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16/ENG04/069

EEE

BIOMEDICAL ENGINEERING EEE578

11.7 Selling new pacemakers in Italy.

According to www.regdesk.co/Italy-reg (REGDESK, 2018), medical devices in Italy are subjected to the same regulations as in all countries in the European union(EU). However, slight variations might exist specific to several countries still within the EU. For example, in Italy, medical devices are regulated by the Ministry of Health Directorate General for Medicines and Medical Devices using the National Health Information System (NSIS).

As a result of the EU harmonized standards, all medical devices in italy are subject to the same classification system as other member states. They include:

- Class I – least dangerous, non-invasive medical devices
- Class IIa – medium risk devices, including devices that are invasive, but that do not interact with the body in a dangerous manner
- Class IIb – medium-high risk devices that interact with the body in a dangerous manner
- Class III – high risk medical devices, implantable devices and devices interacting with the vital organs

My new pacemaker will likely be in class IIa and III because pacemakers are implantable or invasive medical devices.

In order for my device to be registered and consequently accepted, my device must be CE-marked. All devices must have a CE marking before they are allowed into the EU market. A CE mark is a sign of conformity with the current EU Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR) that allows the device to be marketed anywhere in the territory of the EU regardless of where the device has been registered.

Also, as a pacemaker manufacturer, it is advised that I look into picking a Quality Management System(QMS). One of the most popular is the ISO 13485 certification. ISO 13485 is the standard for QMS for the design and manufacture of medical devices. **Certification** to the standard requires an organization's quality management system to pass a third party Medical Device Single Audit Program, or “MDSAP” Audit. The certification has to be renewed every three years.

One final consideration will be the time frame to obtain the approval of the Italian government and consequently the EU for my pacemaker. It has been suggested that time frame is a function of the class of the device. Class III devices will take significantly longer, with good reason, than a class I device.

11.8 ISO 10993: Number and Titles

This code is for the Biological evaluation of medical devices.

Number and Titles (Wallin, 1998):

- ISO 10993-1:2018 Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process
- ISO 10993-2:2006 Biological evaluation of medical devices Part 2: Animal welfare requirements
- ISO 10993-3:2014 Biological evaluation of medical devices Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- ISO 10993-4:2017 Biological evaluation of medical devices Part 4: Selection of tests for interactions with blood
- ISO 10993-5:2009 Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity.
- ISO 10993-6:2016 Biological evaluation of medical devices Part 6: Tests for local effects after implantation
- ISO 10993-7:2008 Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals
- ISO 10993-8:2001 Biological evaluation of medical devices Part 8: Selection of reference materials (withdrawn)
- ISO 10993-9:2010 Biological evaluation of medical devices Part 9: Framework for identification and quantification of potential degradation products
- ISO 10993-10:2013 Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization
- ISO 10993-11:2018 Biological evaluation of medical devices Part 11: Tests for systemic toxicity

- ISO 10993-12:2012 Biological evaluation of medical devices Part 12: Sample preparation and reference materials (available in English only)
- ISO 10993-13:2010 Biological evaluation of medical devices Part 13: Identification and quantification of degradation products from polymeric medical devices
- ISO 10993-14:2009 Biological evaluation of medical devices Part 14: Identification and quantification of degradation products from ceramics
- ISO 10993-15:2009 Biological evaluation of medical devices Part 15: Identification and quantification of degradation products from metals and alloys
- ISO 10993-16:2018 Biological evaluation of medical devices Part 16: Toxicokinetic study design for degradation products and leachables
- ISO 10993-17:2009 Biological evaluation of medical devices Part 17: Establishment of allowable limits for leachable substances
- ISO 10993-18:2020 Biological evaluation of medical devices Part 18: Chemical characterization of medical device materials within a risk management process
- ISO/TS 10993-19:2006 Biological evaluation of medical devices Part 19: Physico-chemical, morphological and topographical characterization of materials
- ISO/TS 10993-20:2006 Biological evaluation of medical devices Part 20: Principles and methods for immunotoxicology testing of medical devices
- ISO/TR 10993-22:2017 Biological evaluation of medical devices Part 22: Guidance on nanomaterials

