The FDA PMA Process for *In Vitro* Diagnostic Devices

FDA/Center for Devices and Radiologic Health/Office of *In Vitro* Diagnostics

April 26, 2011

When is a PMA Necessary?

Presented by

Kathleen B. Whitaker, Ph.D.

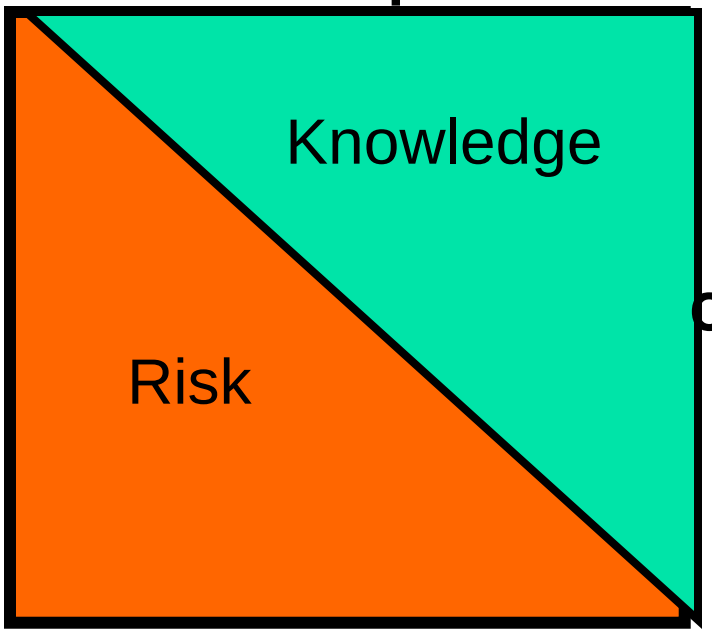
FDA Regulated Uses of IVDs

- **Diagnosis** – Diagnose disease, identify pathogens, confirm, or rule out infection in symptomatic patients
- **Screening** - Intended use population includes individuals **without** signs or symptoms of disease, infection
- **Epidemiology/Surveillance** - To detect and monitor incidence or prevalence of infection for targeting and evaluating health programs
- **Prognosis, prediction** of disease progression

How are IVD Devices Classified?

- **Regulatory path** determined using a risk-based approach
- **Classification** (I, II, or III) depends on risk

Class I – most 510(k) exempt



Low likelihood of harm

Class II - 510(k)

High or unknown likelihood of harm,

or how to prevent harm is unknown

Class III - PMA

Risk is Dependent Upon Intended Use

- Risk (and subsequently classification and submission type) is inherently tied to **Intended Use** of a device.

Risk is Dependent Upon Intended Use

- Level of FDA review and type of studies requested generally depend on the Intended Use claims; not necessarily on type of technology or assay

- Cytomegalovirus (CMV)

  - Management of solid organ transplant patients at risk for CMV (PMA)

  - as an aid in the assessment of serological status for sexually active adults and expectant mothers (510(k))

For Established IVD Devices

- Search our Classification Database to determine device class and required submission type:

  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm

For Novel IVD Devices

- Can the device be placed under existing regulations?
- If not, then the classification and submission type must be determined

When is a Device Class III?

- Class III devices are those:

a) that cannot be classified as class II because insufficient information exists to determine that special controls would provide reasonable assurance of its safety and effectiveness;

b) that cannot be classified as class I because "insufficient information exists to determine that the application of general controls [is] sufficient to provide reasonable assurance of safety and effectiveness of the device";

When Class III ? cont…

c) and that "(I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health,

d) or (II) presents a potential unreasonable risk of illness or injury." Section 513(a)(1)(C) (21 U.S.C. 360c(a)(1)(C)).

