An Introduction to the Worldwide Regulatory Framework for Medical Devices

Elizabeth Malo M.S., Director, Regulatory Affairs
Course Outline / Agenda

» Overview - Device Regulatory Framework
» US/EU/Canada Premarket Requirements & Submissions Comparison
» 510(k) / PMA Detailed Explanation
» Introduction to Design Controls
» Understanding Clinical Trials
» RA / QMS Strategy Development
» Question / Answer Session
» Additional Items
  – FDA and Pre-Market Clearance Impact
  – EU Medical Device Regulation
Medical devices range from simple tongue depressors and bedpans to complex programmable pacemakers with micro-chip technology and laser surgical devices.

Medical devices include *in vitro* diagnostic products, such as general purpose lab equipment, reagents, and test kits, which may include monoclonal antibody technology.

Certain electronic radiation emitting products with medical application and claims meet the definition of medical device.

- Examples include diagnostic ultrasound products, x-ray machines and medical lasers.
If a product is labeled, promoted or used in a manner that meets the following definition in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act it will be regulated by the Food and Drug Administration (FDA) as a medical device and is subject to premarketing and postmarketing regulatory controls. A device is:

"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- 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, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."
Device Classification SIMILAR BUT Not Global

» In one country a product might be regulated as drug in another country regulated as a device (example LVP Balanced Intra-Ocular Saline Solution (BSS) Drug in the US, CE Marked medical device in Europe

» In some countries a product is ‘prescription’ and in other Over The Counter (OTC)
The **Intended Use** of the medical device is the objective intent of the person legally responsible for labeling of a device

- **Indications for Use** of a medical device identify the patient population(s) for which a device can be used, or general or specific conditions a device is intended to treat or diagnose.

The intended use is the driving force behind medical device classification and often specifies one or more of the following specifications:

- Outcome measured (*Ex: clearance of blockage by stent*)
- Purpose for measurement (*determine safety and efficacy*)
- Intended population
- Indication for use
- Qualitative vs. quantitative clinical endpoints
- Testing matrices
- Adjunctive or stand alone tests
Common Global Regulatory Framework Stages

» Pre-Market
  – Conception and Development
  – Manufacture
  – Packaging and Labeling

» Placing on the Market
  – Advertising/Sale

» Post-Market Surveillance / Vigilance
  – Use
  – Disposal
US Regulatory Submissions

• Regulatory Applications for Devices
  – United States
    • 510(k) – Substantial Equivalence w/ Predicate(s)
      – Intended Use / Indications for Use
      – Similar Technology
      – Assumed Safety and Effectiveness
    • PMA – Proves Safety and Effectiveness
      – No Predicate
      – Requires Animal and Human Trials
    • De Novo – Risk & Evidence-based Classification Process Low to Moderate Risk Devices
      – Paths: 510(k) with NSE followed by De Novo Application or straight De Novo Request
    • Others
      – 513(g) – Request for Classification
      – RFD – Request for Designation (combination products)
      – IDE – Investigational Device Exemption
EU & Canada Regulatory Submissions

– Canada
  • License Application
  • QMS Certification
    – CAN/ ISO 13485:2003
    – Canadian Registrar
    – Additional CMDCAS Requirements

– Others
  • Most developed nations have requirements for investigating and marketing medical devices

– Europe
  • CE Marking
    – Product Approval
      • Compliance with Appropriate Directives (MDD, IVDD, AIMDD)
      • Technical File / Design Dossier
  – QMS Approval
    • ISO 13485
    • Notified Body Audit
US vs. the E.U. and Canada

- **Similarities**
  - Risk Based Device Categorization Schemas
    - US – Class I to Class III
    - EU – Class I, Class IIa, Class IIb, Class III
    - Canada – Class I to Class IV
  - Premarket Clearance / Approval Required
    - Significance of Process Based on Risk
    - Clinical Data Required for High Risk Devices
  - Quality Management System Required
    - cGMP and ISO 13485:2003 are very similar
    - Post Market Monitoring and Adverse Event Filing Required
    - Audits are performed to verify compliance
  - Clinical Trials Require Pre-Approval
    - US – IRB + IDE for Significant Risk, IRB only for Non-Significant Risk
    - EU – Ethics Board + Competent Authority for non-CE devices, Ethics Board only for CE devices
    - Canada – Ethics Board + ITA for Class II – Class IV devices, Ethics Board only for Class I devices
US vs. the E.U. and Canada

