection limit:
        e. Analytical specificity:
        f. Assay cut-off:
    2. Comparison studies:
        a. Method comparison with predicate device:
        b. Matrix comparison:
    3. Clinical studies:
        a. Clinical Sensitivity:
        b. Clinical specificity:
        c. Other clinical supportive data
    4. Clinical cut-off:
    5. Expected values/Reference range

Instrument
Software

Information on cleared/approved IVDs-510(k)



- OIVD Review Decision Summary
- Standard template with review data for 510(k)s
- 510(k) database
  http://www.fda.gov/cdrh/oivd/decisionsummaries.html
- For de novo 510(k)s, Special Controls Guidance Documents available
  - Describes 510(k) submission requirements for devices of same type with same/similar intended use
  - http://www.fda.gov/cdrh/oivd/index.html

PMA

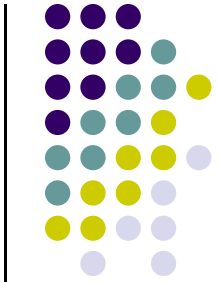
- Premarket approval
- All class III devices
- Demonstration of safety and effectiveness
  - Performance
  - Labeling
- Does not use predicates
- May require advisory panel decision prior to approval
- Summary of Safety and Effectiveness Data (SSED) posted publicly on web

Information on cleared/approved IVDs-PMA

- Summary of Safety and Effectiveness Data (SSED) for PMAs
  - General information
  - Indications for Use
  - Device Description
  - Contraindications, Warnings, and Precautions
  - Alternative Practices and Procedures
  - Marketing History
  - Potential Adverse Effects of the Device on Health
  - Summary of Preclinical Studies
  - Summary of Clinical Studies
  - Conclusions Drawn from the Studies
  - Panel Recommendations
  - CDRH Decision
  - Approval Specifications

http://www.fda.gov/cdrh/pmapage.html

Office of In Vitro Diagnostic Device Evaluation and Safety



- OIVD was created in 2003 to address the complete life cycle of IVD tests
  - Premarket review
  - Postmarket issues
    - MDRs
    - Compliance
- “One stop” shopping for IVD regulatory issues
- Cross-functional staff
  - Premarket review
  - Postmarket surveillance
  - Compliance reviews/action

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OIVD Webpage

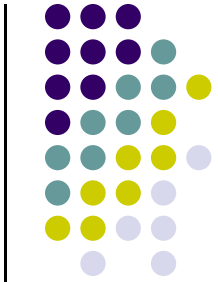
- Access information relevant to IVDs
  - Regulations
  - Guidances
  - CLIA categorizations
  - Standards
  - Lab and user information
  - http://www.fda.gov/cdrh/oivd/index.html

This is what arrives in our Office !

Team formed:

- Lead reviewer
- Statistician
- Compliance
- Epidemiologist
- Internal/external experts
- Instrument/software expert etc.

IVDs: FDA Regulated Uses



In Vitro Diagnostic Tests for:

- Diagnosis
- Screening
- Epidemiology/Surveillance
- First Response

- **Not** Environmental Screening

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

Review Issues (cont)

Software /Hardware

- Documentation and hazard analysis required
- Claims for use on multiple amplification /detection platforms must be validated

Note: RUO labeled platform issues have prevented clearance/approval

Other FDA Regulatory Requirements

- Good manufacturing practice followed (cGMP) –

  QS Reg. 21CFR 820

- Software/Instruments/Reagent validation

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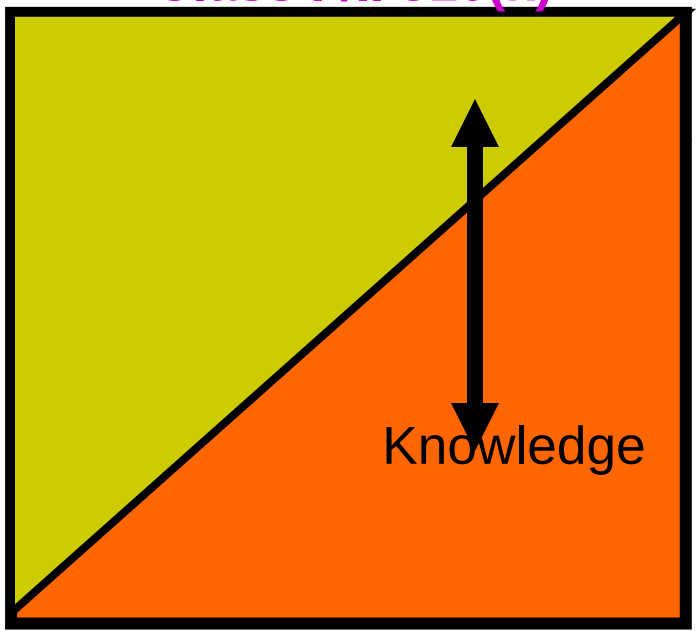
- **Regulatory path a risk-based approach**
- **Categorization (I, II, III) depends on risk/risk mitigation**

Class I /II 510(k)