Before FDA Modernization Act

- 513 (f)(1) of F, D, & C Act automatically classifies **devices that were not in commercial distribution prior to May 28, 1976** into Class III, requiring a pre-market approval (PMA)

FDA Modernization Act of 1997

- Provides a new mechanism for classifying new devices for which there is no predicate device
- Allows an automatic class III designation to be evaluated and overturned
- We call this mechanism **the De Novo Process**

FDA Modernization Act of 1997 (FDAMA) - New Section 513(f)(2) of the F, D, & C Act. Amended November 21,1997

Downclassification of Class III Devices

- Class III devices can be downclassified to Class II when sufficient information becomes available to establish **special controls** that reasonably assure safety and effectiveness

Existing Class III Devices

- Downclassification of an existing Class III device - citizen's petition
- Recent example: Hepatitis A infection diagnostic devices. Reassessment of level of risk

Other Regulatory Tools

- **513g** – Official request for classification of a currently unclassified device

- **Pre-IDE submission** – Informal interactive process allowing early assessment of device class, and least burdensome regulatory route to approved product

Comparison of the PMA and 510(k) Processes

Outline

- Terminology
- Elements - PMA or 510(k)
  - Intended use
  - PMA specific sections
  - Analytical performance
  - Clinical performance
  - Labeling

Terminology

Class	Pre-market Submission	Success Metric	Action
III	PMA	Safety and Effectiveness	Approval
II	510(k)	Substantial Equivalence	Clearance
I	None (if exempt) 866.9 Limitations to exemptions		
II (De Novo)	510(k)	Safety and Effectiveness	Clearance with Special Controls

Class III Devices

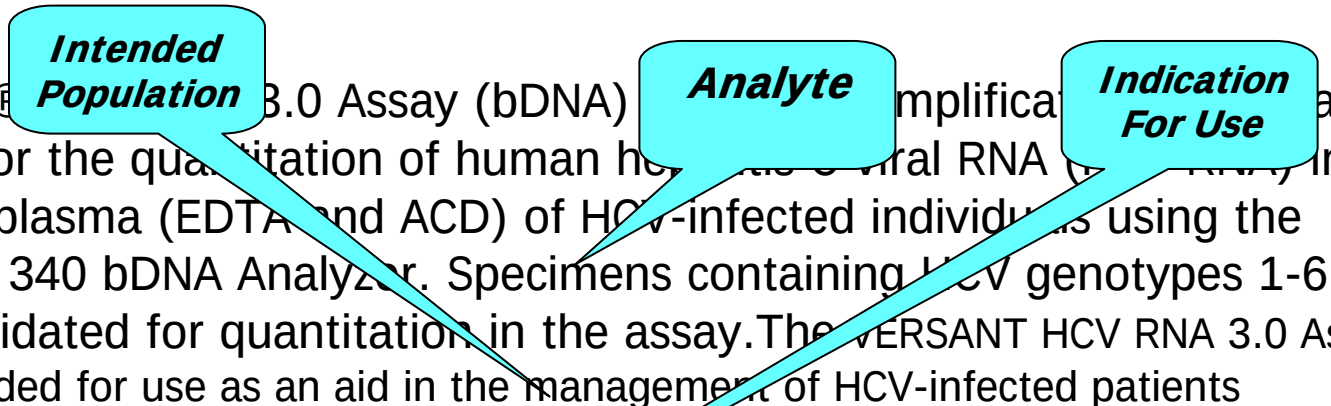
- Regulation governing premarket approval - in Title 21 CFR Part 814
- Act Section 515 (d)(6):
  - PMA supplements required for changes affecting safety and effectiveness
  - For manufacturing changes - a 30-day notice or 135-day PMA supplement
  - Timeline - FDA has 180 days to review the PMA and make a determination

Major Elements of an IVD Submission

- Intended use
- Device description, internal/external controls
- Pre-analytical (e.g. sample prep) and analytical performance
- Clinical performance
- Instrument and software, if applicable
  - If multiple platforms, assay performance on each
- Labeling (package insert)

Intended Use

What assay measures, how to use results



The VERSANT® 3.0 Assay (bDNA) mplifica acid probe assay for the qua itation of human he viral RNA (RNA) in the serum or plasma (EDTA nd ACD) of HCV-infected individu s using the Bayer System 340 bDNA Analyz r. Specimens containing HCV genotypes 1-6 have been validated for quantitation in the assay.The VERSANT HCV RNA 3.0 Assay (bDNA) is intended for use as an aid in the management of HCV-infected patients undergoing anti-viral therapy. The assay measures HCV RNA levels at baseline and during treatment and is useful in predicting non-sustained virological response to HCV therapy. The results from the VERSANT HCV RNA 3.0 Assay (bDNA) must be interpreted within the context of all relevant clinical and laboratory findings. Assay performance characteristics have been established only for individuals treated withinterferon alfa-2b plus ribavirin.

