

Regulatory Challenges of Combination Products in EU and US

Afternoon seminar, 24 January 2018
by COBIS and IWA Consulting



Content

- **Introductions by COBIS and IWA Consulting**
- Definition of combination products
- Overview of applicable regulations
- Discussion of the regulatory challenges

Who We Are

- Founded in 1997
- Located in Køge
- Satellite office at COBIS
- 21 employees
- Dedicated to regulatory affairs
 - Medicinal products
 - Medical devices
- ISO 9001 certified

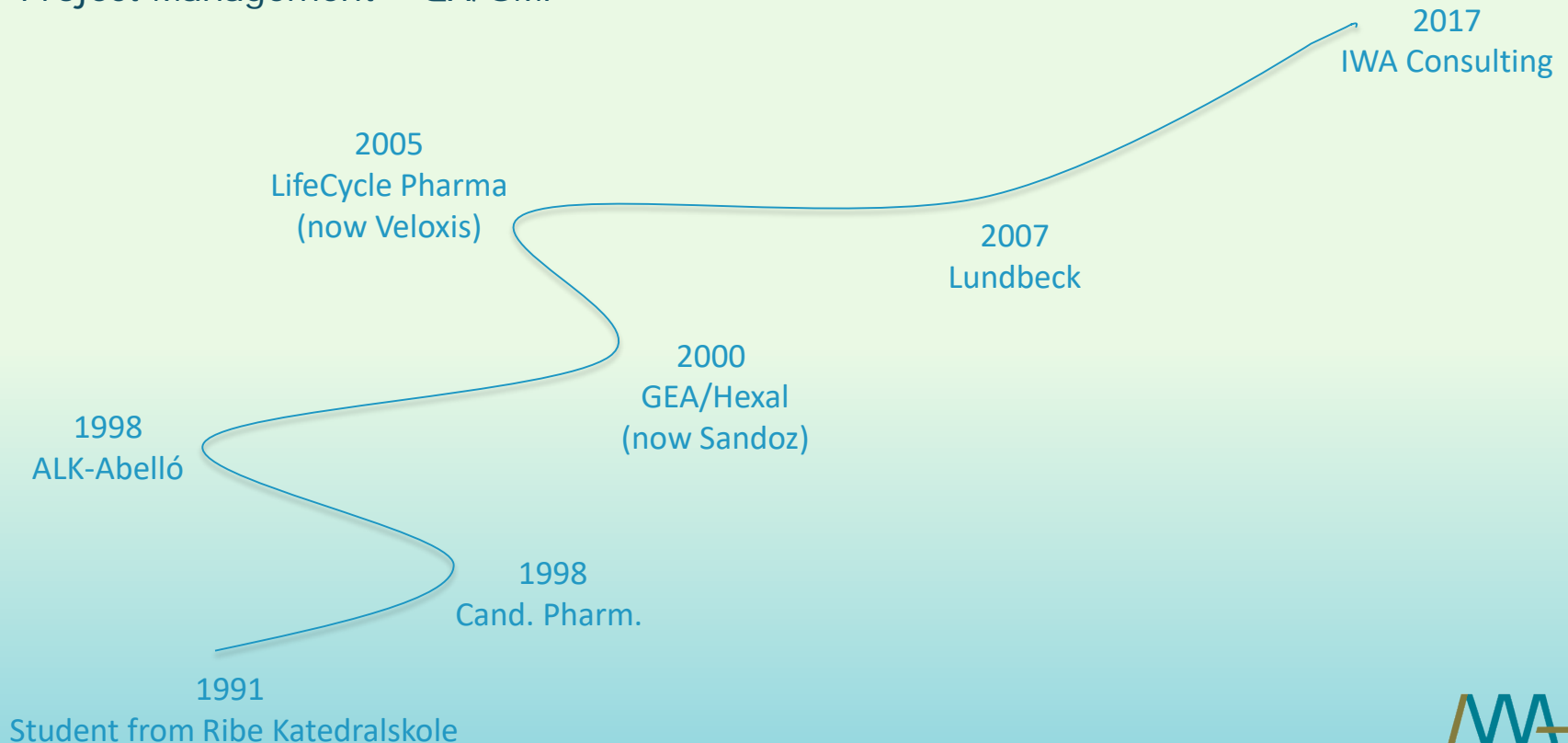