• Differences
  – Risk Based Device Categorization Schemas
    • Canada and EU use “Rules Based” approach, not lists of devices and associated classifications (pro-codes)
    • Dramatic Differences in resulting Device Classifications (i.e. – US Class III could be EU Class I)
  – Premarket Clearance / Approval Required
    • Canada and EU have a single, scalable application type vs. US with two distinct dissimilar applications (tech file and design dossier vs. 510(k) and PMA)
    • Canadian Review done by Governmental Agency
    • EU Review done by Third Party (Notified Body) or Self Declaration
    • US Review done by both FDA and Third Parties
    • ISO 13485 Cert required PRIOR to pre-market approval in EU and Canada
US vs. the E.U. and Canada

- Differences (Cont.)
  - Quality Management System Required
    - Enforcement of ISO 13485 and QSR are very different
    - FDA acts as a law enforcement agency to gather evidence of non-compliance
    - Non-compliance with ISO results in CE loss, FDA non-compliance can result in civil and criminal penalties
  - Clinical Trials
    - EU - All Devices Require Clinical Evaluation Report (Annex X)
      - Allows a combination of Literature Review, Clinical Information, and Clinical Data
      - Class IIb and Class III typically require Clinical Trail
    - Canada – Class III and Class IV typically require clinical data
    - US – Class III PMA Devices require Clinical Data. Some 510(k) devices require clinical data to support Substantial Equivalence.
US Premarket Submission Concepts

- **Product Codes**
  - Used to Categorize Devices (~1700 Generic Device Types in 16 Medical Specialties)
  - Specifies
    - Device Class / Classifying Regulation
    - TPLC Report
    - GMP Exemptions
    - Submission Type
    - Mandatory Standards

- **Predicate Devices**
  - Same Intended Use
  - Same or Similar Technology
  - No Predicate = Automatic Class III Designation

- **Device Classifications**
  - **Class I – Low Risk, General Controls**
    - Most 510(k) Exempt
    - Some QSR (cGMP) Exempt
      - Most Design Control Exempt
  - **Class II – Medium Risk, Special Controls**
    - Few 510(k) Exempt
    - None QSR (cGMP) Exempt
    - May Require Human Clinical Data
  - **Class III – High Risk, Special Controls or PMA**
    - Most Require PMA
    - None QSR (cGMP) Exempt
      - None Design Control Exempt
    - All PMAs Require Clinical Data
Typical US Premarket Submissions

• **PMA**
  - Three Flavors
    • Standard
    • PMA Supplement
      - Significant Changes
    • PMA Amendment
      - Amends an unapproved PMA or PMA Supplement
  - Demonstrate Safety and Effectiveness in Class III Devices
  - No Predicate Device Exists
  - Requires Human Clinical Data
    • One or More Pilot Studies
    • Significant Pivotal Study
  - Includes Significant Manufacturing Information
  - Requires Pre-Approval Inspection
  - 180 Day Review Target

• **Pre-Market Notification- 510(k)**
  - Three Flavors
    • Traditional
    • Special (Device Modification)
    • Abbreviated (consensus standards & special controls)
  - Substantial Equivalence
    • One or More Predicate Devices
    • Intended Use Comparison
    • Technology and Specification Comparison
    • Technology Differences may drive Bench, Animal or Human Testing to address
  - Human Clinical Data Typically NOT Required
  - 90 Day Review Target
Traditional 510(k) Submission – Required Components

» Description of Medical Device
  - Photographs
  - Engineering (CAD) drawings

» Proposed Labeling
  - Promotional Materials (Drafts, not Final required)

» Identification of Predicate Device(s)

» Narrative and tabular comparison to Predicates

» Predicate Device(s) Intended use, Indications for Use

» Technological Characteristics

» Principles of Operation

» Software Documentation

» Sterility information

» Biocompatibility Testing

» Statement or Declarations of Conformance (to applicable Standards and FDA Guidance Documents)

» Performance testing (bench, animal, clinical) based on Standards. Ex:
  - Risk Assessment (ISO 14971 Standard)
  - Electromagnetic Compatibility and
  - Electrical Safety (ISO 60601-1 Standard)