PMA Specific Elements

- Manufacturing section
- Pre-approval inspection (GMP compliance)
- BIMO (bioresearch monitoring visit to clinical and/or sponsor sites)
- Possible Panel meeting (novel IU)
- Post-approval – annual reports, PMA supplements for well defined modifications

http://www.fda.gov/cdrh/ode/guidance/1584.pdf

Analytical Validation – Quality of Measurement

- **Analytical performance measures**
  - 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
  - Stability (for PMA)
- **Studies may vary depending on**
- Technology, end user
  - Quantitative or qualitative assay
  - What is reported (individual analytes vs. composite score)

Performance

- **Analytical performance** — does my test measure the analyte I think it does? Correctly? How reliably?

- **Clinical performance** — does my test result correlate with the expected clinical presentation? How reliably?

Accuracy / Clinical Performance

- Real clinical samples where feasible
- Prospective or retrospective evaluation
- Comparison to a reference method
  - e.g., bi-directional DNA sequencing for genotyping; viral culture; composite methods
- Comparison to a predicate device
  - 510(k)
- Comparison to a clinical outcome
  - PMA, but also some 510(k)s & de novo 510(k)s

Clinical Validation – Significance of Result

- Study plan for an *in vitro* diagnostic product depends on the intended use / indications for use/end user
- Diagnosis, residual disease, etc. (current state)
- Recurrence (change in state)
- Risk of disease, prognosis, prediction (future state)

Clinical Section of a PMA Submission

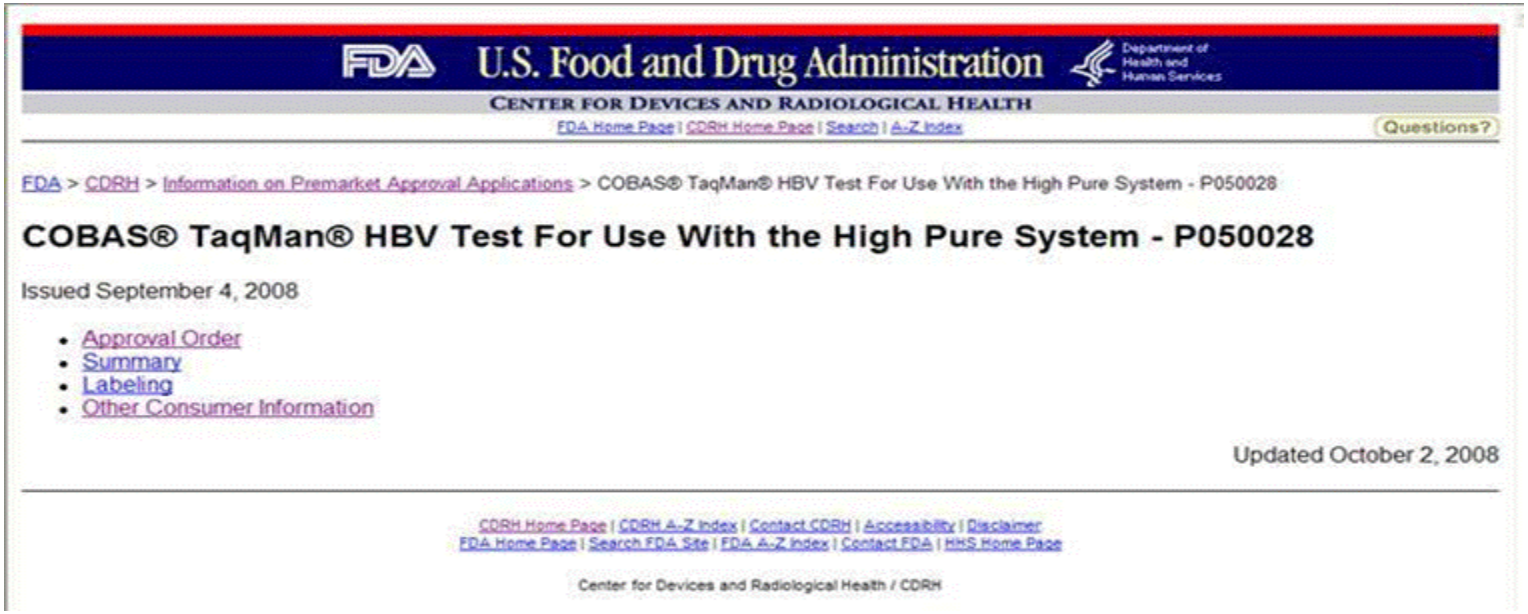
- Study protocols including IRB approval letters/informed consent
- Safety and effectiveness data
- Adverse reactions and complications
- Device failures and replacements
- Case report forms, patient information, patient complaints, any studies done under IDE
- Line data from all individual subjects
- Data analysis, results of statistical analyses
- Any other information from the clinical investigations
- Literature