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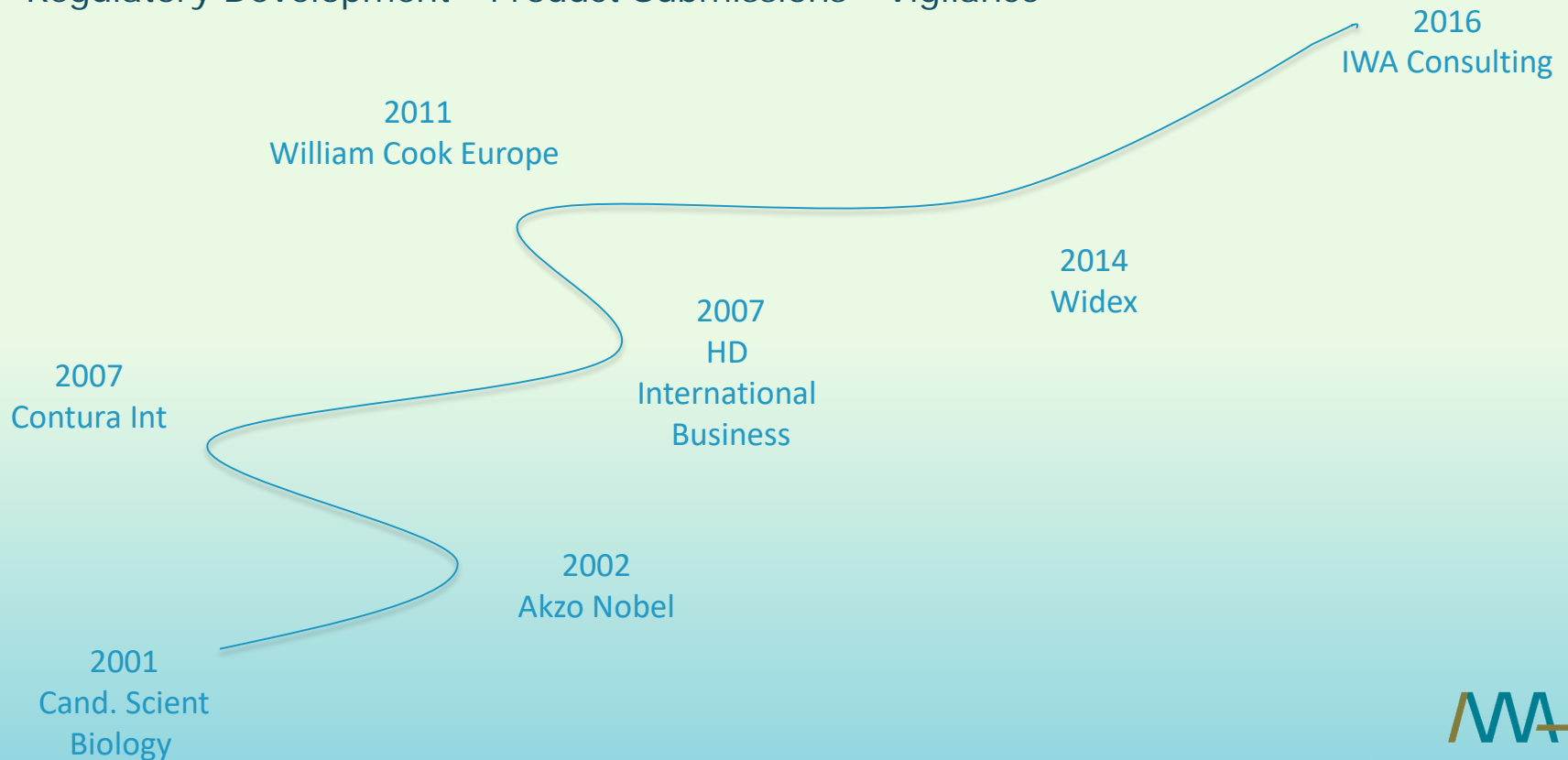


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Regulatory Affairs – Regulatory Strategy - Quality Management
Regulatory Development - Product Submissions - Vigilance



Organisation



IWA Consulting competences

Regulatory services for medicinal products and medical devices

We specialise in:

- Regulatory Intelligence
- Regulatory Development
- Regulatory Affairs
- Market Approvals
- Medical Affairs
- Global eCTD Submissions
- Document Management
- Quality Management

Why use IWA Consulting ?

