Premarket Approval Applications
An IVD Manufacturer's View

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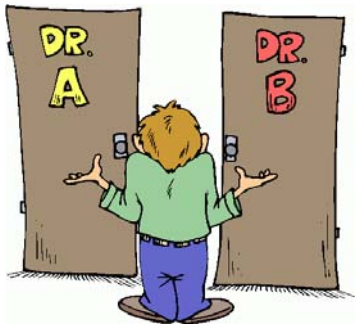
Items for Today's Presentation

Decision to Develop a Class III (PMA Product)

- Requirements
  - Product Requirement
  - Regulatory Requirements



The Premarket Approval Application

Managing Changes

Compliance Opportunities

Added Value

The Path for Premarket Approval Application

Decision to Develop a Class III (PMA Product)

Product Requirements / Regulatory Requirements

Infectious Disease—Easy Decisions

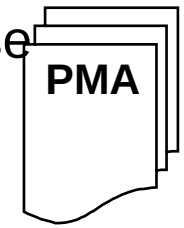
- Risk Associated with Infectious Agent / Disease Target
  - Infectious Diseases: contagious condition with poor outcome / public health impact
    - HBV, HCV, HIV, HPV, *M. tuberculosis*
  - Agreement with Other Classification Schemes
    - IVDD
      - » High Risk: HBV, HCV, HIV
      - » Lower Risk: HPV, *M. tuberculosis*
    - GHTF
      - » High Risk: transmissible agent that causes a life-threatening, often incurable, disease with a high risk of propagation

Decision to Develop a Class III (PMA Product)

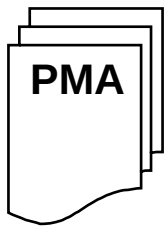
Product Requirements / Regulatory Requirements

Infectious Diseases--More Complicated Decisions

- Risk Associated with Infectious Agent / Intended Use
  - HBV, HCV HIV Viral Load Monitoring
  - HIV Drug Resistance Genotyping



  - Other Infectious Disease (Normally Class II)
    - Detection
    - Viral Load Monitoring



Decision to Develop a Class III (PMA Product)

Product Requirements / Regulatory Requirements

Infectious Disease—More Complicated Decisions

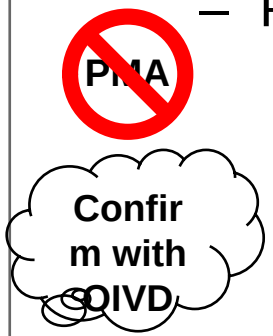
- Risk Associated with Infectious Agent / Intended Use
  - Agreement with Other Classification Schemes
    - GHTF
      - HBV, HCV, HIV Diagnostic Tests
        - » Highest Risk
      - HBV, HCV, HIV Viral Load Monitoring
        - » Lower Risk

Decision to Develop a Class III (PMA Product)

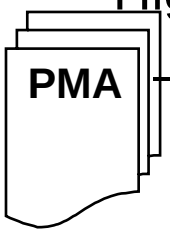
Product Requirements / Regulatory Requirements

Other More Complicated Decisions--Cancers

- Lower Risk Intended Uses
  - Prognosis / Monitoring
    - Tumor markers as an aid in monitoring patients for disease progress or response to therapy or for the detection of recurrent or residual disease
    - as an aid in management (monitoring) of prostate cancer patients



- Higher Risk Intended Uses
  - Diagnosis
    - aid identification of patients with gastrointestinal stromal tumors
    - an aid in discriminating between prostate cancer and benign disease



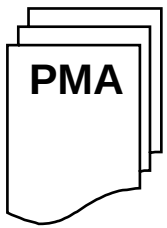
Decision to Develop a Class III (PMA Product)

Product Requirements / Regulatory Requirements

Still More Complicated Decisions

- Pharmacogenetic / Biomarker Assays
  - Lower Risk Intended Uses

    - aid in determining treatment choice and individualizing treatment dose for therapeutics that are metabolized primarily by the (specific enzyme)
    - Certain drugs that are metabolized by
    - aid in the identification of patients with greater risk for decreased UDP-glucuronosyltransferase activity.
  - Higher Risk Intended Uses