Labeling of *In Vitro* Devices

- 21 CFR 809.10
- Clear instructions for use
- Need to capture expected analytical and clinical performance of device
- Prospective performance in intended use population

Approval Documents

- PMA approval - summary of the safety and effectiveness data upon which the approval is based, labeling available (http://www.fda.gov/cdrh/pmapage.html#monthly)



Some Common Questions

- Are clinical studies for a PMA always more extensive than for a 510(k)?

  Not Always

- When to register and list?

  http://www.fda.gov/cdrh/registration/whento.html

How to Avoid Potential Pitfalls in the PMA Process

Presented By

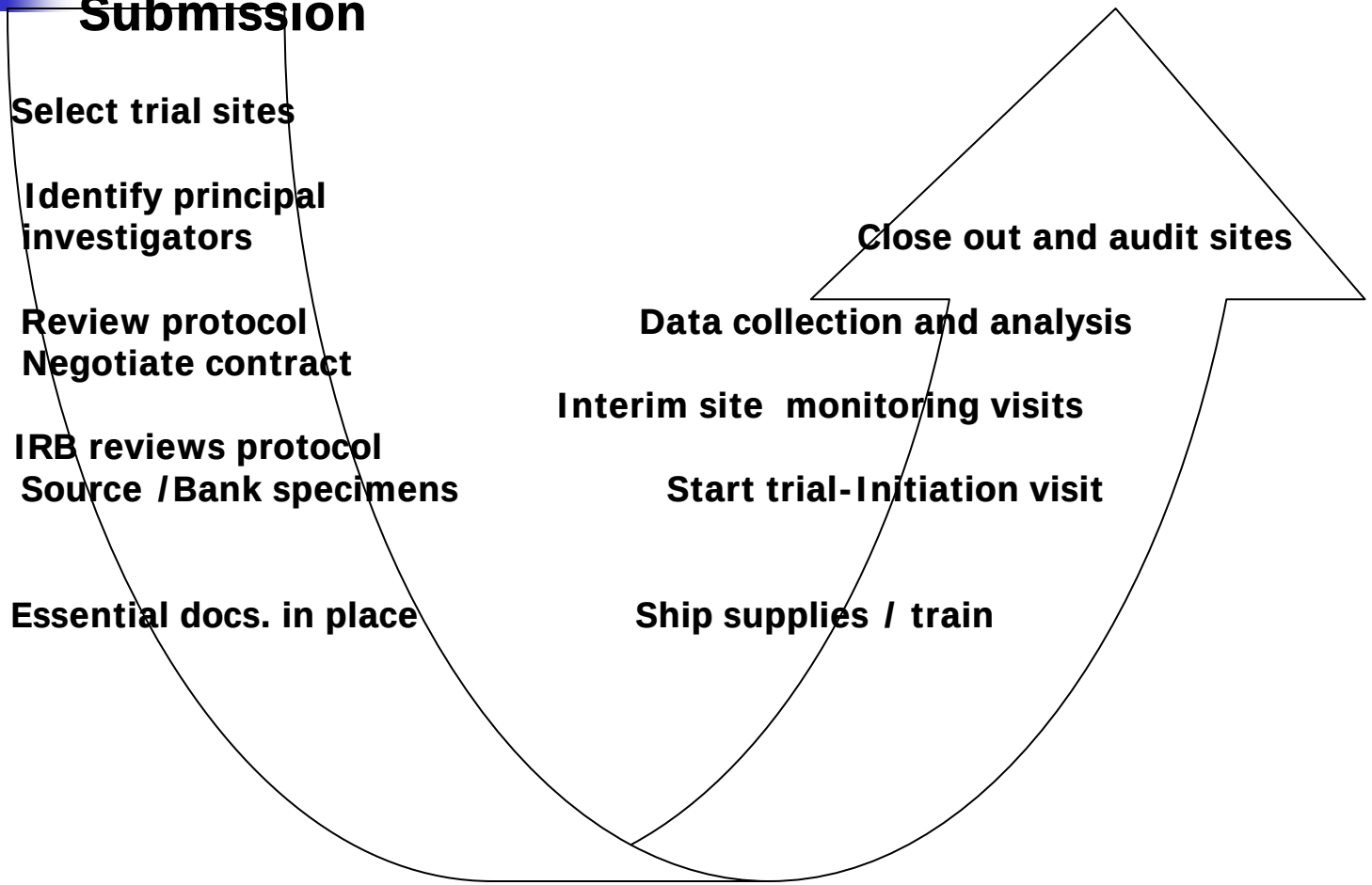
Uwe Scherf, Ph.D.