Class III PMA

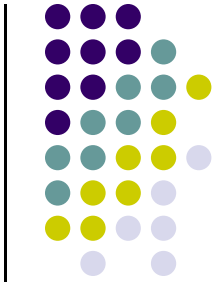
Low likelihood of harm

High likelihood of harm, harm unknown, or prevention unknown.
IDE

Key Elements of a Submission

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

Major elements of IVD submission

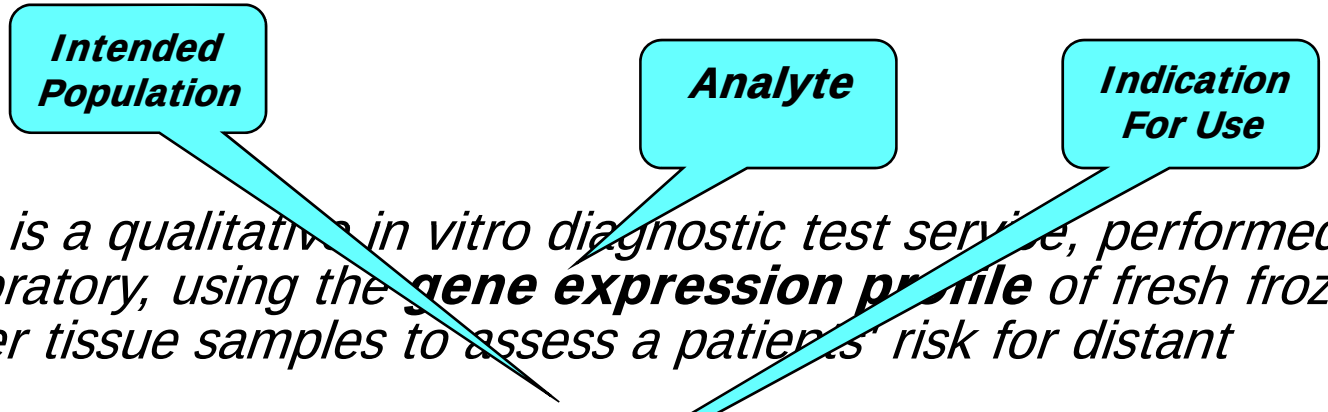


- Intended use/indications for use
- Pre-analytical (e.g. sample prep) and analytical validation
- Clinical validation/clinical utility
- Device description, internal and external controls
- Instrumentation (if multiple, assays need to be validated for each platform)
- Labeling (package insert) - "**truth in labeling**"

- For PMA - manufacturing, design controls, quality system requirements (QSR/GMP) (products must follow 21 CFR 820)

Intended Use

What assay measures, how to use results

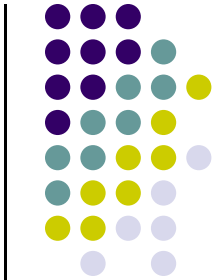


Example:

*MammaPrint® is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the **gene expression profile** of fresh frozen breast cancer tissue samples to assess a patients' risk for distant metastasis.*

*The test is performed for **breast cancer patients** who are less than 61 years old, with Stage I or Stage II disease, with tumor size <= 5.0 cm and who are lymph node negative. The MammaPrint® result is indicated for use **by physicians** as a **prognostic marker** only, along **with other clinicopathological factors**.*

Analytical & Clinical Validity



Analytical validity of the test:

- Does my test measure the analyte I think it does?
- Correctly?
- Reliably?

Clinical validity of the biomarker:

- Does my test result correlate with the expected clinical presentation?
- How reliably?

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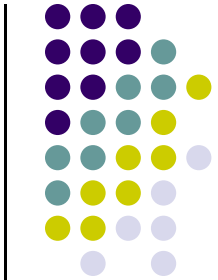
Analytical Performance

- Precision (repeatability, reproducibility)
- Accuracy
- Sensitivity, Limit of Detection
- Specificity (interference, cross-reactivity)
- Sample type / matrix
- Sample preparation / conditions
- Performance around the cut-off
- Potential for carryover, cross-hybridization
- etc….

Analytical Performance



Precision / Reproducibility:

- Studies should demonstrate that the intended users can get reliable results
- Reproducibility at external sites for commercially distributed devices
- Should use clinical samples when possible through all pre-analytical and analytical steps

Analytical Performance

Accuracy:

- Real clinical samples
  - Retrospective samples, appropriately collected and stored
  - Prospectively collected samples
- Compare assay results to:
  - Comparator (predicate) device results
  - a gold standard method (510(k), PMA, or de novo)
  - Clinical diagnosis

Clinical Performance

Clinical performance – clinical validity

- How reliably test measures clinical condition?