    - an aid in identifying colorectal cancer patients eligible for treatment with erbitux (cetuximab), or vectibix (panitumumab)
    - an aid in the assessment of patients for whom herceptin (trastuzumab) treatment is being considered

Decision to Develop a Class III (PMA Product)

Conclusion

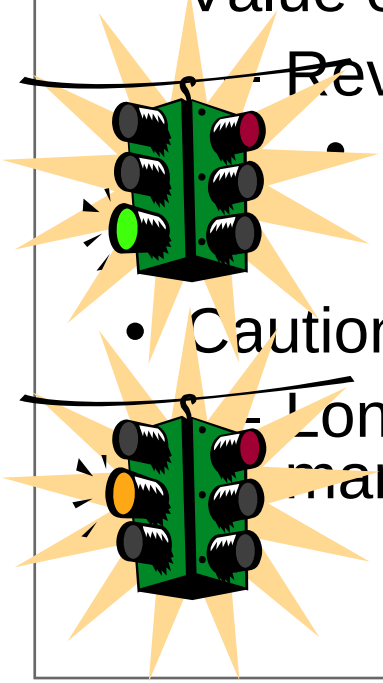
- If not clear on whether a PMA is required
  - Contact your reviewer 
  - File a pre-IDE 

513(g) Request for Classif

Preparing the Premarket Approval Application

Traditional of Modular PMA

- Value of Modular
  - Review can begin prior to complete information available
    - Pre-clinical, manufacturing information while waiting for final clinical trial information
- Caution
  - Long lead time before clinical trial info may require updates manufacturing information.



Preparing the Premarket Approval Application

Documentation

- Templates for pre-clinical reports and manufacturing summaries
  - Best practices documents
  - Part of Design Output documentation
    - Flow diagrams
- Software documentation
  - Traceability to requirements in software validation guidance
- Quality Systems documentation
  - Concise summaries

Low Risk Devices Used with Class III Devices

Treatment of Non-Class II Devices in a Premarket Approval Application

- Low Risk Devices Take on Risk of Class III Devices
  - Specimen Preparation Materials
    - Normally Class I Exempt
      - RNA Specimen Preparation Devices = Class II
    - Approved as part of the class III test system
  - Software
    - Level of Concern According to Intended Use

Managing Changes

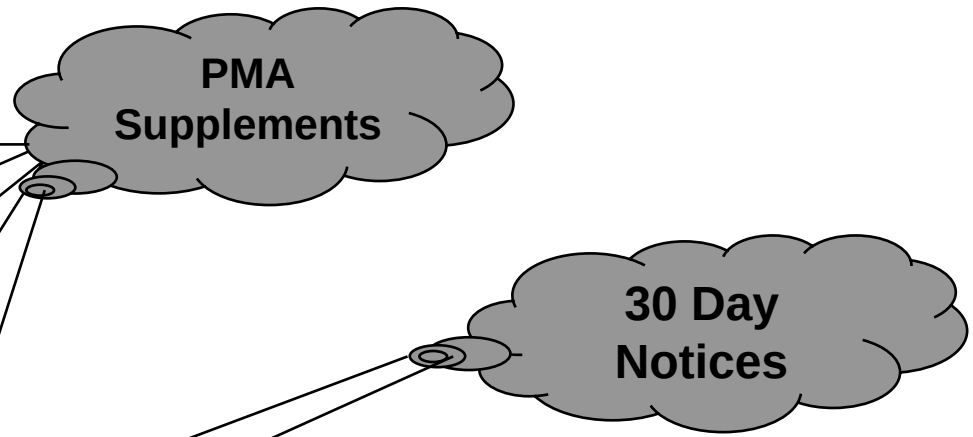
The Basics

- Annual Report
  - No pre-Approval Requirement
- PMA Supplements
  - Require Pre-Approval

Managing Changes

PMA Supplements

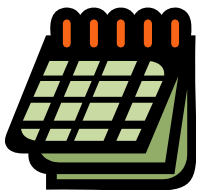
- Panel Track Supplements
- 180 Day Supplements
- 135 Day Supplements
- Real Time Supplements
- Manufacturing Site Change Supplements
- Special PMA Supplements—Changes Being Affected
- 30 Day Notices