- Extensive experience in the regulatory field
- Have all types of regulatory competences in-house
- Operates as part of your team
- Work on-site or from IWA Consultings offices
- High quality deliverables
- Timely and cost efficient
- ISO 9001 certified quality system

There are many ways to heaven

(and much can go wrong...)



When you start – start right!



**The IWA Consulting team
helps you achieve your regulatory goals**

That was us....

Who are you?

- Take you smartphone
- Wifi: COBIS Guest, password: spring15
- Go to www.kahoot.it
- Enter Game PIN

Content

- Introductions
- **Definitions**
- Overview of applicable regulations
- Discussion of the regulatory challenges

Definition of combination products - US

FDA: “Combination products are therapeutic and diagnostic products that combine drugs, devices, and/or biological products.”

- Can be **single entity**, **Co-packaged** or **cross labeled** combination product
- We focus on drugs and devices in this presentation
- “drugs” covers both drug and biologics
- Devices does not include *in vitro* diagnostic devices

Definition of combination products - EU

Combination products are not defined, but is mentioned in the scope of the medical device regulation:

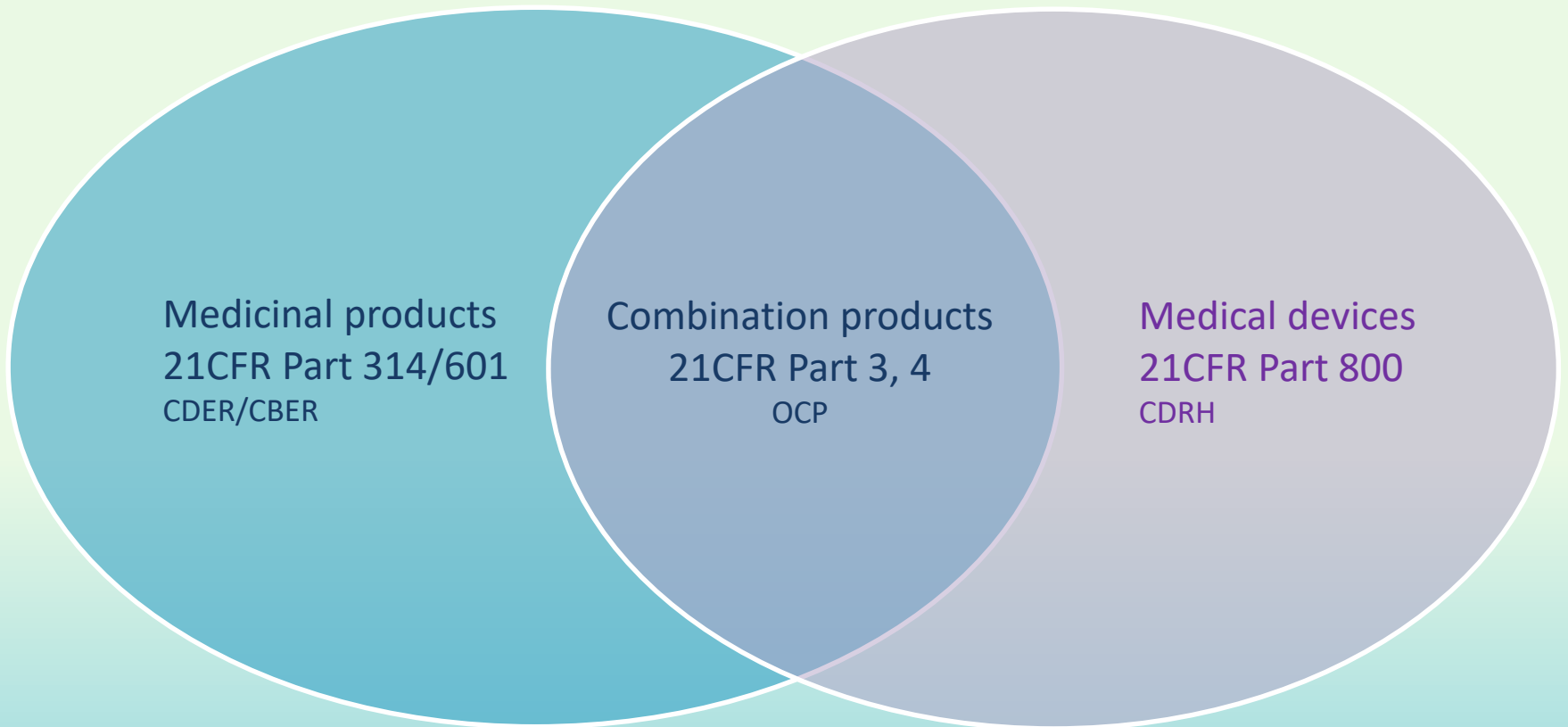
- Device integrating a medicinal product
- Medicinal product integrating a device
- Devices intended to administer a medicinal product

