SESSION II

Global Regulatory Approach to Combination Products

EU Medical Device Regulation (MDR) vs US FDA Requirements for Devices in Sterile Combination Products

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Combination products - USA

- Combination Products - a product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another).
- The drugs, devices, and biological products included in combination products are referred to as “constituent parts” of the combination product.
- The combination product can be:
  - A Single Entity combination product where two or more regulated components are physically or chemically combined or mixed such as a pre-filled syringe or drug eluting stent
  - A Co-packaged combination product where two or more separate products are packaged together such as a surgical pack or first aid kit
  - A Cross Labelled combination product where a component is packaged separately but intended only for use with another separately available component such as a light emitting device and a light activated drug product
- Cross labelled combination products also covers investigational use situations

Combination products regulation

- All components will be included in regulatory review and approval
- Overseen by the Office of Combination Products
- FDA considers the primary mode of action when assigning an Agency Center as the lead for the audit, other centers are consulted as needed
  - Medicines regulated under 21 CFR Part 210/211
  - Medical devices regulated under 21 CFR Part 820
  - Biological products are regulated under 21 CFR Part 600-680

Combination products streamlined approach

Device QSR plus

- 21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures
- 21 CFR 211.103 Calculation of yield
- 21 CFR 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products
- 21 CFR 211.137 Expiration dating
- 21 CFR 211.165 Testing and release for distribution
- 21 CFR 211.166 Stability testing
- 21 CFR 211.167 Special testing requirements
- 21 CFR 211.170 Reserve samples

Drug GMPs plus

- 21 CFR 820.20 Management responsibility
- 21 CFR 820.30 Design controls
- 21 CFR 820.50 Purchasing controls
- 21 CFR 820.100 Corrective and preventive action
- 21 CFR 820.170 Installation
- 21 CFR 820.200 Servicing

Combination products sterilisation approach

- Determine appropriate sterilisation approach / mechanism
- Identify optional consensus standards (e.g. AAMI/ANSI/ISO standards)
- Apply technical controls as per chosen combination product framework (i.e. device / drug product)
  - Validate the process (820.75)
  - Control and monitor the process (820.50, 820.70, 820.72, 820.75, 820.80)
  - Ensure the process is operating within limits (820.75)
  - Manage non-conformances (820.90, 820.100)
  - Qualify and calibrate equipment (820.70, 820.72)
  - Validate the software (820.70)
  - Train personnel (820.25, 820.70, 820.75)

Sterilisation consensus standards

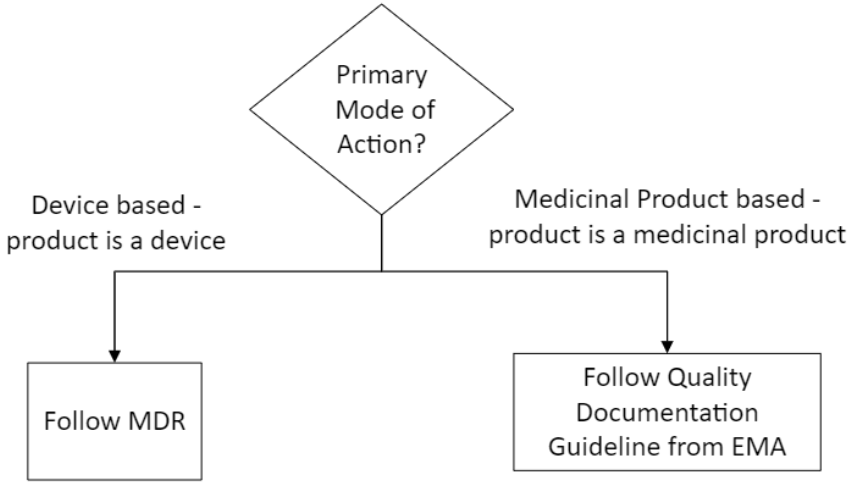
- EN ISO 11137-1:2015 Sterilization of health care products - Radiation - Part 1: Requirements for development validation and routine control of a sterilization process for medical devices
- EN ISO 11137-2:2015 Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose
- EN ISO 11135:2014 Sterilization of health-care products - Ethylene oxide - Requirements for the development validation and routine control of a sterilization process for medical devices
- EN ISO 10993-7:2008 +AC:2009 Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals
- EN ISO 11607-1:2017 Packaging for terminally sterilized medical devices - Part 1: Requirements for materials sterile barrier systems and packaging systems
- …

Medicinal products used with a device - EU

- An Integral product where device and the medicinal product form an integral product that is not reusable
  - Devices that incorporate a medicine where the medicinal product action is principal, e.g. medicinal products that include a sensor
  - Devices that incorporate a medicine where the device action is principal, e.g. drug coated stent
  - Devices intended to administer a medicinal product, exclusive use and not reusable, e.g. single use prefilled syringe
- A Co-packaged product where two or more separate products are packaged together such as a surgical pack or first aid kit
- A Referenced product where a component is packaged separately but intended only for use with another separately available component such as a light emitting device and a light activated drug product

