XENDO
SOLUTIONS FOR LIFE SCIENCES

PPN Najaarsbijeenkomst
21 November 2017

CONSULTANCY | PROJECTS | INTERIM MANAGEMENT | AUDITING & TRAINING

Changes in the Medical Device Legislation; the day after.

How much time do we have left?

Jan Bart Hak

Company

XENDO
SOLUTIONS FOR LIFE SCIENCES

Leading consultancy and project management organisation in the fields of (bio)pharmaceutical products, medical devices and healthcare.

- Headquarters in Leiden
- Affiliates in Berlin, London, Stockholm, Tokyo

REGULATORY AFFAIRS

PRODUCT DEVELOPMENT

QUALIFICATION & VALIDATION

PHARMACO VIGILANCE

QUALITY MANAGEMENT & LEAN SIX SIGMA

ENGINEERING & FACILITY SUPPORT

AGENDA: MDD -> MDR

- Overview of the main changes
- Clinical Evidence
  - Clinical Evaluation
  - Post Market Surveillance
    - PMS Plan
      - PMCF
      - Vigilance
    - Analysis, PSUR
  - Clinical Evaluation Report
- Implementation
- START NOW!

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

A medical device

- & Combination products
  - Medical device with pharmaceutical
    - E.g. Drug eluting stents
  - A pharmaceutical with a medical device
    - E.g. Patches for transdermal drug delivery

The MDD Transposition to the MDR

- the Medical Device Directive 93/42/EEC (MDD)

COUNCIL DIRECTIVE 93/42/EEC

of 14 June 1993

concerning medical devices

(OJ L 169, 12.7.1993, p. 1)

- the Medical Device Regulation EU 2017/745 (MDR)

I

(Legislative acts)

REGULATIONS

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

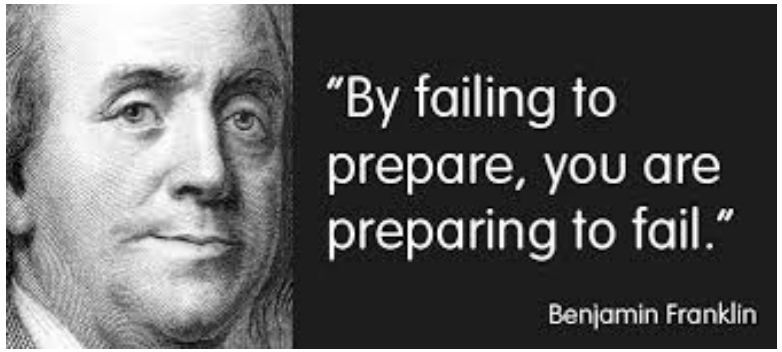
of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

Transition to the MDR

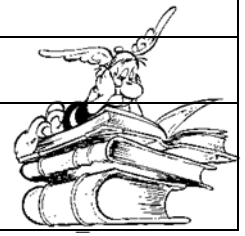
- Transition plan
  - Identify Relevant differences
  - Risk Class Determination
  - Conformity Assessment Procedure
  - Management Awareness and Commitment

- Implementation Plan
  - Assessment Partner
  - Technical File upgrade
  - Quality Management System
  - Post Market Activities and Reporting



Overview of the MDR

Chapter	Chapter Title
Chapter I	Scope & Definitions
Chapter II	Making Available and Putting into Service, Obligations of Economic Operators Reprocessing CE-marking Free Movement
Chapter III	Identification & Traceability Registration of Devices Registration of Economic Operators Summary of Safety and Clinical Performance European DataBank on Medical Devices
Chapter IV	Notified Bodies
Chapter V	Classification Conformity Assessment



Overview of the MDR

Chapter	Chapter Title
Chapter VI	Clinical Evaluation Clinical Investigation
Chapter VII	Post-Market Surveillance Vigilance Market Surveillance
Chapter VIII	Cooperation between Member States, the Medical Devices Coordination Group, Expert Laboratories, Expert Panels and Device Registers
Chapter IX	Confidentiality Data Protection Funding Penalties
Chapter X	Final Provisions

Deliverables of first Preparation

- MDD -> MDR

Medical Device Directive 93/42/EEC				Medical Device Regulation EU 2017/745			
				Chapter I Scope and Definition			
Article #	Article Title	Relevant part of Article	Comments	Article #	Article Title	Relevant part of Article	Comments
		(a) 'medical device' means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of: -diagnosis, prevention, monitoring, treatment or alleviation of disease, -diagnosis, monitoring,	-In the Medical device Regulation EU 2017/745, the definition of a medical device has changed to include a larger range of medical devices and the definition is much more specific.	Art 2	Definitions	(1)'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: —diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, —diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability, —investigation, replacement or modification of the anatomy or of a physiological or pathological process or state, —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	-The definition of a medical device has char become significantly broader. - See Article 2(1) Definitions for 'medical device' -In the first sentence of the definition the word 'software' is now included. -in the first bullet point the words 'prediction' and 'prognosis' are now included -In the third bullet point the end of the sentence is additional 'or pathological process or state' -The complete fourth bullet point of the definition is additional. -The last bullet point is also additional to the Medical Device Directive 93/42/EEC.
				ANNEX XVI	List of groups of products without an intended medical purpose referred to in article 1(2)	p173	- This Annex XVI lists additional devices in which are now regulated medical devices. -The devices are mainly aesthetic medical devices or without intended medical purpose which now apply to the Regulation. -These were not previously covered by directive 93/42/EEC. -The Medical Device Regulation therefore applies to a broader range of medical devices.