11.9 FDA standards for Tissue Engineered Medical Products (TEMPs)

Table 1

Regulatory Framework Parameters

Guidance	Key features
Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception—Final[a]	Describes the exception from Food and Drug Administration oversight that applies to "same surgical procedures," as described in the Code of Federal Regulations, Title 21, Part 1271. It includes: • The types of interventions that generally meet the agency's definition of "the same" procedure. • The ways that products can be processed and still meet the exception.
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use—Final[b]	Provides FDA's definition of key regulatory terms; namely, minimal manipulation and homologous use. Provides information on how to apply these definitions to a human cell or tissue product. Articulates FDA's compliance and enforcement policy for human cell and tissue products.
Evaluation of Devices Used With Regenerative Medicine Advanced Therapies—Final[c]	Describes how FDA will approach the evaluation of devices used in the recovery, isolation, or delivery of regenerative medicine advanced therapies (RMATs).
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions—Final[d]	Describes the expedited development program available for qualifying regenerative therapies, known as RMAT designation. Outlines a collaborative development model for RMAT products.

a U.S. Food and Drug Administration, "Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception: Guidance for Industry" (2017), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf.

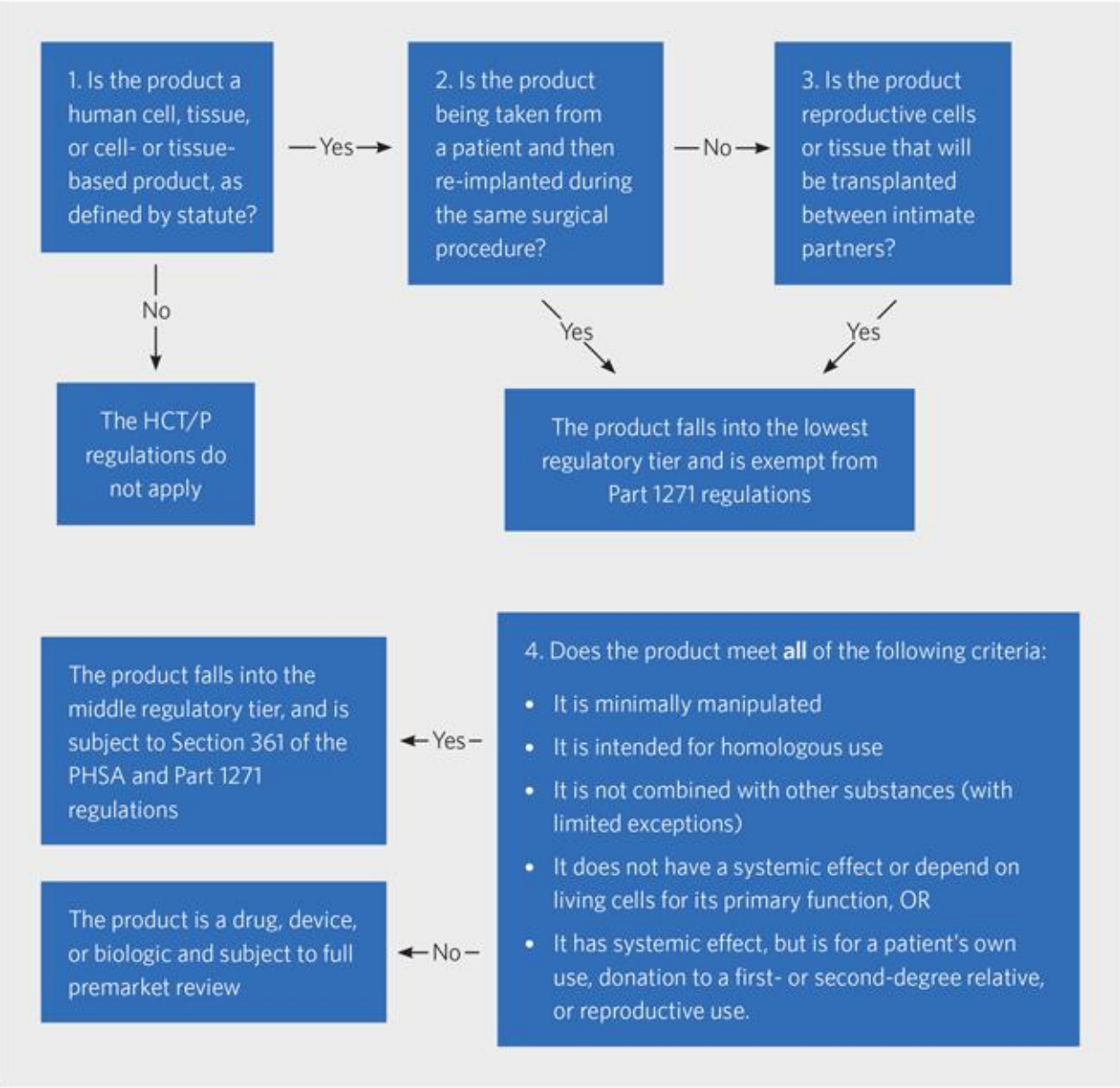
b U.S. Food and Drug Administration, "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use: Guidance for Industry and FDA Staff" (2017), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf.