When presented as a single, integral unit, not reusable

Content

- Introductions
- Definitions
- **Overview of applicable regulations**
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Applicable regulation - US



Medicinal products
21CFR Part 314/601
CDER/CBER

Combination products
21CFR Part 3, 4
OCP

Medical devices
21CFR Part 800
CDRH

Applicable Regulation – US

Code of Federal Regulations (CFR) Title 21, subpart A

- **Part 3 – Product Jurisdiction**
 - Organizational components
- **Process for designated agency**
 - To designate the agency component with **primary jurisdiction** for the premarket review and regulation of a combination product, the agency shall determine the **primary mode of action** of the product
 - Intended therapeutic action
 - Letter of designation specifies the agency with primary jurisdiction for a combination product

Applicable Regulation – US

Code of Federal Regulations (CFR) Title 21, subpart A

Part 4 – Regulation of Combination Products

- Addresses Current Good Manufacturing Practice (GMP) and Quality System (QS) requirements (part 820)
- Post-marketing safety reporting for combination products
 - Requirements depending on primary mode of action

FDA guidance: Current good Manufacturing Practice Requirements for Combination Products, January 2017

Applicable Regulation – US

21 CFR **Part 4** – Regulation of Combination Products, Sec. 4.4:

(b)(1) (...) The current good manufacturing practice operating **system** has been shown to comply with the drug CGMPs the following provisions of the device quality system regulation must also be shown (...):

- (i) Section 820.20. Management responsibility.
- (ii) Section 820.30. Design controls.
- (iii) Section 820.50. Purchasing controls.
- (iv) Section 820.100. Corrective and preventive action.
- (v) Section 820.170. Installation.
- (vi) Section 820.200. Servicing.