Deputy Director, Division of Microbiology

Outline

- Reasons why the PMA submission review/approval process may take longer than you expected
- How to improve your PMA submission
- Ways to streamline the PMA approval process

Chronology of an IVD Clinical Study (3m – 1 yr+)



FDA PMA Review Oversight

- **This is how a PMA arrives to our Office !**

PMA Team Formed

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

Review/Approval Takes Longer than Expected. Why? (1)

Global Issues with Submissions

- Disorganized
  - Table of contents missing, pages not numbered
  - Check tables/figs./text for clarity, consistency and accuracy
  - “Put together in a hurry”-multiple cut-and-paste errors
- Poor statistical analysis of data
  - Line listings not included
  - Discordant analysis- check new statistical guidance

Why ? (2)

- Administrative gaps- missing documents
  - Copies of IRB approval letters, IC ,financial disclosure forms, list of investigators....
  - Clinical registration trial form, names and location of clinical sites....
- Lack of monitoring/auditing of clinical sites Approval delayed by BIMO inspection findings

Why ? (3)

- Lack of knowledge about the clinical disease state - end user Focus Panels!
- The “Intended Use” is the driving force of the review. Claim- supporting studies not adequate
- Literature to support device-

  Not analyzed appropriately, not summarized, organized
- Issues with Quality System Inspection of manufacturing facility. Poorly written manufacturing sections

Specific Software/Hardware Section (1)

- Hardware:

  -Differences between clinical and launch platform not shown. Use of prototype for clinical trial not justified

  - Claims for use needed for multiple amplification /detection platforms

  - Assays need to be validated and cleared for each platform

  - RUO labeled platform issue has prevented approval

Software/Hardware Section (2)

- Software :

  -Guidance Document not followed

http://www.fda.gov/cdrh/ode/guidance/337.pdf

-Summary of validation/verification testing not sufficient

-Need to link test results back to functional requirements & link hazard analysis mitigations back to functional requirements

-"Off the Shelf" software not sufficiently documented

Guidance for Off-the-Shelf Software Use in Medical Devices

- Minor "bugs" at launch? Justify why not a hazard and mitigate through labeling

Device Design Section

Reagents

- Serological assays

  - Were the antibodies/antigens well-characterized?

- Nucleic acid assays

  - primer/probe design justification required

  - include blast search results demonstrating specificity & inclusivity

- Include detailed description of appropriate internal and external controls/calibrators

Analytical/Clinical Study Sections (1)

- Precision/Reproducibility- minimum of 3 sites

  -Do panels assess variability of the assay at the cutoff/LOD?

- Samples/Populations/Sites

  -Do they represent the "Intended Use" population/end user?

- Non-US Patient Data-appropriate or not?

  - Check with FDA first

Analytical/Clinical Study Sections (2)

- Specimen Type

  Were full analytical and clinical validation data supplied to support claims for:

  - Each specimen type
  - All matrices
  - All specimen collection devices
  - All transport media
  - All transport and storage conditions
  - All collection methods

Analytical/Clinical Study Sections (3)

All NAAT assay extraction methods

-Should be validated with your assay

If “required but not part of kit", check its regulatory status

RUO labeling of “ancillary reagents” has been an issue preventing device approval

What is Available to Streamline the Process?