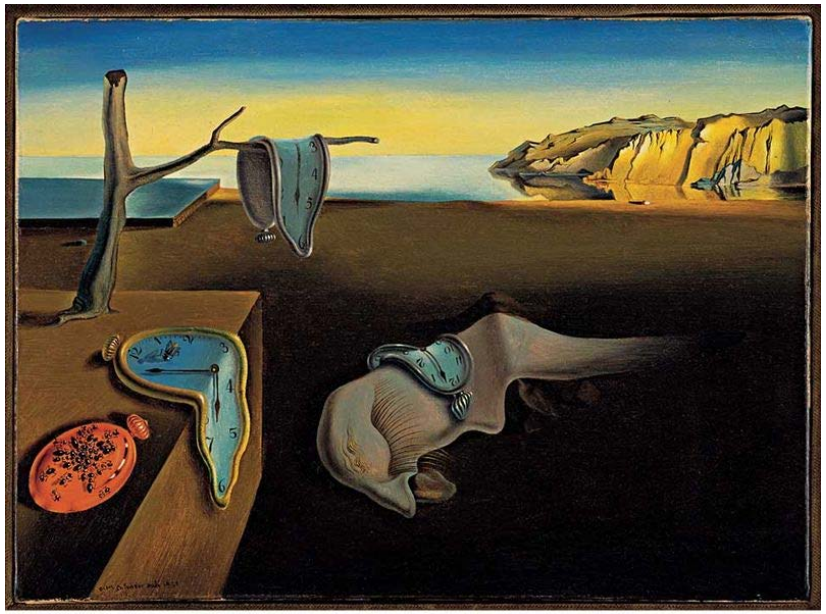
Introduction | Index | Chapter I | Chapter II | Chapter III | Chapter IV | Chapter V | Chapter VI | Chapter VII | Chapter VIII | Chapter IX | C ...

No Grandfathering

- All currently certified Medical Devices must be re-certified in accordance with the new requirements.
- Implications
  - all devices which are currently on the market will need to comply with the new regulations by the end of transition period;
  - requiring new Conformity Assessments under new rules for all devices currently circulating within the European Union.
  - manufacturers of devices falling under the scope of the new Medical Devices Regulation will have to comply with new legislation until 25th May 2020.

Time constraints for implementation

- Select notified body to issue CE mark
  - Will your NB be accredited for the MDR in relation to your device.
    - If not, what is the alternative
    - If yes, will they have time to review your Tech File
- Quality Management System
  - Upgrade to include the MDR aspects
    - E.g. Economic operator, OBL, PMS
    - ISO13485 does not cover all MDR aspects,
    - The MEDDEVs do not cover all MDR aspects
- Tech file
  - Device Classification
  - Clinical data (CER and PMS)



Example: Clinical Evidence & Timelines

- GAP analysis CE marked product, technical file versus MDR requirements
- What needs to be done when clinical evidence proves not to be sufficient.

Classification and Conformity Assessment

Notified Body review and approval required

Increasing risk

Class III
- Pacemakers
- Heart Valves
- Implanted cerebral simulators

Class IIb
- Condoms
- Lung Ventilators
- Bone Fixation plate

Class IIa
- Dental Implants
- Surgical Clamps
- Tracheotomy tubes

Self Assessment

Class I
- Wheelchairs
- Spectacles
- Stethoscopes

Process according to MDR

- CHAPTER VI: CLINICAL EVALUATION AND CLINICAL INVESTIGATIONS
  - Article 61: Clinical evaluation
    - expert panel
  - Articles 62-82: Clinical Investigations
- CHAPTER VII: PMS, VIGILANCE AND MARKET SURVEILLANCE
  - SECTION 1: PMS
    - Article 83: PMS system of the manufacturer
    - Article 84: PMS plan
    - Article 85: PMS report
    - Article 86: Periodic safety update report (PSUR)
  - SECTION 2: Vigilance
    - Article 87: Reporting of serious incidents and field safety corrective actions
    - Article 88: Trend reporting
    - Article 89: Analysis of serious incidents and field safety corrective actions

CLINICAL EVALUATION (Annex XIV)

- To plan, continuously conduct and document a clinical evaluation, manufacturers shall:
  - Establish and update a clinical evaluation plan

  - Clinical data relevant to the device and its intended purpose and any gaps in clinical evidence through a systematic scientific literature review; evaluating suitability for establishing the safety and performance of the device;
  - Generate, through clinical investigations, any new or additional clinical data necessary to address outstanding issues; and

  - Analyse all relevant clinical data to reach conclusions about the safety and clinical performance of the device including its clinical benefits.