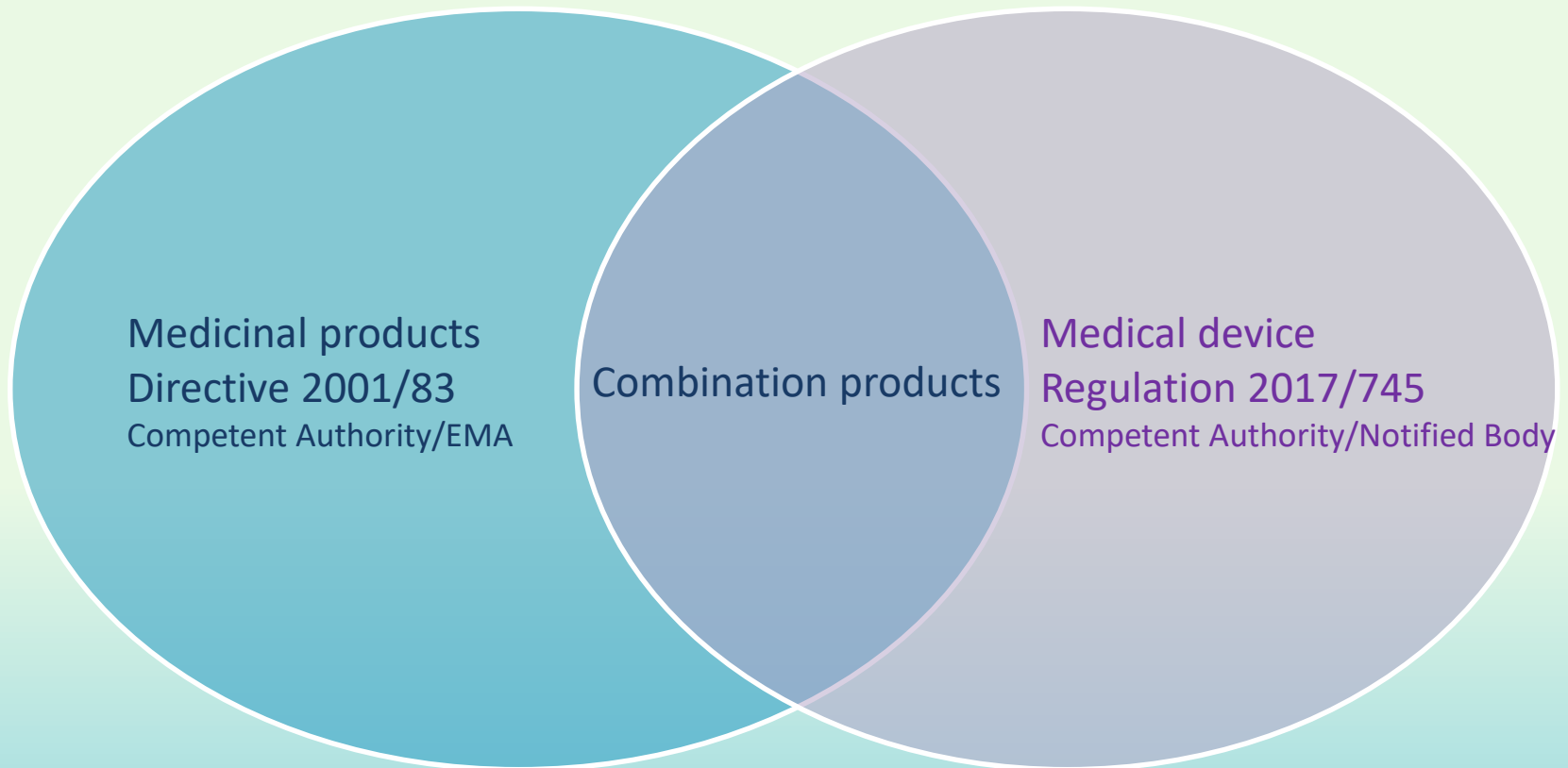
Applicable Regulation – US

21 CFR **Part 4** – Regulation of Combination Products, Sec. 4.4:

(b)(2) (...) The current good manufacturing practice operating system has been shown to comply with the device quality system regulation the following provisions of the drug CGMPs must also be shown (...):

- (i) Section 211.84. Testing and approval or rejection of components, drug product containers, and closures.
- (ii) Section 211.103. Calculation of yield.
- (iii) Section 211.132. Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.
- (iv) Section 211.137. Expiration dating.
- (v) Section 211.165. Testing and release for distribution.
- (vi) Section 211.166. Stability testing.
- (vii) Section 211.167. Special testing requirements.
- (viii) Section 211.170. Reserve samples.

Applicable regulation - EU



Applicable Regulation – EU

Medicinal products

No specific regulation for combination products

Medicinal products are governed by **Directive 2001/83**

Guideline (2004) on the suitability of the graduation of delivery devices for liquid dosage forms

Concept paper (2016) on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product

Applicable Regulation - EU

Medical devices

- No specific regulation for combination products
- Medical devices are governed by Regulation 2017/745 (and Directive 93/42/EEC)
- Harmonized standards
- Requirements for combination products are addressed in the MEDDEV guidance 2.1/3 rev 3
 - Incl. Consultation Procedure
- Current directive versus new medical device regulation
 - No difference regarding combination products
 - But a “position statement” that the medicines directive should address combination products



Applicable Regulation - EU

Medical Device Regulation

Article 117

Amendment to Directive 2001/83/EC

In Annex I to Directive 2001/83/EC, point 12 of Section 3.2. is replaced by the following:

‘(12) Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council (*), a product is governed by this Directive, **the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body** allowing the manufacturer to affix a CE marking to the medical device.

