AN INTRODUCTION TO THE WORLDWIDE REGULATORY FRAMEWORK FOR MEDICAL DEVICES

BioBoot Camp
Building Life Science Businesses

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COURSE OUTLINE / AGENDA

• Regulatory Framework Review Worldwide
• 510(k) / PMA Detailed Explanation
• US/EU/Canada Premarket Requirements Comparison
• Understanding Clinical Trials
• Introduction to Design Controls (US/EU/Canada)
• RA / QMS Strategy Development
• Changes at FDA and Pre-Market Clearance Impact
• Changes in Global and EU Medical Device Regulation
• Question / Answer Session
US FDA MEDICAL DEVICE
REGULATORY DEFINITION

- Medical devices range from simple tongue depressors and bedpans to complex programmable pacemakers with microchip 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.
US FDA MEDICAL DEVICE REGULATORY DEFINITION

• 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)
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
BACKGROUND INFORMATION

- 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
    - DeNovo – Risk Based Classification
      - 510(k) – NSE + DeNovo Application or straight DeNovo
      - Requires Special Controls Guidance Document
  - Others
    - 513(g) – Request for Classification
    - RFD – Request for Designation (combination products)
    - IDE – Investigational Device Exemption
BACKGROUND INFORMATION (CONT.)

- **Europe**
  - CE Marking
    - Product Approval
      - Compliance with Appropriate Directives (MDD, IVDD, AIMDD)
      - Technical File / Design Dossier
    - QMS Approval
      - ISO 13485
      - Notified Body Audit

- **Canada**
  - License Application
  - QMS Certification
    - Canadian Registrar
    - Additional CMDCAS Requirements

- **Others**
  - Nearly all 1st and 2nd World Countries have requirements for investigating and marketing medical devices
US PREMARKET SUBMISSION CONCEPTS

• 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

• 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
TYPICAL US PREMARKET SUBMISSIONS

- **Pre-Market Notification, 510(k)**
  - Three Flavors
    - Traditional
    - Special (Device Modification)
    - Abbreviated (Accepted Performance Standards)
  - 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??

- **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??
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.
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)
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
DESIGN CONTROL OVERVIEW

• 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
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
REGULATORY / QA STRATEGY

OVERVIEW

• 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?
RA/QA STRATEGIES AND VALUATION

• 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.)
STRATEGIC PRIORITIES
FDA CENTER FOR DEVICES AND
RADIOLOGICAL HEALTH (CDRH)

- Strengthen the Clinical Trial Enterprise
  • Reduce the time and number of cycles needed to reach appropriate IDE full approval
  • Increase the number of early feasibility/first-in-human IDE studies

- Strike the Right Balance Between Premarket and Postmarket Data Collection
  • Focus on high-risk devices of public health importance.

- Provide Excellent Customer Service
  • Focus on stakeholders, including patients, industry, and health care professionals.

- Unique Device Identifier (UDI)
  • UDI Final Guidance issued and implementation milestones defined system will help the FDA identify product problems more quickly.

- Medical Device User Fee and Modernization Act (MDUFMA)
  • Year-by-year goals for improvement in device review times, and expanded use of outside consultants and contractors, modular reviews, and improving the timeliness of premarket inspections.
CDRH TODAY

• Changes to the 510(k) Process
  - New Guidance (SE and When To File an New 510(k))
  - Limitations on Predicates and Reference Device concept
  - Improvements to the De Novo Process

• Increased Enforcement Action
  - Complaints / MDR Reporting
  - Off Label Promotion
  - Extension of Regulatory Authority
  - Clinical Studies

• Increased Attention to Part 11
  - Validation
  - Security
  - Data Integrity

• Other Looming Issues
  - eMDR
  - eSubmissions
  - UDI / Structured Product Labeling

Stress Reduction Kit
Bang
Head
Here

Directions:
1. Place kit on FIRM surface.
2. Follow directions in circle of kit.
3. Repeat step 2 as necessary, or until unconscious.
4. If unconscious, cease stress reduction activity.
510(K) PROCESS CHALLENGES

• 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

• 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
GLOBAL REGULATORY LANDSCAPE - HARMONIZATION

- MDD
- ISO/EN
- FDA Combination Products
EU MEDICAL DEVICE REGULATORY OVERHAUL

• Historical Legislation - Rules relating to the safety and performance of medical devices were harmonized in the EU in the 1990s. The core legal framework consists of 3 directives:
  - Directive 90/385/EEC regarding active implantable medical devices,
  - Directive 93/42/EEC regarding medical devices and
  - Directive 98/79/EC regarding in vitro diagnostic medical devices
  - These 3 main directives have been supplemented over time by several modifying and implementing directives, including the last technical revision brought about by Directive 2007/47/EC

  - Target for adoption: 2014
  - The new rules would then gradually come into effect from 2015 to 2019
EU MED DEVICE REGULATIONS
WHAT EXACTLY WILL CHANGE?

- Wider, clearer scope for EU legislation on medical devices
- Stronger supervision of independent assessment bodies by national authorities
- More powers for assessment bodies to ensure robust testing, regular checks on manufacturers, including unannounced factory inspections
- Clearer rights & responsibilities for manufacturers, importers and distributors
- Extended Eudamed database on medical devices - Non-confidential data will be publicly available
- Better traceability of medical devices throughout the supply chain
- Stricter requirements for clinical evidence to support assessments of medical devices
- Updated classification rules dividing medical devices into 4 different risk categories and health & safety requirements, including labelling rules – to keep pace with technological and scientific progress
- Better coordination between national surveillance authorities, with the Commission providing scientific, technical and logistic support
- International guidelines to be incorporated into EU law.
QUESTIONS