» Administrative requirements
  - Truthfulness and accuracy statement
  - 510(k) summary
  - Payment of User Fee
De Novo Process

The De Novo Process establishes new “device type” along with classification, regulation, necessary controls and product code where the cleared device is eligible to serve as a predicate for new medical devices, where appropriate [510(k) process]

2 Paths:

1. De Novo Request: devices which do not fall within any classification regulation, where the de novo requester either determines that there is no predicate device (consider pre-sub)

2. Upon NSE determination on a 510(k) submission where no predicate exists with following criteria:
   
   » low to moderate risk and should appear, based on what is known about the device, to meet the statutory standards for classification into class I or class II

   » Sufficient understanding and presentation of
      
      – Strong risk-benefit analysis and risk mitigation
      
      – Device effectiveness through general and/or special controls
510(k) summaries, decision summaries, or summaries of safety and effectiveness (SSEDS) for similar legally marketed devices, may be helpful resources, and are available on FDA websites.
Design Control Overview

- 21 CFR § 820.30 – Design Control
  - Requires a “SYSTEM” including policies and procedures intended to control the product development process
  - Applies to Nearly All Medical Device Except:
    • Some Class I Devices (US / EU / Canada)
    • Some Class IIa Devices (EU)
  - Intended to Provide Structure to the Development Process to Ensure Outputs meet Input Requirements
  - Provides Documentation to Support Pre-Market Submission
    • 510(k) / PMA
    • Technical File / Design Dossier
    • License Applications
    • Etc.
  - Is Not Intended to be Executed Retrospectively
Design Control Overview (cont.)

• **Required Elements**
  - Design and Development Planning
  - Design Input
  - Design Output
  - Design Review
  - Design Verification
  - Design Validation
    - Risk Analysis
    - Software Validation
  - Design Transfer
  - Design Changes
  - Design History File

• **Other Elements for Consideration**
  - Control of Design and Development Subcontractors and Consultants
  - Software Lifecycle
    - Configuration Management
    - Bug Tracking
  - System Configuration Management
  - Equipment Maintenance and Calibration
  - Document Controls
  - Test Method Validation
  - Purchasing of R&D Materials
Process Overview (Industry View)

Project Planning and Requirements Definition

- Specification Development
  - System
  - Domain
  - Sub-System
  - Assembly
  - Component

Design Transfer

- Verification Validation
  - Clinical Trial & Design Validation
  - Integration & Functional Verification
  - Failure Modes Effects Analysis
  - Assembly Function Verification
  - Inspection & Component Testing
**Clinical Trials Overview**

» Approvals to Conduct Human Clinical Studies

- US / EU / Canada
  » All require Institutional Review Board (IRB) / Ethics Board / Ethics Committee Approval PRIOR to Study Initiation
  » In MOST cases IRB, EB, or EC may determine the necessity for other Regulatory Involvement (FDA, Competent Authority)
  » High Risk Studies / High Risk Devices generally require direct regulatory body involvement via an Application Process
  » Requirements in the EU vary Country by Country

- Other Countries
  » Nearly ALL First and Second World Countries Require some type of Approval to Initiate Human Clinical Studies

» Clinical Studies MAY be discoverable by Regulatory Authorities regardless of where conducted (e.g. Truthful and Accurate Statement)
Clinical Trials Overview (cont.)

• Things To Know about FDA and Device Trials
  – OUS Studies MAY be acceptable to Support a 510(k) or PMA BUT;
    • Use the Pre-IDE Process BEFORE Initiating the OUS Trial
    • Choose a Country whose Demographics and Clinical Practices are comparable to the US
      (Canada / EU most readily accepted)
  – Pre-IDE Process
    • Non-Binding on FDA
    • Helps Understanding of FDA Expectations
    • Is NOT generally a Pre-Submission Meeting but.......  
    • Establishes Company’s willingness to “Work with FDA”
    • Don’t Ignore what FDA tells you!
  – Don’t Assume a US Trial is Non-Significant Risk without confirmation from FDA
    • Reliance solely on IRB can bring unpleasant surprises
  – More 510(k) Devices are likely to require significant Clinical Data
Regulatory / QA Strategy Overview