c U.S. Food and Drug Administration, "Evaluation of Devices Used With Regenerative Medicine Advanced Therapies: Guidance for Industry" (2019), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585417.pdf?utm_campaign=021519_FIB_FDA%20finalizes%20two%20guidances%20as%20part%20of%20regenerative%20medicine%20policy%20framework&utm_medium=email&utm_source=Eloqua.

d U.S. Food and Drug Administration. "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions: Guidance for Industry" (2019), https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585414.pdf?utm_campaign=021519_FIB_FDA%20finalizes%20two%20guidances%20as%20part%20of%20regenerative%20medicine%20policy%20framework&utm_medium=email&utm_source=Eloqua.

Figure 2

How FDA Determines Regulation of a Regenerative Therapy



Source: U.S. Food and Drug Administration, "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" (2017), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal

The Table and Figure above: (PEWTrusts, 2019)

11.10 Laws guiding Prosthetics in USA, Europe and Japan

The USA (FDA)

Most, but not all, prosthetic components and controls are classified as class I (minimal risk and general controls for risks). Nearly, all class I devices are exempt from premarket notification by FDA. Although data on safety and clinical effectiveness may not be required to obtain FDA clearance to market in the United States, most class I devices, manufacturers, or researchers may still wish to conduct studies using these devices. Studies of low risk to study subjects are called "nonsignificant risk investigational devices studies" and are regulated by Federal codes but do not ordinarily require approval of an investigational device exemption from FDA. (Resnik, Klinger, Krauthemer, & Barnabe, 2010)

Japan

Bone prosthesis falls under class III on the classification and regulation regarding medical devices. I must obtain approval from the following (Pharmaceuticals and Medical Devices Agency, 2020):

- Certification by third party certification (limited to devices for designated controlled Medical Device, complying with certified standards).
- Approval by the Minister of Health, Labor and Welfare (reviewed by PMDA)

European Union (EU)

This has been explained above in my answer to pacemakers (Italy is in the EU and regulations are generally the same).

With the aforementioned:

- I will first register my device in each region.
- I would have obtained for the company the ISO certificate (ISO is worldwide) giving my device clearance
- For EU my device must be CE marked.
- For the USA I would obtain FDA approval depending on what class my device falls under
- For Japan I will have obtained clearing from PMDA

- A post marketing analysis (if required by the regulatory bodies) will be made available.