Post Market Surveillance

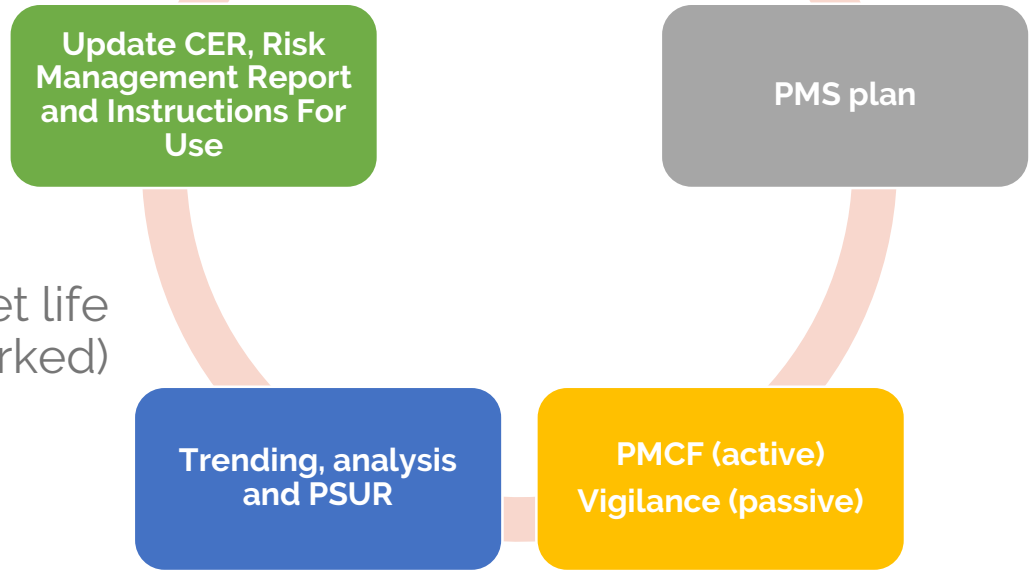
- effective and appropriate methods and processes to assess the collected data
- suitable indicators and threshold values that shall be used in the continuous reassessment of the benefit-risk analysis and of the risk management
- effective and appropriate methods and tools to investigate complaints and analyse market-related experience collected in the field
- Methods and protocols to communicate effectively with competent authorities, notified bodies, economic operators and users
- Procedures for the PMS system, PMS plan and PSUR
  - Vigilance
  - PMCF

Process and deliverables

Clinical Evaluation Plan → Pre-Clinical Evaluation Report → Clinical Investigation → Clinical Evaluation Report

Starts during design phase of the medical device (pre market release)

and continues during post market life cycle of the device (CE marked)



Post Market Surveillance data and Clinical Evaluation Report

- PMS activities
  - Vigilance
  - PMCF

- PSUR
  - depending on the risk class of the product:
    - Class I Not required
    - Class IIa every 2 years
    - Class IIb & III yearly

- Update of the Clinical Evaluation Report

Planning and timing

- No grand fathering
  - If the manufacturer delays: loss of CE mark
    - loss of revenue
    - PMCF not possible but investigation only route

- Strategy on extending clinical data
  - In transition period, update clinical data
  - If not available (sufficiently) use PMS, specifically PMCF

- There are 2.5 years left to make the change!

How much time do you still have?

Example

- It is a CE marked implantable device (class IIb or III)
- It was CE marked based on a Clinical Evaluation with limited clinical data
- GAP-Analysis shows that under the new MDR, additional clinical data is necessary

- It is decided to perform a PMCF to collect this data

- Let's assume
  - a randomized controlled clinical study with 200 patients, 100 in each arm is necessary.
  - that 6 month patient follow up is necessary
  - 15 sites, 2 patient per month

How much time do you still have: the math

Activity	Through put time (months)	Remaining months
		As of today: 30
GAP Analysis Clinical Evaluation	2	28
Preparation PMCF (e.g. protocol, ICF, CRF, site selection)	4	24
Submissions and initiation	3	21
Recruitment period	7	14
Follow up period	6	8
Close out, analysis and reporting	3	5
Update Clinical Evaluation Report	2	3
Submission to Notified body and review period	2	1

- **1 month slack: Start NOW!**

Summary and message

- **START NOW!**

- The MDR is more stringent on clinical data
- PMS to update the clinical evaluation
  - PSUR data of previous years included in the clinical evaluation
- There is no grandfathering: 2.5 years left to make the change
- If a PMCF is required to collected missing info, do you still have time?

- **START NOW!**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