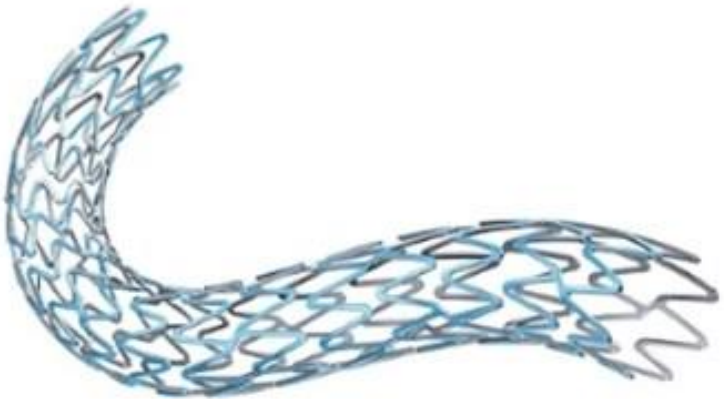
Medicinal products used together with medical devices (drug AND device) - EU

- The combination product is defined either as a medicinal product or medical device, depending on the primary mode of action



Devices that incorporate a medicinal product

- Device is the primary mode of action
- Drug eluting stent intended to prevent clotting in the stent (restenosis)
- FDA regulates as a combination product



Device products that incorporate medicinal product

- Devices that incorporate a medicinal product where the principal action is device based are regulated as devices and must meet device GSPR as per MDR. Notified body must seek an opinion from EMA or a competent authority regarding the quality and safety of the incorporated medicinal product including benefit / risk assessment.
- Favourable EMA / Competent Authority advice must be received before the notified body can issue a CE mark
- QMS according to EN ISO 13485:2016 (including ISO 14971:2019)

Device products that incorporate medicinal product - sterilisation approach

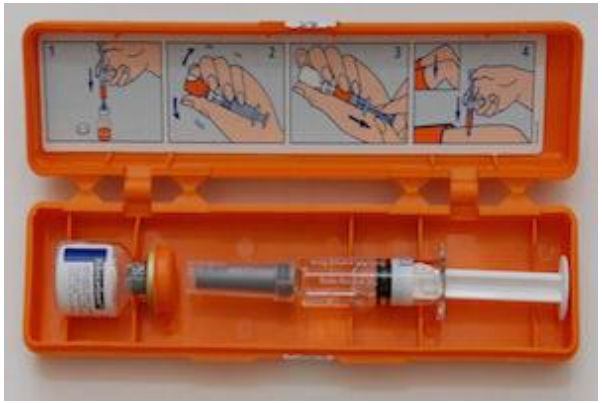
- Determine appropriate sterilization approach / mechanism
- Identify optional consensus standards (e.g. AAMI/ANSI/ISO standards)
- Apply technical controls as per EU governed MDR or EMEA framework as appropriate (i.e. device / medicinal product)
  - Designed to reduce risk of infection (Annex 1 - 11.1)
  - Designed to facilitate cleaning (Annex 1 - 11.2)
  - Packaged to remain in sterile state (Annex 1 - 11.4)
  - Sterilized according to validated methods (Annex 1 - 11.5)
  - Manufactured and packed in appropriate controlled conditions (Annex 1 - 11.6)
  - Sterile barrier system (Annex 1 - 11.7)
  - Sterility labelling (Annex 1 - 11.8)

Medicinal products that incorporate a device

- Medicinal product is the primary mode of action
- Pill including a sensor to track ingestion and compliance to treatment regime
- FDA regulates as a combination product

Co-packaged products

- Two or more separate products packaged together
- FDA regulates as a combination product – selection of components, labelling, assembly, packaging



Regulation of Integral and Co-packaged products

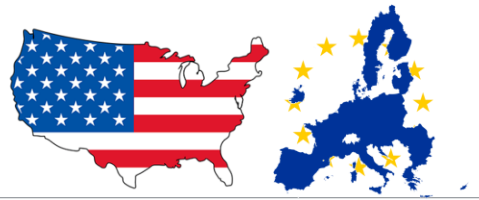
- Integral products where the principal action is medicinal product based and Co-packaged products are regulated as medicinal products and must meet medicinal product GMP and also device GSPR
- Where the separate use of the device component would require the involvement of a NB, the applicant must provide the Competent Authority with a Notified Body Opinion (BPOn) on the conformity of the device component
- The device component does not require CE marking
- The Competent Authority evaluates the device specific aspects relevant to the safety and efficacy of the medicinal product and vice versa

