Right Submission Regulatory Foundations
CRAASH Barcelona
May 2018

SECTION 1. EUROPEAN REGULATIONS

Medical Devices Regulation 2017/745

The new MDR promotes a shift from the pre-approval stage (i.e., the path to CE Marking) to a life-cycle approach. This approach is similar to the life-cycle view advocated by the US Food and Drug Administration and advanced by many international standards. The life-cycle approach is illustrated by the incorporation of European guidance (MEDDEVs) into the Regulation: Guidance on Authorized Representation, Clinical Evaluation, Vigilance, and Post-Market Clinical Follow-Up has been integrated into the MDR. Life-cycle is generally understood to include product feasibility through post approval studies and product vigilance.

CE Mark Approval Process

1. Determine device classification
2. Implement Quality Management System
3. Prepare a Technical File (Class I, Class IIa, Class IIb) or Design Dossier (Class III) and a Clinical Evaluation Report
4. Submit Technical File or Design Dossier to a Notified Body (accredited third-party authority to audit medical device companies and products) (Class I non-measuring, non-sterile exempt)
    - Upon successful completion of Notified Body audit, receive CE Marking Certificate and ISO 13485 certificate
5. Prepare Declaration of Conformity, a legally binding document stating that the device is in compliance with applicable Medical Device Directive
6. Register device with the Competent Authority
7. Maintain CER and technical file, if not Class I non-measuring, non-sterile, undergo annual audits a Notified Body to ensure ongoing compliance and maintain certification

SECTION 2. US REGULATIONS

FDA Mission Statement

The Food and Drug Administration is responsible for protecting the public health by ensuring the **safety, efficacy**, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

FDA is responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.

FDA Approval Process

1. Determine device classification
    - Class I – exempt from premarket submission
        - Subject to general controls
    - Most Class II – Prepare 510(k) with or without clinical data
        - Subject to general controls and special controls, may or may not require clinical data
        - Prove substantially equivalent to a legally marketed device
    - Most Class III – Prepare PMA (life supporting or sustaining, or important in preventing impairment of human health)
        - Subject to general controls and special controls, requires nonclinical and clinical data
        - Prove possible benefits to health from intended use outweigh possible risks
2. Implement Quality Management System
3. Submit application to FDA
4. Receive clearance to market device in US
5. Post-Market Safety Monitoring

Harmonization

International Medical Device Regulators Forum

The International Medical Device Regulators Forum (IMDRF) was created in 2011 to evaluate requirements in individual countries, and **harmonize regulatory approaches** to digital health medical devices, where possible. Members include Australia, Brazil, Canada, China, the European Union, Japan, Russia, Singapore and the United States.

Current work items:

Unique Device Identification Application Guide – Promote globally harmonized approach to the application of a UDI system, contribute to benefits of UDI for regulators and stakeholders implementing UDI around the globe. Develop IMDFR Technical Document that will provide an Application Guide for UDI providing guidance (definition, instruction, context, etc.) needed for globally harmonized approach.

Personalized Medical Devices – Develop guidance that establishes definitions and regulatory pathways for Regulatory Authorities to consider in the regulation of medical devices that are intended for individual patients. The goal is to promote global harmonization in the terminology and premarket requirements for such devices.

The working group will develop an IMDRF Technical Document that will provide recommendations to support a harmonized approach to defining different categories of medical devices that are intended for individual patients.

Improving quality of international medical device standards for regulatory use – identify and explore possibilities to improve the process of developing international standards used for regulatory purpose in the medical technology domain. Further information on this Work Item is included in the attached presentation.

The scope of this Work Item will include the mapping of technical issues and concerns, with regard to regulatory aspects of standards developed by some major international standardization committees. It will also explore possibilities for improvement and discuss these with stakeholders and SDOs, and describe possible actions IMDRF could take to influence and support the development or amendment of standards for regulatory purposes.

Adverse event terminology – To improve, harmonize and where necessary expand the terminology and systems being used to code information relating to medical device adverse events, and to establish IMDRF adverse event terminology composed of the following three parts: terms for medical device malfunction, terms for patient/user outcome and terms for part/component of medical device. (Note: Evaluation terms and code are out of the scope of this Working Group.)

Regulated Product Submissions – Take advantage of a project underway internationally that will result in a messaging standard that supports the electronic transmission of regulatory submissions. This work will define a common 'Table of Contents' for medical device regulatory submissions as a first step in defining a common data set.

Good Regulatory Review Practices – The charter of the Working Group (WG) is to develop guidance that establishes good regulatory review practices for Regulatory Authorities and/or their Conformity Assessment Bodies. The goal is to promote global harmonization in the premarket review processes. The purpose of the current Work Item is to develop a common set of competency, training, and conduct requirements for regulatory reviewers that perform premarket reviews/assessments of the technical documentation of a submission/design dossier and is intended to develop confidence in the consistency of regulatory reviews across jurisdictions.

