Agenda

- Current Medical Device regulatory landscape
- New Medical Device Regulation EU
- Interaction & impact Medical device with pharma
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 on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:
- devices for the control or support of conception;
- products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.
Examples medical devices
How to market

- Development
- CE mark
- Essential requirements
- QMS
- Manufacturing

EU Market
Current Medical Device Directive (MDD)

- Product classification I, IIa, IIb, III
- Market authorization routes
- Notified body
- Economic operators
- Risk management
Current Medical Device Directive (MDD)

- Performance
- Safety
- Labeling
- QMS/manufacturing/development
- Post market surveillance
Technical documentation

- Essential requirements (Annex I)
- Risk Management File
- Clinical evaluation
- Biological safety evaluation
- Control of manufacturing
- Stability
- Quality management system
- Performance testing
- Used guidelines
Guidance documents

- **MEDDEV**
  - Classifications of Medical Devices
  - Clinical Investigation, clinical evaluation
  - Notified Bodies
  - Market Surveillance (vigilance reporting, PMCF studies,..)

- **ISO standards**

- **NB-MED**

- **IMDRF (harmonization)**
Shortcomings MDD

- Borderline products classification
- Clinical requirements (equivalence vs clinical trials)
- Notified body competence
- Economic operator responsibilities
- Post market requirements
- Medical device traceability
Incentive new regulation

Health risk for women
Call to remove implants
Fraudulent use of non-medical grade silicone in breast implants by company PIP (Poly Implant Prothèse) in France

- 1997: PIP is authorized to produce implants made of medical silicone
- 2001: PIP starts using industrial silicone in their in-house produced implants, with:
  - Cost savings of around 90%
  - 500% higher risk of rupturing or leaking
- Between 2001 and 2010: reports of several incidents (death/breast cancer)
- ~300,000 women affected in 65 countries
Actions

PIP action plan (2012)
- Tighten controls
- Guarantee safety
- Restore patient confidence in law
MDR 2017/745

- Regulation vs Directive
- 175 page document vs 60 MDD
- 123 articles and 16 Annexes vs 23 articles and 12 Annexes
- MDD and AIMDD integrated
- MEDDEV guidelines integrated
- Shift from pre-approval stage to ‘life-cycle approach’
- More EU control
- More NB harmonization
- Active 26 May 2020
- New MDR CE certificates for existing devices.
Key changes in the MDR

New product types and classification rules
- Software
- Substance based medical devices
- Non-vital human tissue
- Cosmetic devices

Clinical requirements
- Equivalency limitations
- PMCF requirements
- Annual update safety & performance

Notified bodies
- Increase designation requirements
- Harmonization of quality NB’s (e.g. joint audits)

General safety and performance requirements
- Risk/benefit
- QMS
- UDI
- Labeling
- Toxic substances
Key changes in the MDR

- **Pre-market requirements**
  - Responsible person for RA
  - Common specifications
  - High risk device approval involvement of EU body (scrutiny)

- **Post market requirements**
  - Technical documentation requirements
  - Eudamed
  - Vigilance & Trend reporting obligations

- **Traceability**
  - Central registration economic operators
  - UDI
  - Implant cards

- **More EU control**
  - MDCG
  - Expert panels
  - Harmonization clinical evaluation
Meet with ZWIERS!

timelines

- **2017**: Regulations enter into force
  - **26 May 2017**

- **2018**
  - **26 May 2020**: MDR fully applies

- **2019**
  - **26 May 2020**: MDR fully applies

- **2020**
  - **26 May 2022**: IVDR fully applies

- **2021**
  - **25 May 2020 – 25 May 2024**: Certificates issued under the MDD before the MDR fully applies will be valid for up to 4 years

- **2022**
  - **2024 – 2025**: MDD devices on market can continue to be made available

- **2023**

- **2024**

- **2025**

- **26 May 2017 – 25 May 2020**: Certificates under Medical Device Directive (MDD) are valid

- **26 May 2017 – 25 May 2024**: Devices in conformity with the Medical Device Regulation (MDR) can be certified under the MDR and placed on the market

- **26 May 2024**: Devices placed on the market must be certified under the MDR
MDR interaction with pharma

Medical device with Medicinal Product

Medicinal Product with Medical device

• Devices intended to administer MP are defined as a Medical Device
MDR interaction with pharma

- Medicated condoms
  - Intraocular irrigation
  - Contact lens
- Treated examination gloves
- Media products for assisted reproduction technology
- Organ preservation liquids and solutions
- Drug eluting stents
- Coated vascular prosthesis
- Antimicrobial catheter

- Haemostats
  - Wound powders, dressings barriers and films
  - Skin preparations
  - Sutures
  - Wound debridement and irrigation solution
  - Creams