Devices that are intended to administer a medicinal product

- Devices which administer an integrated medicinal product and are intended exclusively for use in the given combination, e.g. single-use pre-filled syringe or dry powder inhaler (reusable or non-reusable)

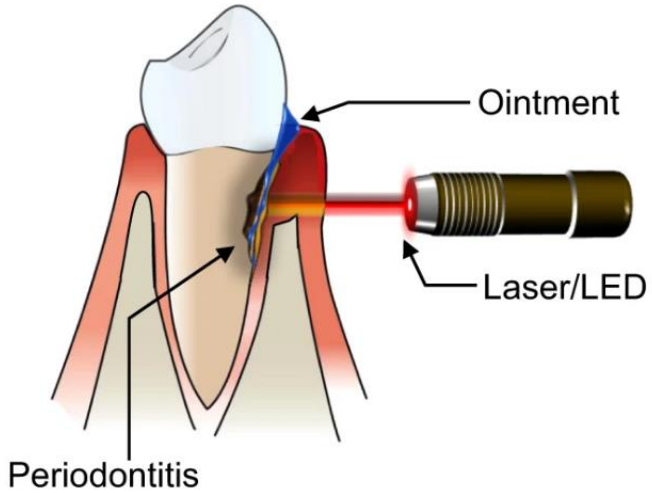
Combination products – devices that are used to administer a medicine

- Empty delivery devices such as syringes, medicine spoons, droppers. These can be sold separately so are regulated as devices.
- Empty delivery or measuring devices that are co-packaged with the medicine to be delivered (such as a measuring cup for cough medicine) are treated as an entire product which is regulated as a medicine.
- Delivery devices filled with medicine as an integral product, and are not refillable or reusable, are regulated based on their primary mode of action



Co-labelled / referenced products

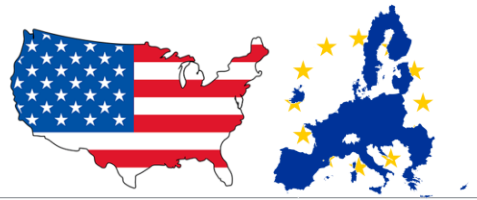
- Two or more separate products sold separately but intended to be used together, e.g. photosensitizing drug and activating laser/light source



Regulation of co-labelled / referenced products

Co-labelled or Referenced product components are generally regulated and need to comply with the requirements according to the type of individual product.

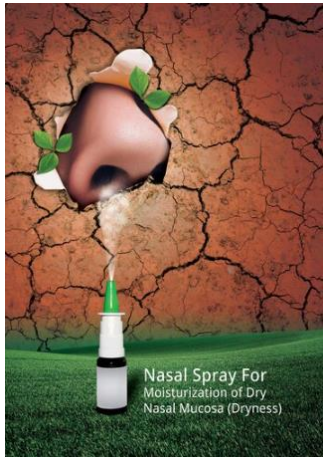
- The device component is regulated as per the medical device framework
- The medicinal product component is regulated as per the drug framework
- Clinical evaluation / performance evaluation relates to the product as a whole, based on primary mode of operation



Boundary or borderline products

- Therapeutic goods that may have some of the attributes of two or more categories of regulated goods, or they may simply be products for which the appropriate regulatory pathway is not immediately obvious.
- Regulatory approach is based on primary mode of action

Artificial Tears



Throat lozenges

Borderline products (drug OR device)

- Medical devices that are substance based can be regulated as either medicinal products or substance based medical devices.
- A device cannot fall under both legal regulations, i.e., it cannot be a medicinal product and a medical device at the same time.
- In the case that a device can fall under both the definition of "medical device" and the definition of " medicinal product," the device is a medicinal product

Substance-based medical device

Primary mode of action is physical

Examples of substance-based medical devices include:

- Saline nasal or throat sprays
- Mucous membrane-moistening syrups, throat sprays, or lozenges
- Artificial tears
- Oral products to neutralize gastric acid
- Devices with a defoaming effect for gastrointestinal complaints caused by gas

Medicinal product

Primary mode of action is pharmacological, immunological, or metabolic

- If a product corresponds to a medical device in its presentation (submission, claims, advertising) but uses a pharmacological, metabolic, or immunological effect of an ingredient to achieve the intended use, the device must instead be approved as a medicinal product.

Differences in regulatory approach & challenges

- FDA has a dedicated Office of Combination Products and dedicated regulation (21 CFR Part 4)
- Streamlined approach can be chosen by multi product manufacturer, but may not match that of the FDA branch assigned to audit
- The EU does not have a category for medicinal product and medical device combination products, Europe involves separate regulatory pathways based on primary mode of action
- When in doubt, Europe considers combination products as medicinal products
- A product may be regulated as a medical device in one jurisdiction and a medicinal product in another

Thank you