Managing Changes

Terms Used Here

- Minor Changes
  - Highly unlikely (“minimal potential”) to impact safety and effectiveness
  - Controlled by established procedures
  - Annual Reports
- Moderate Changes
  - Not likely (“moderate potential”) to impact safety and effectiveness
  - 30 Day Notice



- Major Changes
  - 180 Day Supplements
  - Could reasonably be expected (“substantial potential”) to impact safety and effectiveness

Managing Changes

Prior to Filing the Premarket Approval Application

- Minor Changes
  - Amendments
    - Changes early on during review process
      - Little or no impact on approval time
    - Changes late in review process
      - Annual Report after approval

Managing Changes

Prior to Filing the Premarket Approval Application

- Moderate / Major Changes
  - Amendments
    - Changes early on during review process
      - Not likely to impact review
    - Changes late in review process
      - Likely to delay approval
  - Supplements
    - Change cannot be implemented until after approval of PMA and of PMA Supplement

Managing Changes

Changes Made After PMA Approval

- Minor Changes
  - No Pre-approval requirement
  - Notification in Annual Report
- Moderate Changes
  - Requires Pre-approval
  - 30 Day Notice
- Major Changes
  - 180 Day Supplement
  - May also Have Pre-approval Requirements Outside US

Managing Changes

Changes to Multiple Products

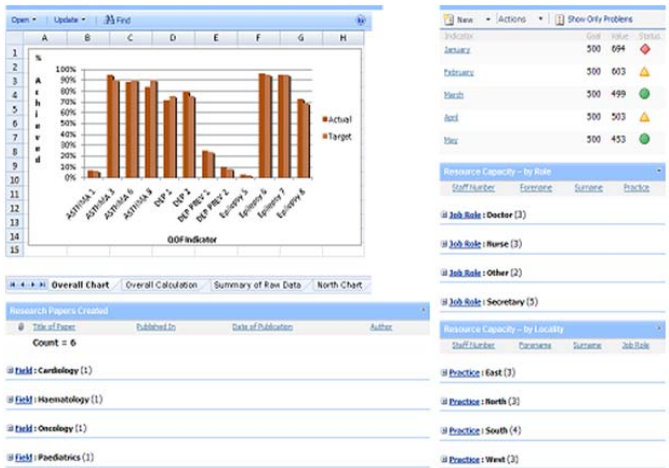
- Products in Early Review
  - In US
  - In Other Countries
- Products in Late Review
  - In US
  - In Other Countries
- Approved Products
  - In US
  - In Other Countries
- Bundling of PMA Supplements

Compliance Opportunities Prior to PMA Approval

BIMO Inspection

Pre-Approval Inspection

PMA Review



Compliance Opportunities After PMA Approval

Inspections After PMA Supplements

Post Approval Inspection

QSIT Level 2 Inspections

Advantages of Class III Approvals

- Approved Class III IVD Products Are a Select Group
  - Original PMAs Approved for IVD Products at CDRH Since 2005
    - Microbiology: 25
    - Immunology: 8
    - Clinical Chemistry: 2

Advantages of Class III Approvals

- Approved Class III IVD Products Have Demonstrated Clinical Utility
  - Useful in predicting non-response to HCV therapy, and predictive of non-sustained virological response.
  - Guide the intra operative or post-operative decision to remove additional lymph nodes
  - Can be used to measure HBV DNA levels at baseline and during treatment to aid in assessing response to treatment

Some Challenges for Class III Products

- Genetic Tests
  - Competition from Laboratory Developed Tests
    - Existing Laboratory Developed Test Targeting Same Genetic Condition and Intended Use as for PMA Product

Some Challenges for Class III Products

- De Novo Classification or Premarket Approval Applications
  - Prior to the FDA Modernization Act of 1997
    - Any device that was not classified at that time is automatically assigned to Class III, requiring a premarket approval (PMA) application
  - FDAMA Amendment to Section 513(f)
    - New mechanism for reclassifying new Class III devices for which there is no predicate device
  - Decisions for De Novo Classification
    - Can the device be considered Low Risk?
    - Is there adequate evidence exists to demonstrate its safety and effectiveness?

And What Will the Road Ahead be Like?

Least Burdensome

510(k) Reform

GHTF Model

Regulation of Laboratory Developed Tests

Companion Diagnostics