PMA and Panel Review Process and Decision Making from FDA's Viewpoint

AMDM: *2012 Annual Meeting*

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FDA PMA Review

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.
- BIMO

Review/Approval Takes Longer than Expected. Why?

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 ? (cont.)

- 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
- 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. Approval delayed by compliance inspection findings

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

Did you work with FDA through pre-IDE discussions?

Analytical/Clinical Study Sections

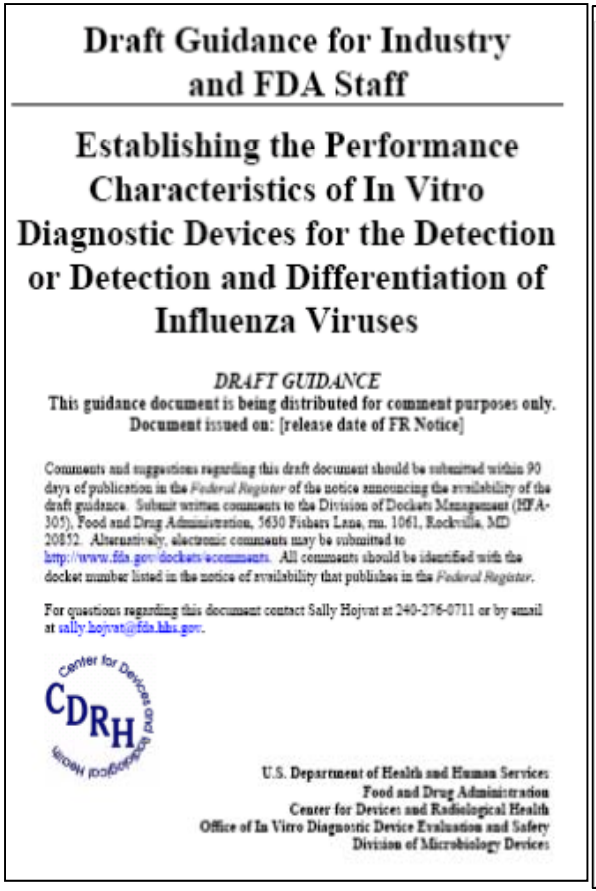
- Precision/Reproducibility - minimum of 3 sites

  -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
- 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