Advice/Guidance Documents

FDA Pre-IDE Consultation

- Face-to-Face meetings
- Telecons

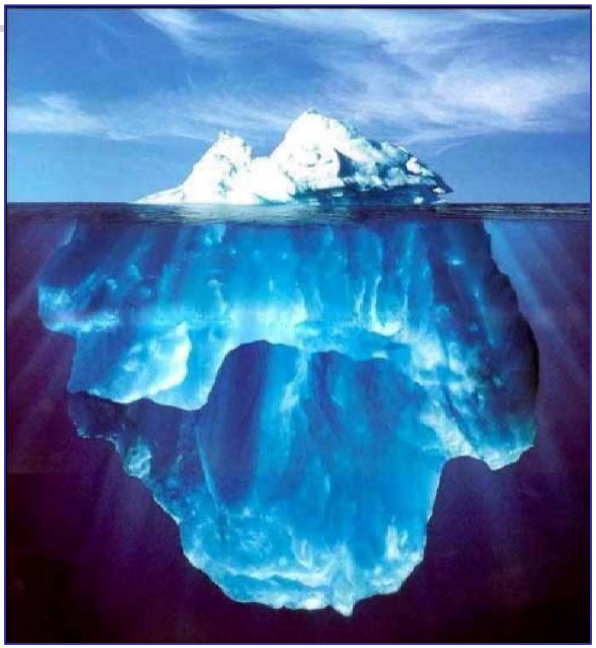
Interactive Submission Reviews

Pre-IDE Process

- Free FDA consult
- Protocol review and regulatory guidance
- Unique interactive opportunity (Non-binding)
- Especially recommended for novel devices/uses
  http://www.fda.gov/cdrh/oivd/presentations/042203-Altaie.html