- Vascular
- Active Implantable
- Orthopaedic and Dental
- Drug Device Technologies
- Active Medical Devices
- Woundcare
- Others

- Bone cement / graft
- Injectable spine cement
- Dental varnishes
- Blood parameter monitoring System
- Systems to preserve and treat the blood
- Haemodialysis equipment

Antibacterial envelope in a mesh pouch for ICD

Meet with ZWIERS!
MDR interaction with pharma
‘combination’ product

‘Combination’ options

• Single integral products
  • the device and the medicinal product form a single integral product;
  • intended exclusively for use in the given combination;
  • not reusable

• Co-pack
  • MP and MD are packed together and intended to be used together
Current role EMA

~13% of MAA contain device

Single integral:
- EMA assesses compliance with MDD requirements
  - Labeling/instruction for use
  - PMS for device
  - Authorise changes to device

CE marketed devices:
- Check validity CE certificate
- Evaluate compatibility with medicinal product.
What is the impact of MDR on pharma

Classification
Art 117
Notified body interaction
• CE certificate from NB
• NB opinions
Device changes
New CE certificate
## Classification

<table>
<thead>
<tr>
<th>Medical Device</th>
<th>Classification</th>
<th>Rule</th>
<th>Annex I</th>
<th>NB Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syringes</td>
<td>I</td>
<td>2</td>
<td>Required</td>
<td>Yes, sterile &amp; measurement</td>
</tr>
<tr>
<td>Needles</td>
<td>IIA</td>
<td>6</td>
<td>Required</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhalers</td>
<td>IIA/B</td>
<td>20</td>
<td>Required</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Article 117 (medical device as part of medicinal product)

The marketing authorisation dossier shall include

• Conformity of the device part with the relevant general safety and performance requirements set out in Annex I
  • Manufacturer declaration of conformity for class I devices
  • Notified body declaration of conformity higher class

• If declaration of conformity is not included an opinion from Notified body on compliance with Annex I for the device must be provided.
Device change

- General safety & performance requirements
- Device QMS
- NB approval/Opinion
Impact on medicinal product dossier

CTD module?
Requirements opinion art 117 by NB?
Labeling requirements?
UDI for device?
Variations?
Device specific post market requirements?
Proposal for EMA guideline on quality requirements for drug device combination products (2)

**Dossier requirements** for integral and non-integral combination products
- Lack of clear guidance for industry or assessors for assessment of medical device component along with medicinal product

**Product Information**
- Considerations for specific information to be included in the SPC, labelling and leaflet

**Usability study requirements**
- Target patient population with relevant clinical conditions

**Product lifecycle management**
- Data requirements for variations

In EU, no definition in regulation for a medicinal product and medical device presented together (except for ATMPs)
Uncertainties

EBE paper

- Art 117 opinion content
- NB assessment and opinion in parallel with MAA
- Opinion not required in development
- Class I devices no opinion required
- One opinion for a group of devices
- Device information in section 3.2.P.2.4 (container closure)
- No full labeling requirements MDR
## Variations proposed on EBE paper

<table>
<thead>
<tr>
<th>Change</th>
<th>Justification</th>
<th>Variation strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefilled syringe with fixed needle and the dimensions change</td>
<td>B.II.e.4 Change in shape or dimension of the container or closure</td>
<td>Type IB variation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B.II.e.4.z</td>
</tr>
<tr>
<td>Changes or additional vendors for device component</td>
<td><strong>Conditions:</strong> No change to registered detail. No anticipated impact of product quality, safety or efficacy.</td>
<td>Non-reportable change</td>
</tr>
<tr>
<td>Change of supplier of the needle for PFS</td>
<td>Assessed to be ‘non-reportable’ under EU variation categories</td>
<td>Non-reportable change</td>
</tr>
<tr>
<td>Change in the assembly process of the device</td>
<td>If the assembly operation is reported within the dossier</td>
<td>Type IA change under category B.II.b.1.a</td>
</tr>
</tbody>
</table>

---

EBE Reflection Paper Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment. 15 January 2018
Open issues for devices in medicinal product

- UDI requirements
- EUDAMED obligations
- Review time NB
- Device specific post market requirements
- Contractual agreements
How to comply with MDR

- Gap analysis of product
- Identify medicinal products containing devices
- Classify
- General safety and performance requirements gap analysis
- Update technical data
- Identify need and type of variation
- Update Q agreements with supplier & distributor & importer
- Role device provider/subcontractor
Take home message

- MDR will be in effect from May 2020
- NB involvement
- Start general safety & performance requirement gap analysis
- Communicate with device suppliers
- EMA guidance document under development
Meet with ZWIERS!

Questions?