If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to **provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body** designated in accordance with that Regulation for the type of device in question.



Applicable Regulation – EU

Drug/Device combination

- Medical device action is ancillary
 - Single integral unit
 - Intended exclusively for use in the given combination
 - Not reusable

Example: Prefilled syringe or prefilled inhalator

- Reusable? – CE mark



Legislation:

- Governed by Directive 2001/83/EC
- Evaluated/approved by medicinal agencies and notified body
- Requirements of **Annex I** of the **Medical Device Regulation** apply for the device

Applicable Regulation – EU

Annex I of the Medical Device Regulation

General Safety and Performance Requirements

“Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose....”

- Risk management system
- Usability evaluation
- Clinical Evaluation
- Biocompatibility
- Labeling

**Annex I of Device Regulation:
Management of risks**

Must be updated regularly, e.g. :

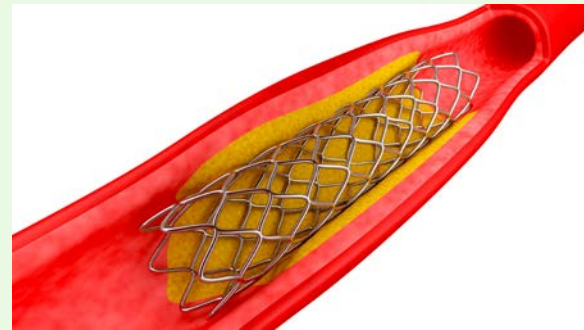
- Design changes
- Clinical follow-up
- Post market surveillance

Applicable Regulation – EU

Device/Drug combination

Medicinal product action is ancillary

Example: Drug eluting stent and anti-biotic implants



Legislation:

- **Governed by Regulation 2017/745**
- Evaluated/approved by a Notified Body
- Safety, performance and quality of the drug to be verified for the intended use with the device
- ANNEX I of Directive 2001/83 applies for the medicinal product

Applicable Regulation – EU

Device/Drug combination

In principle, Annex I of Directive 2001/83 requires a full data package

However, in practise, a full data package is normally not required for a medicinal product incorporated into a device (known substance)

- Requirements for submission content is outlined in MEDDEV 2.1/3 rev 3 and Guidance (2010) "Procedural aspects and dossier requirements for the consultation to the European Medicines Agency by a notified body:
 - Scientific explanation for ancillary function
 - Device assessment report from notified body
 - Critical summaries on quality, non-clinical and clinical data provided
 - Relevant non-clinical and clinical documentation
 - Full technical documentation (Module 3)

Content

- Introductions
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- **Discussion of the regulatory challenges**

Categorisation

Drug/Device or Device/Drug combination?

- Prefilled syringe or prefilled inhalator – **Drug/Device**
- Drug eluding stent or anti-biotic implants – **Device/Drug**
- Wound dressing / Patch - ?
 - Primary mode of action: wound healing
 - Primary mode of action: transdermal drug delivery



General Regulatory Challenges

- Start out by defining business case and regulatory strategy
- **The regulatory strategy** should include
 - An overall description of the product incl. intended use
 - Identification of desired markets
 - Determine the regulatory path in each market incl. classification and approval proces
 - Identify key data needed to establish safety and performance of the product in relevant markets
- Present the regulatory development plan for Notified Body/EMA/FDA, as relevant
 - Ensure authority agreement on the categorisation (drug/device or device/drug) Must be in accordance with claims and labelling
 - Clarify authority expectations for pre-clinical and clinical data to be generated
 - Present and discuss the investigational plan prior to submission of clinical trial applications

Case 1 – Prefilled Syringe

Applicable regulation: 2001/83 (medicinal product)
+ Annex I of the Medical device regulation



Case 1 – Prefilled Syringe

Points to consider

Annex I of Device Regulation:
Management of risks

- Usability (Human factor testing)

Inappropriate use of devices may compromise drug safety and efficacy and result in **adverse drug reactions** (ADRs) or **medication errors**

- ISO 62366-1:2015 Application of usability engineering to medical devices
- Study the user interface
- Must take into account the users, use environment and user interfaces
- FDA guideline:
Applying Human Factors and Usability Engineering to Medical Devices (2016)



- Is a medical device quality management system needed?