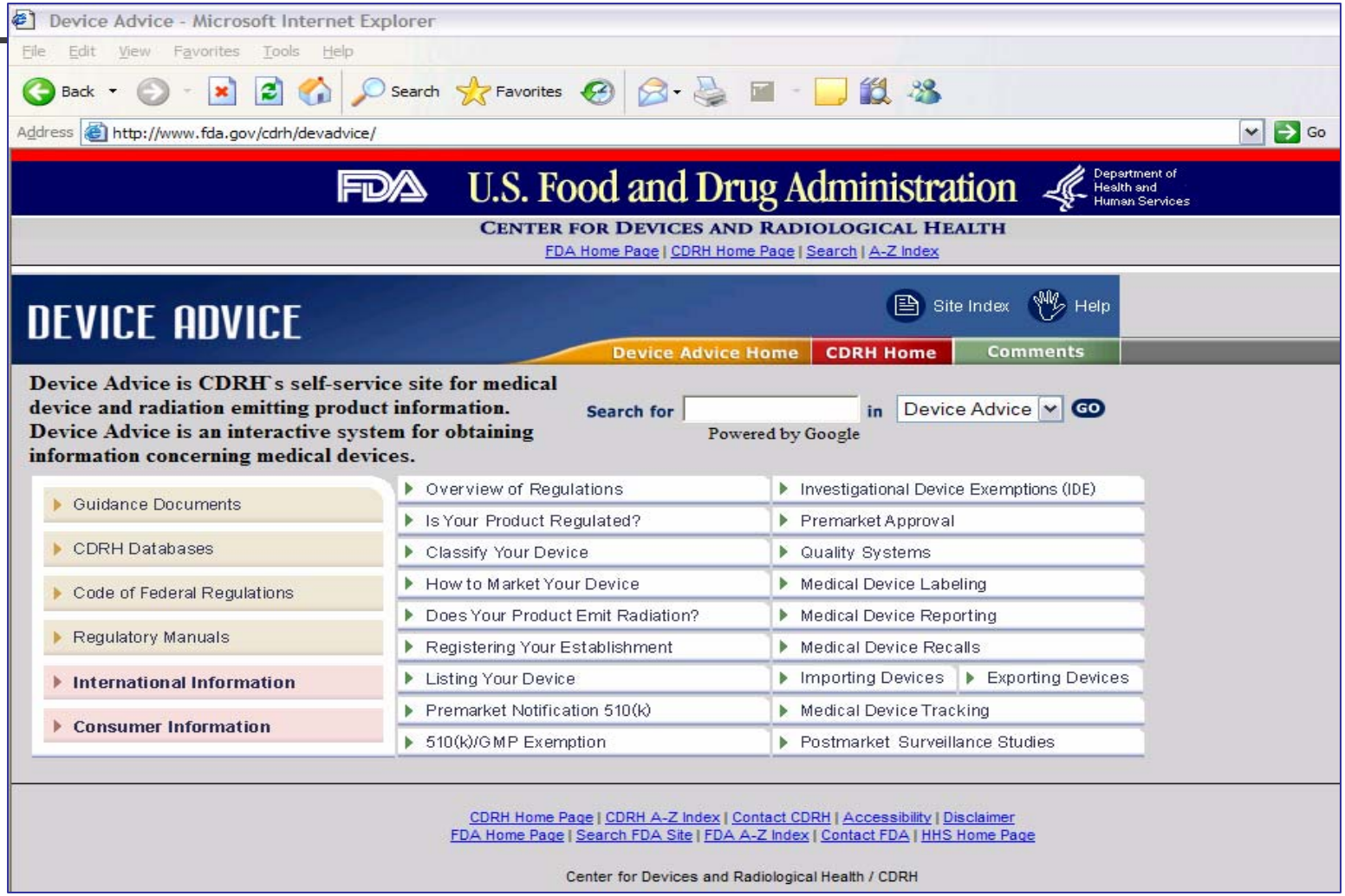
Information: CDRH Homepage

www.fda.gov/cdrh



- **Device Classification Database**
- **Device Advice**
  - http://www.fda.gov/cdrh/devadvice
- **Register for "What's New"**
- **Guidance Documents**
- **IDE Information**
  - http://www.fda.gov/cdrh/devadvice/ide/index.shtml
- **Much more…**

Device Advice



Guidance Documents

Draft Guidance for Industry and FDA Staff

Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection or Detection and Differentiation of Influenza Viruses

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on: [release date of FR Notice]

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact Sally Hojvat at 240-276-0711 or by email at sally.hojvat@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety
Division of Microbiology Devices

Guidance for Industry and FDA Staff

Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements

Document Issued on: [release date as stated in FR Notice]

The information collection provisions in this guidance have been approved under OMB control number 0910-xxxx . This approval expires ???. An agency may not conduct, or sponsor and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number." (OMB Nos. and expiration dates are available at this site: http://intranet.fda.gov/omp/pra/Approved_ICRs.htm#CDRH Please contact the Regulation: *Staff, if you do not know the appropriate approval number or expiration date).*

For questions regarding this document, contact the Premarket Notification (510(k)) Section or the Premarket Approval Section of CDRH at 240-276-4040 or Leonard Wilson of CBER by phone at 301-827-0373 or by email at leonard.wilson@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Other Related Guidances

- FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals, June 30, 2008
  http://www.fda.gov/cdrh/mdufma/guidance/1218.html#2a
- Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements, December 28, 2007
  http://www.fda.gov/cdrh/ode/guidance/1655.html
- Real-Time Premarket Approval Application (PMA) Supplements
  http://www.fda.gov/cdrh/ode/guidance/673.html
- Premarket Approval Application Modular Review, November 3, 2003
  http://www.fda.gov/cdrh/mdufma/guidance/835.html
- Premarket Approval Application Filing Review, May 1, 2003 - http://www.fda.gov/cdrh/ode/guidance/297.html
- Post-Approval Studies –
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm

Transparency, Information on Web

- **http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/default.htm**
- **Trade Name:** COBAS AMPLIPREP/COBAS TAQMAN HCV TEST
- **Classification Name:** assay, hybridization and/or nucleic acid amplification for detection of hepatitis C RNA, hepatitis C virus
- **Applicant:** ROCHE MOLECULAR SYSTEMS, INC.
- **PMA Number:** P060030
- **Date Received:** 10/27/2006
- **Decision Date:** 10/30/2008
- **Product Code:** MZP
- **Docket Number:** 09M-0033
- **Notice Date:** 01/27/2009
- **Advisory Committee:** Microbiology
- **Expedited Review Granted?:** No
- **Information About:** Labeling, Approval Order, Summary of Safety and Effectiveness

FOI ITEM **LETTER**

FDA Review **Decision Summary**
(for a 510(k); **SSED** for a PMA)

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

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

Summary :Keys to a Successful PMA Submission

- Scientifically designed and well executed studies
- Good manufacturing practice documentation
- Appropriate statistical analysis of data
- Well written submission based on scientific principles
- Make use of available FDA documents and resources on the web
- Good communication with FDA throughout the entire process; pre-IDE meetings highly recommended

Questions ?