Guidance Documents/SSED



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

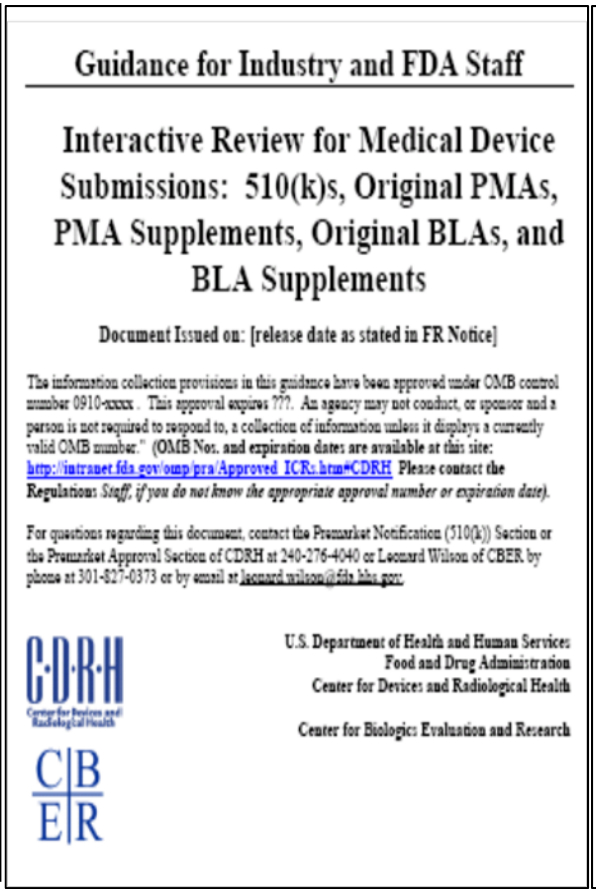
DRAFT GUIDANCE

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

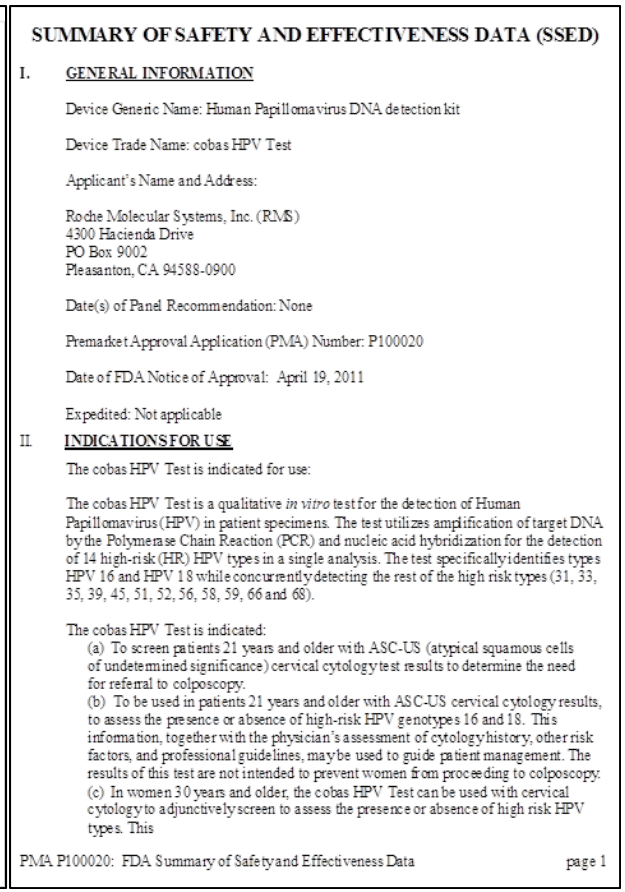
Document Issued on: [release date as stated in FR Notice]

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



SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Human Papillomavirus DNA detection kit

Device Trade Name: cobas HPV Test

Applicant's Name and Address:

Roche Molecular Systems, Inc. (RMS)
4300 Hacienda Drive
PO Box 9002
Pleasanton, CA 94588-0900

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P100020

Date of FDA Notice of Approval: April 19, 2011

Expedited: Not applicable

II. INDICATIONS FOR USE

The cobas HPV Test is indicated for use:

The cobas HPV Test is a qualitative *in vitro* test for the detection of Human Papillomavirus (HPV) in patient specimens. The test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk (HR) HPV types in a single analysis. The test specifically identifies types HPV 16 and HPV 18 while concurrently detecting the rest of the high risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).

The cobas HPV Test is indicated:
(a) To screen patients 21 years and older with ASC-US (atypical squamous cells of undetermined significance) cervical cytology test results to determine the need for referral to colposcopy.
(b) To be used in patients 21 years and older with ASC-US cervical cytology results, to assess the presence or absence of high-risk HPV genotypes 16 and 18. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management. The results of this test are not intended to prevent women from proceeding to colposcopy.
(c) In women 30 years and older, the cobas HPV Test can be used with cervical cytology to adjunctively screen to assess the presence or absence of high risk HPV types. This

PMA P100020: FDA Summary of Safety and Effectiveness Data page 1

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

Medical Device Advisory Committee (MDAC)

Function:

- Provides independent expert advice
- Lends credibility to the product review process
- Allows for a public discussion of controversial issues
- Keeps consumers abreast of trends in product development

MDAC: Function (cont.)

Advise and/or make recommendations regarding:

- Device marketing applications (PMAs, 510(k)s, HDEs)
- Classification, reclassification of devices
- Guidance documents
- Specific issues or problems concerning the safety and effectiveness of devices
- Trial design issues
- Postmarket study design
- Postmarket study progress

PreMarket Approval (PMA)

- Reasonable Assurance of Safety and Effectiveness for the proposed Intended Use
  - Benefit / Risk
  - Clinically significant results
- Consists of:
  - Clinical data from the IDE or other sources of Valid Scientific Evidence
  - Summary of Safety and Effectiveness
  - Proposed labeling for the product

Valid Scientific Evidence

- Well-Controlled Investigations
- Partially Controlled Studies
- Objective Trials Without Matched Controls
- Self Controls
- Historical Controls
- Well-Documented Case Histories by Qualified Experts

21 CFR 860.7

PMA Independence

- Each PMA should establish the safety and effectiveness of each device

- Data from one PMA cannot be used in support of another device

Appointments to Advisory Committees

- FDA must undertake effective outreach activities, including external input, to recruit MDAC members

- FDA must review financial disclosure report and expertise before appointment to reduce likelihood of subsequent waivers

Prohibition and Waiver Provisions

- MDAC member may not participate if member or immediate family member has a financial interest that could be affected (excluding *de minimus* interests exempted by Office of Government Ethics)

- Waiver may be granted if <u>necessary to afford committee essential expertise</u>

MDAC:18 Device Panels

- Anesthesiology and Respiratory Therapy
- Circulatory System
- Clinical Chemistry and Clinical Toxicology
- Dental Products
- Dispute Resolution
- Ear, Nose and Throat
- Gastroenterology and Urology
- General and Plastic Surgery
- General Hospital and Personal Use
- Hematology and Pathology
- Immunology
- Microbiology
- Molecular and Clinical Genetics
- Neurological
- Obstetrics and Gynecology
- Ophthalmic
- Orthopaedic and Rehabilitation
- Radiological

Panel Membership

- 7 Voting Members on each panel selected by the Agency
  - Clinical and administrative medicine
  - Engineering
  - Biological and physical sciences
  - Other related professions
- Temporary voting members may be added as needed
  - Expertise required if absent among standing members
  - To comprise a quorum