Case 1 – Prefilled Syringe

Information to include on the medical device in the dossier to the Competent Authority (Module 3)

Directive 2001/83 Annex I requirements for devices:

- Description of the device
- Compatibility of the device with the medicinal product
- Accuracy of dosing
- Safety and performance requirements acc. Annex I of the Medical Device Regulation

The Competent Authority will review the information on the medical device

Note: More detailed requirements for devices in advanced therapy medicinal products

Case 2 – Wound dressing including anaesthetic


Classification?

- Applicable regulation: Regulation 2017/745 (medical device)
+ Annex I of Directive 2001/83



Case 2 – Wound dressing

Points to consider:

- If product is regulated as a medical device
 - Medical device classification based on risk
 - All devices incorporating a medicinal product is highest risk class in EU (class III)
 - A design dossier must be submitted to a suitable Notified Body
 - It must include information on the medicinal product which is specified in MEDDEV 2.1/3 rev 3 and the guidance “Procedural aspects and dossier requirements for the consultation to the European Medicines” 
 - The Competent Authority will review the information on the medicinal product

Understand you challenges, manage your risks





Back-up slides

Source information

Medicinal products - EU

- Directive 2001/83/EC
- Notice to Applicant's Volume 2B, presentation and format of the dossier (CTD)
- EMA/CHMP/QWP/BWP/661488/2016: Concept paper on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product
- EMEA/CHMP/QWP/178621/2004: Guideline on the suitability of the graduation of delivery devices for liquid dosage forms

Medical devices - EU

- Regulation 2017/745
- MEDDEV 2.1/3 rev 3
- EMA/CHMP/578661/2010: Procedural aspects and dossier requirements for the consultation to the European Medicines Agency by a notified body
- "Regulatory Pathways of Drug-Device and Device-Drug Combination Products in the EU", whitepaper from NSF Health Sciences Medical Devices
- ISO 62366-1:2015 Application of usability engineering to medical devices

Combination products - US

- 21CFR Part 3, 4
- **FDA guidance:** Current good Manufacturing Practice Requirements for Combination Products, January 2017
- **FDA Guidance:** Applying Human Factors and Usability Engineering to Medical Devices (2016)

Definition of Medicinal product, EU

(Simplified)

Directive 20017/83/EC

A medicinal product:

- Is a substance
- Has properties for treating or preventing disease in human beings; or
- Is used for **restoring, correcting or modifying physiological functions** by exerting a **pharmacological, immunological or metabolic action**, or to making a medical diagnosis.

Definition of Medical device, EU

(Simplified)

Regulation 2017/745

A medical device:

- Is an instrument, apparatus, appliance, software, implant, reagent, material or other article
- Is intended by the manufacturer to be used for
 - diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of **disease**; or
 - diagnosis, monitoring, treatment, alleviation of, or compensation for, **an injury or disability**; or
 - investigation, replacement or modification of the **anatomy** or of a physiological or pathological process or state; or
 - providing information by means of ***in vitro* examination of specimens derived from the human body**, including organ, blood and tissue donations
- Does not achieve its principal intended action by pharmacological, immunological or metabolic means

Quality Management System Requirements

Device/Drug combination

- Quality Management is a requirement
- Mostly, ISO 13485 certification
- Is comparable to ISO 9001, but with additional device related requirements
- Smaller companies with e.g. with one product could choose not to be certified in the full system
- The drug component of the device should be in compliance with Annex I of the medicines directive (includes GMP)
- Hence, no requirements for specific drug Quality Management System

Quality Management System Requirements

Drug/Device Combination Products

- Medicinal products must be developed ensuring adequate quality at all levels:
 - Animal studies to be performed acc. **GLP** (Directives 2004/9/EC and 2004/10/EC)
 - Human studies to be performed acc. **GCP** (Directive 2001/20/EC)
 - Medicinal product to be manufactured acc. **GMP** (Directive 2003/94/EC)
- The term "Quality Management" for medicinal products normally refers only to GMP
- ISO 13485 certification is not required