• What Is A Regulatory Strategy?
  – A Path for Regulatory Clearance / Approval in a Market
  – Understanding of the Requirements to Obtain Clearance or Approval
    • Application Type
    • Requirements for Bench Testing
    • Requirements for Animal Testing
    • Requirements for Human Testing
    • Quality Management System Requirements
    • Quality Management System Certifications
  – Understanding the Sequence of Events and Timing
  – Understanding the Integration of Business and Regulatory Activities
  – Understanding of Expected Regulatory / QMS Costs
• How Do I Know If My Current Strategy Is Good Enough?
  – Your Strategy Should Answer All Of The Following:
    • Where will the product be distributed in the first 36 months after launch?
    • What Regulatory Applications will be required in each country?
    • Which applications require clinical or animal data?
    • If Clinical Data is required, where will trials be conducted and what applications / approvals are required for the clinical trial?
    • How long is the average review time for my application type and product type in each country?
    • Are there fees associated with the Regulatory Application?
    • For each application, what is the likelihood of approval / clearance and what are the risk areas?
    • Do any of the applications require corresponding QMS inspections / certifications (pre-approval inspection, ISO certification, etc.)?
    • Do Design Controls apply to my product and if so, how will I meet these requirements?
    • Where the finished product will be manufactured?
• Potential Investors
  – Becoming More and More Educated About Medical Products
  – Understand that the Regulatory Strategy, along with IP Protection and Re-imbursement Strategy are key to Medical Device Company Success
  – Often Require both QA and RA due diligence by an expert prior to large round investing

• Potential Acquirers
  – Large US Device Companies
    • Have a history of QA / RA problems w/ Acquisitions
      – Massive Cost
      – Product Liability
      – Problems with FDA
    • Are looking for easily integratable QA / RA systems w/o major risk
    • Want QMS systems designed to comply with US cGMP requirements
    • Don’t want RA surprises (i.e. – poor submissions, off-label-use, etc.)
Additional Items
Current Events in FDA Device Regulations
510(k) Process Challenges

» More Burdensome Additional Information Process
  - More Questions
  - Requests for More Detail
  - NSE Decisions Based on Lack of Performance Data

» Longer Total Review Times

» More Influence by Medical Officers and Clinical Reviewers

» Process can be Unpredictable
  - Device Bench Testing Requirements
  - Need for Animal or Human Data
  - Changing of Requirements Mid-Process

» Increase in Data Requirements
  - Biocompatibility
  - Verification and Validation
  - Animal and Clinical

» More Scrutiny of Predicates
FDA “A-List” for Final Guidances in 2017

» Postmarket Management of Cybersecurity in Medical Devices
» Medical Device Accessories: Describing Accessories and Classification Pathway for New Accessory Types
» Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices
» Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions
» Suggested Format for Developing and Responding to Deficiencies
» Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics
» Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS) - Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases
» Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS) – Based In Vitro Diagnostics
» Infectious Disease Next Generation Sequencing Based Diagnostic Devices: Microbial Identification and Detection of Antimicrobial Resistance and Virulence Markers
» Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices510(k) Third Party Review Program
» New or revised procedural guidances for MDUFA IV implementation
CDRH 2016-2017 Strategic Priorities

- Establish a National Evaluation System for medical devices
  - Increase access to and use of real-world evidence to support regulatory decision-making
    - Thus far, gained access to more than 28 million electronic patient records (from national and international clinical registries, claims data, and EHRs) with device identification using a variety of mechanisms, such as cooperative agreements and access through regulatory process.

- Partner with patients
  - Promote a culture of meaningful patient engagement by facilitating CDRH interaction with patients
  - Increase use and transparency of patient input in regulatory decision-making
    - Identify/define the various pre- and post market regulatory uses of patient reported outcome measures (PROMs) and issue a report summarizing current PROM regulatory usage patterns and gaps.
    - Work with members of the medical device ecosystem to develop a framework for patient input to inform clinical study design and conduct, with a goal of reducing barriers to patient participation and facilitating recruitment and retention.