May be based on:

- Existing clinical data
- New clinical trial data
- Review of information in the literature
- Current clinical knowledge

Transparency, information on web

New Search | Back To Search Results

510(k) Premarket Notification Database

Device Classification Name	Classifier, Prognostic, Recurrence Risk Assessment, Rna Gene Expression, Breast Cancer
510(K) Number	K062694
Device Name	MAMMAPRINT
Applicant	AGENDIA BV Louwesweg 6 Amsterdam, NL 1066 EC
Contact	Guildo Brink
Regulation Number	866.6040
Classification Product Code	NYI
Date Received	09/11/2006
Decision Date	02/06/2007
Decision	Cleared For Marketing Automatic Class Iii Designat (AN)
Classification Advisory Committee	Immunology
Review Advisory Committee	Immunology
FOI ITEM	LETTER
FDA Review	Decision Summary
Type	Cleared For Marketing Automatic Class III Designation

AHWP FDA

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FOI ITEM LETTER

FDA Review Decision Summary

DEPARTMENT OF HEALTH & HUMAN SERVICES

FEB - 6 2007

Agendia BV
c/o Mr. Guido Brink
Director Quality Management & Regulatory Affairs
Slotervaart Hospital, Floor 9D
Louwesweg 6, 1066 EC Amsterdam
The Netherlands

Re: k062694
Evaluation of Automatic Class III Designation
MammaPrint®
Regulation Number: 21 CFR 866.6040
Classification: Class II
Product Code: NYI

Dear Mr. Brink:

The Center for Devices and Radiological Health (CDRH) o
(FDA) has completed its review of your petition for classifi
intended as a qualitative *in vitro* diagnostic test service, per

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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 facility.

E. **Applicant:**
Agendia BV

F. **Proprietary and Established Names:**
MammaPrint®

G. **Regulatory Information:**
1. Regulation section:
21 CFR 866.6040 Gene expression profiling test system for breast cancer prognosis
2. Classification:
Class II
3. Product code:
NYI, Classifier, prognostic, recurrence risk assessment, RNA gene expression, breast cancer
4. Panel:
Immunology (82)

H. **Intended Use:**
1. Intended use(s):
MammaPrint® is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the gene expression profile of fresh frozen breast cancer tissue samples to assess a patients' risk for distant metastasis.

The test is performed for breast cancer patients who are less than 61 years old, with Stage I or Stage II disease, with tumor size ≤ 5.0 cm and who are lymph node negative. The MammaPrint® result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors.
2. Indication(s) for use:
Same as intended use
3. Special conditions for use statement(s):
For prescription use only
MammaPrint® is not intended for diagnosis, or to predict or detect response to therapy, or to help select the optimal therapy for patients.
4. Special instrument requirements:
Agilent 2100 Bioanalyzer: Serial number DE54700497 en DE24802382
Agilent DNA microarray scanner: Serial number us22502555

ers
of Commerce and Industry


Thanks!!

The Following Slides Provide Additional Information on the Following Topics

- Research Use Only (RUO)
- Analyte Specific Reagent (ASR)
- Laboratory Developed test (LDT)
- Clinical Laboratory Improvement Amendments (CLIA)

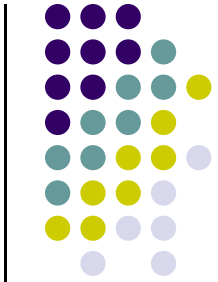
Research Use Only (RUO)

RUO instruments/reagents - regulatory status:

- Labeled as "*for research use only, not for use in diagnostic procedures* "
- Not reviewed by FDA
- Not manufactured under Quality System Regulations
- Not subject to Medical Device Reporting
- Not Registered and Listed

- RUO Device or Device with RUO component =
  No assurance of safety & effectiveness regarding test result

Analyte Specific Reagents



- Analyte specific reagents (ASR's) are antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens. (21 CFR 864.4020)

ASRs

- Analyte specific reagents (ASRs)
  - “active ingredients” of tests
  - Mostly class I exempt, some class II and III
- Commercial distribution of ASRs
  - No intended use, performance claims
  - No instructions for use
  - Proper labeling
- Draft guidance *“Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions”*

ASR Q & A Guidance

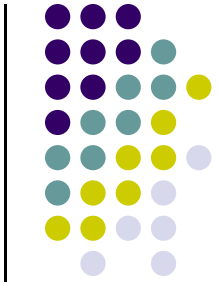
(http://www.fda.gov/cdrh/oivd/guidance/1590.pdf)

- Intended to prevent ASRs from being sold in kit form without premarket review
- Finalized last fall
- Not new, but clarifying

- Released September 16, 2007
- 1 year grace period for compliance

Companies should be in compliance by September 16, 2008

CLIA—Laboratory Developed Tests



- Laboratory developed tests (home brew) automatically *high complexity*
  - With or without use of commercial ASRs
  - No cleared/approved label
  - No FDA determination

CLIA elements

- Accreditation/certification
- Laboratory quality system
  - Qualified personnel
  - Established procedures
  - Analytical assessment of test performance
  - QC and PT requirements
- Does not specifically address
  - Development (research/investigational) phase
  - Clinical validity

CLIA Test Complexity

- Test complexity
  - High
  - Moderate
  - Waived
- Determination based on
  - Difficulty of test procedure
  - Skills of staff required
  - Test label for cleared/approved tests