Panel Membership

- **FDA wants to have its Advisory Committee Members mirror the population of the United States with regard to**
  - Age
  - Race
  - Sex
  - Ethnicity
  - Geographic location

Consumer Representative

- Selected by Consumer Nominating Group
- Provide Consumer perspective on issues before the Committee
- Serve as a liaison between the panel and consumers, associations and organizations
- Consult with interested consumer groups to determine how consumer concerns can best be addressed
- Establish a link to the diverse constituencies served by FDA

Industry Representative

- Selected by Industry
- Represent ALL members of the affected industry
- Consult with all interested industry groups on the matter coming before the panel
- Communicate with manufacturers that are interested in a particular panel discussion
- Review material provided by the DFO

Patient Representative

- Share personal experience
- Present the perspective of patients
- Provide liaison with advocacy groups

Responsibilities of the Panel Member

- Attend Scheduled Meetings *for the duration of the meeting*
- Disclose conflicts of interest
- Refrain from discussing or providing oral or written advice to Agency staff on any matter coming before the Committee until the COI screen is completed
- Review the briefing material received prior to the meeting

Responsibilities of the Panel Member

- Be an active participant in the Panel discussions
- Question the presenters and applicants during the meeting
- Vote when appropriate and provide the reason for your vote
- Protect confidentiality of privileged information
- Complete necessary documentation to ensure proper compensation

Conflicts of Interest

- Prior to every meeting each Special Government Employee (SGE) is evaluated for any potential conflicts of interest relative to the meeting topic
- Experts by definition are engaged in cutting edge bench science, “clinical trial” research and independent consulting work
- By virtue of the above, these individuals are sought out by regulated industry to assist in product development

Panel Topics

- First of a Kind Medical Device - New device type
- A PMA that raises New issues of safety and effectiveness (change in Intended Use)
- Device clinical performance demonstrates unanticipated safety and effectiveness questions
- New data or information developed after approval of a product raises questions about safety and effectiveness

Panel Discussion

- Aspects of device use that raise safety concerns for patients and/or users
- Potential long-term effects that have not been evaluated (Post Approval Issues)
- Significance of disclosed adverse events when a benefit/risk test is applied
- Proposed indications for use or claims not adequately supported by evidence presented (Labeling)
- The actual clinical significance (to patient health) of statistical analysis data presented

Topics Outside FDA Purview

- Cost (actual or estimated) of device to users
- Cost incurred in development of device
- Cost of clinical trials conducted
- Cost of Post-Approval studies (if any)
- Manufacturing and marketing costs
- Costs to maintain and/or service a device
- Impact of device approval/non approval on insurance reimbursement
- Any speculation regarding off-label use

Post-Approval Studies as Conditions of Approval

CFR Title 21 Section 814.82 states that…..FDA may impose post-approval requirements at the time of approval of the PMA or by regulation subsequent to approval and may include:

Need for Post-Approval Studies (PAS)

- Gather essential postmarket information
  - Longer-term performance including effects of re-treatments & product changes
  - Community performance (clinicians & patients)
  - Effectiveness of training programs
  - Sub-group performance
  - Outcomes of concern, real & potential
- Account for Panel recommendations

Panel Meeting Agenda

- Introductions, Division Updates, Special Topics
- Sponsor Presentations
- FDA Presentations
- Open Public Session
- Panel Deliberations
- FDA Discussion Questions
- FDA and Sponsor Final Comments
- Panel Vote
- Adjournment

Panel Meeting Agenda

- Closed Session (when announced)
  - Review confidential information
  - Present FDA's workload and anticipated submissions

  (Industry Representative Does Not attend closed session)

Panel Vote on a PMA

The Designated Federal Officer (DFO) reads the definitions:

- Safety
- Effectiveness
- Valid Scientific Evidence

Voting Questions

- Is [there a reasonable assurance that] X device is safe for indication(s) X (and Y, etc.)?
- Is [there a reasonable assurance that] X device is effective for indication(s) X (and Y, etc.)?
- Do the benefits of device X for indication(s) X (and Y, etc.) outweigh the risks of device X for indication(s) X (and Y, etc.)?

Panel Vote on a PMA

- The panel makes its recommendation(s) for action and votes in open public session
- The CHAIR votes only to break a tie vote
- The transcript must provide the basis for the panel's recommendations

Panel Vote on a PMA

- Chair will ask each panel member to discuss why they voted yes or no on the questions
- Panel members will be asked whether changes to labeling, restrictions on use, longer term follow-up, or other controls, would change their response
- Panel members are asked to provide a description of any remedial studies or actions

Post-Panel Meeting
FDA Actions on a PMA

- A 24hr Summary is posted on the FDA Website
- FDA considers the panel's Recommendation(s), and the other information in reaching a decision on the PMA
- FDA informs the sponsor of the regulatory decision determined by FDA:
  - Approval
  - Approvable with conditions
  - Not approvable
- FDA makes the Summary of Safety and Effectiveness Data (SSED) from the PMA available for public review

QUESTIONS?

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