- Promote a culture of quality and organizational excellence
  - Strengthen FDA’s culture of quality within CDRH
    - In FY 2016, CDRH tripled the number of staff with quality credentials by providing on-site quality training and certification examinations.
  - Strengthen product and manufacturing quality within the med device ecosystem
Medical Device Webinars & Workshops

Webinars
» Regulatory Overview for Developers and Sponsors of Neurological Devices: An Introduction to the De Novo Pathway
» Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions Final Guidance
» Final Guidance on Medical Device Accessories: Describing Accessories and Classification Pathway for New Accessory Types

Public Workshops
» The Role of Hospitals in Modernizing Evidence Generation for Device Evaluation: Harnessing the Digital Revolution for Surveillance
» CDRH Veteran Amputee Device Workshop
» Refurbishing, Reconditioning, Rebuilding, Remarketing, Remanufacturing, and Servicing of Medical Devices Performed by Third-Party Entities and Original Equipment Manufacturers
» Controlling the Progression of Myopia: Contact Lenses and Future Medical Devices
» Adapting Regulatory Oversight of Next Generation Sequencing-Based Tests
EU Medical Device Regulations

Current Events
EU’s new Medical Device Regulations

- 2008: EU Commission launches consultation on MD framework
- 2012: EU Commission publishes proposal for new MD Regulation
- 2014 Q2: EU Parliament adopts position on MDR
- 2015 Q3: EU Council adopts position on proposed Regulation
- 2015 Q4: Trilogues between Commission, Parliament and Council starts
- mid 2017: Expected publication of the adopted MDR/IVDR in EUCJ

EU Graphics borrowed from BSI Medical Devices Regulation Update
Key Changes from MDD to MDR

**Notified Bodies**
- Strengthened Designation Criteria
- Joint Audits: Three Member States and Commission (FHAA)
- Unannounced audits

**Clinical Evidence**
- Less Equivalence, More Data for High Risk Devices
- Publish Safety and Performance Data
- Post Market Clinical Follow-up

**Pre-market**
- Scrutiny for High Risk Devices
- Common Specifications
- Responsible Person for Manufacturers and Authorised Representatives
Key Changes (cont.)

- **Post-Market Surveillance and Vigilance**
  - Central Database and Co-ordination
  - Trend Reporting
  - Enforcement Activities

- **Transparency and Traceability**
  - Devices and Economic Operators Registered Centrally
  - Unique Device Identification (UDI)
  - Implant Cards

- **Governance and Oversight**
  - Central Committee: MDCG
  - Expert Panel, Expert Laboratories
Changes in Medical Device Classification Rules

- New Process in case of dispute between NB and Manufacturer
- Addition of the active implantable medical devices to the classification rules
- Addition of tissue engineered products
- Up-classification of devices in direct contact with the heart or the central circulatory system
- Up-classification of orthopedic devices and devices in contact with the spinal column
- Addition of Nanomaterials
- Update of the wording regarding human origin material
Classification & Conformity Assessment – Regulation

Commission Assessment

Competent Authority Assessment

Notified Body Conformity Assessment

Self-Certification

Risk

Class III

Class IIb

Class IIa

Class I

Custom Made

Class III Implants & Class IIb active – delivering medicines

Animal tissues, human tissues, medicinal substances, absorbable

Class IIb Implants

Class IIa – more sampling

Custom Made Class III Implants

© Dohmen 2017. All rights reserved. May not be copied or distributed.
## MDR CE Marking on a Single Slide

1. Check **Device** is within Scope of MDR
2. Determine “**Device Class**”
3. Select “**Conformity Assessment Procedure**”
4. Identify Applicable “**Safety and Performance Requirements**”
5. Assign UDI
6. Assemble “**Technical Documentation**”
7. Apply Conformity Assessment Procedure
8. Complete “**Declaration of Conformity**”
9. Affix “**CE Mark**”
10. Post Market Surveillance & Updates **Technical Documentation**

(Chapter I, Articles 1, 2, Annex XVI)
(Chapter V, Article 51, Annex VIII)
(Chapter V, Article 52)
(Chapter II, Article 5, Annex I)
(Chapter III, Article 27, Annex VI)
(Annex I => Annex II, Annex XV)
(Annexes IX, X, XIA or XIB)
(Chapter II, Article 19, Annex IV)
(Chapter II, Article 20, Annex V)
(Chapter VII, Articles 83 to 86, Annex XIV => Annex III)
Contact Information

Eliza Malo, M.S. RA  
Director, Regulatory Affairs

Dohmen Life Science Services  
11925 W. I-70 Frontage Rd. North, Suite 900  
Wheat Ridge, CO 80033  
eliza.malo@dlss.com  
http://www.dlss.com/  
Phone: 303 952 7267  
Cell: 520 334 0959
thanks