Patient registries – Registries of patients undergoing medical device procedures represent a growing potential electronic resource for local and global medical device evaluation and tracking. To integrate such established data resources with new tools (such as UDIs) and optimize their regulatory applications, shared essential principles of informatics infrastructure and best epidemiologic and statistical analytic methodologies could enhance the quality, speed and cost-efficiencies of regulatory science for medical devices. Therefore, the purpose of this Work Item is to collaboratively develop a shared set of those essential principles.

Recently closed work items include Software as a Medical Device guidance, Medical Device Single Audit Program, Roadmap for UDI System, IMDRF Recognized Standards

US v. EU Regulatory Considerations

	US FDA Clearance	EU CE Mark
Risk Classification	Class I (low risk) Class II (medium risk) Class III (high risk)	Class I (non-measuring, non-sterile devices) Class I (most non-invasive devices) Class IIa (non-invasive devices or invasive devices for short term use Class IIb (invasive devices intended for long term use) Class III (high risk, biological, or absorbed devices)
Application Types	510(k), De Novo Premarket Approval (PMA)	Technical File with Clinical Evaluation Design Dossier with Clinical Evaluation
Fees	510(k) filing fee, currently $10,556 or $2,642 for small businesses PMA filing fee, currently $310,764 or $77,691 for small businesses	Class I - $5,000 - $15,000 Class I - $15,000 - $30,000 Class IIa - $30,000 - $50,000 Class IIb and Class III - $50,000+

SECTION 3. WHAT IS A MEDICAL DEVICE?

EU MDD's definition of a medical device

'Medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

1. diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease
2. diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability
3. investigation, replacement or modification of the anatomy or of a physiological or pathological process or state
4. providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations

And which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

FDA's definition of a medical device

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

1. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
2. 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
3. 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 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 its primary intended purposes.

SECTION 4. MEDICAL DEVICE CLASSIFICATION

CE Mark Device Classification

Four basic categories:

- Non-invasive devices
- Invasive medical devices
- Active medical devices
- Special Rules (including contraceptive, disinfectant, and radiological diagnostic medical devices)

Devices are further segmented into the classes noted below. IVDs have their own classification scheme and while active implantable devices do not follow the same classification system as provided by the MDD, they are subject to similar requirements as Class III devices:

- Class I – Provided non-sterile or do not have a measuring function (low risk)
- Class I – Provided sterile and/or have a measuring function (low/medium risk)
- Class IIa (medium risk)
- Class IIb (medium/high risk)
- Class III (high risk)

FDA Device Classification

Class I = Low Risk Devices

- Subject to general controls
- Most but not all exempt from premarket notification [510(k)]

Class II = Moderate Risk Devices

- Subject to general and special controls
- Most but not all require a premarket notification [510(k)]

Class III = High Risk Devices

- Subject to general controls and premarket approval

Regulation Number and Product Code

Medical device classification determined by CFR Regulation Number (e.g., 21 CFR 892.1000 for magnetic resonance diagnostic devices) and three-letter Classification Product Code (e.g., LNH for Nuclear Magnetic Resonance Imaging System).

SECTION 5. GETTING TO MARKET IN THE US

Types of Premarket Notification

Class I Exempt – Class I, General Controls
- Most Class I devices and a few Class II devices are exempt from premarket notification requirements

510(k) – Class II, Special Controls
- Demonstrate Substantial Equivalence to a predicate device in terms of intended use, technological characteristics, and performance testing

PMA – Class III, Premarket Approval
- Provide valid scientific evidence demonstrating reasonable assurance of safety and effectiveness for device's intended use

De Novo – Class I or Class II
- For low to medium risk devices with no identifiable predicate device

510(k) Submissions

What is Substantial Equivalence (SE)?
- Demonstration that a new device, as compared to a predicate device, has the same intended use and the same technological characteristics
- Or differences in technological characteristics do not raise different questions regarding safety and effectiveness.

What is a Predicate Device?
- A legally marketed device, previously cleared through the 510(k) process mainly, that is used for comparison to a new device for the purpose of determining substantial equivalence.

Intended Use

Describes the general purpose of the device or its function, and encompasses the indications for use.
Must be consistent throughout your 510(k), including the indications for use statement, proposed labeling, etc.

Indications for Use

Describes the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.
Must be consistent throughout your 510(k), including the indications for use statement, proposed labeling, etc.

510(k) Decision-Making Flowchart

510(k) submissions aim to prove Substantial Equivalence (SE) to a legally marketed predicate device. First, similarities in intended use are assessed (your predicate device must have the same intended use), and then similarities in technological characteristics. If differences in technological characteristics raise different questions of safety and effectiveness, data can be submitted to support a substantial equivalence argument.

PMA Submissions

FDA determines if PMA applications provide "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors.

FDA reviews valid scientific evidence to determine if data support claims made by Sponsor:

- Clinical data
- Non-clinical data
- Intended use/Indications for Use

De Novo Submissions

Any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence via the 510(k) pathway may submit a De Novo request for the FDA to make a risk-based classification of the device into Class I or II. Devices that are classified through the *de novo* process may be marketed and used as predicates for future 510(k) submissions

Questions? Contact Right Submission:
Elizabeth FitzGerald
Director, Regulatory Intelligence
elizabeth@rightsubmission.com