Successful notified body opinion and Marketing Authorization Application, and an approach to life cycle management

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Inspired by patients.
Driven by science.

Disclaimers

The experience shared is that of the company and does not preclude for Health Authority or Notified Body positions.

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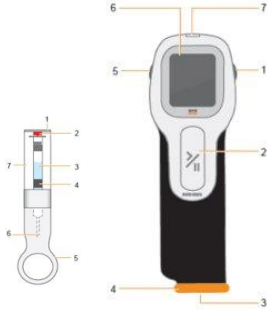
Agenda

- Examples of UCB drugs used with medical devices
- Learnings from notified body opinion and Marketing Authorization Application for a pre-filled pen
- Life cycle management challenges across a range of configurations of drugs used with a device
- Example of borderline presentation

Examples of UCB drugs used with medical devices

- Drugs referencing specific devices
  - Example: dose-dispenser cartridge used with an electromechanical device
  - Device CE-marked



- Drugs delivered with co-packaged devices
  - Example: syrup with dosing cup
  - Device CE-marked

- Drugs-device single integral medicinal products
  - Examples: pre-filled pen
  - Device constituent parts subject to notified body opinion as per Medical Devices Regulation article 117

Learnings from NBOp and MAA for a pre-filled pen

new MAA filed shortly after 26 May 2020

Notified Body administrative interaction

- Started 1 year prior to MAA submission
- Demonstration of compliance to GSPR): alignment on contents and format
- No platform approach for the device constituents
- Define procedure timelines

As early as possible:
Negotiations with Contract Manufacturing Organizations on information required to support General Safety and Performance Requirements (GSPRs)

Notified Body opinion(NBOp) application

- 6 months prior to MAA submission
- GSPR and Technical documentation review
- Waves of questions
- Timelines for review of complementary documentation

Marketing Authorization Application (MAA)

- Pre-submission meeting discussion 6 months prior to MAA submission
- Status of NBOp
- Sections built based on EMA guideline * (draft at the time)

*** Draft EMA guideline on quality requirements for DDC EMA/CHMP/QWP/BWP/259165/2019 of 29 May 2019 now superseded by Guideline on quality documentation for medicinal products when used with a medical device EMA/CHMP/QWP/BWP/259165/2019 22 July 2021**

Lessons learned from NBOp submission activities

Technical documentation
Agreement with Notified Body:
- **Technical documentation** supporting compliance with GSPRs (MDR Annex I)
    - Post-Market Surveillance **N/A**
    - Clinical Evidence: **Summary of CTA where the device was used**
    - Instructions for Use: **draft**
- High level introductions / summaries + reports
- Maintenance: internally by Marketing Authorization Holder

Documentation from external companies

Device components manufacturers:
- **Internal documentation** supporting GSPR compliance claims provided in technical documentation file
- Agreed to **directly interact** with Notified Body if needed for confidential information

NB submission and review process
- Initiate contact with Notified Body 1 year ahead of MAA
    - Contractual aspects
    - Alignment on documentation
- Submission 6 months before MAA
- Review timelines
- Review process 4-6 months
- Additional review slots

Review output

Level of detail ✓
Shipping qualification data
Stability protocol and data
Additional review round → clock stop

Lessons learned from MAA submission activities

CTD documentation

- Module 1: Devices reviewer's guide
- Module 5: Human Factors Study reports
- Module 3: Sections in 3.2.P + 3.2.R *

Avoid redundancies.

Documentation from external companies

No confidential information
Certificates of Analyses,
Certificate of absence of phthalates,
Transmissible/Bovine Spongiform Encephalitis TSE/BSE

EMA submission and review process

Pre-submission meeting
- NBOp availability **
- EMA internal alignment

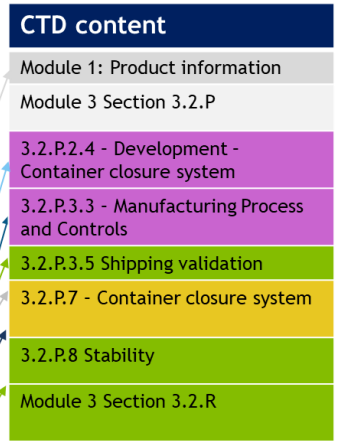
Review output

Device reviewer's guide much appreciated
Question on Specification of device components (incoming specification prior to assembly)

* Draft EMA guideline on quality requirements for DDC EMA/CHMP/QWP/BWP/259165/2019 of 29 May 2019
now superseded by Guideline on quality documentation for medicinal products when used with a medical device EMA/CHMP/QWP/BWP/259165/2019 22 July 2021

** EMA Q&A on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746) – (Q&A °2.5 At what stage do I need to provide the Notified Body Opinion?)

Examples of observed redundancies of requested documentation



Looking at the information from different angles

Health Authority: final world on authorization

Clear Life Cycle Management rules needed

Design Transfer / Manufacturing

Device components manufacturing prior to assembly : only to Notified Body.

Notified Body focus on sterilization process and validation for primary pack.

Health Authority reviews Drug Product filling and assembly process.

Level of information provided for specific topics

Topic	Technical documentation	CTD sections	Comments
Design verification	• High level introduction with key functional properties • DV report	High level summary and key data	
Aging	Accelerated aging protocol + report	• Summary of accelerated aging data, real time aging protocol • Long term stability of final assembly (6 months)	Real time aging protocol required by NB during NBOp review
Shipping	Shipping qualification protocol	Summary of shipping qualification data	Shipping qualification reports required during NBOp review
Dimensions / drawings	Technical drawings	Pictures, exploded view, critical dimensions only (control strategy)	Changes to non-critical dimensions are not subject to variation

Life Cycle Management

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

REGULATORY GUIDANCES RECOMMENDATIONS

- Quality agreement with supplier of device constituent parts
- Not just **changes on devices constituents**, also **changes to the drug**, which could **impact the safety and performance of the device** in such a way that it may require further verification/validation, or to the **target population**.
- New NBOp required if **change to the design or intended purpose of the device (part), or a new device is introduced**
- Variation ? based on the variation regulation 1234/2008. **impact on the quality, safety and/or efficacy?** Impact on critical quality attributes or control strategy?

NBOp required for a change?

→ Assessment of Change Controls on a case by case basis

→ Risk assessments & checklist

→ MAH determination of need for NBOp

→ Internal justification (no justification in variation cover letter)

→ Getting ready in case of future change requiring NBOp

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***** Variation regulation 1234/2008**

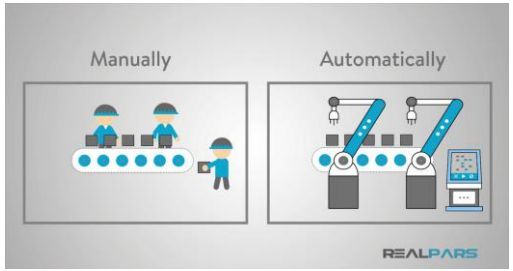
Life cycle management examples

Example 1: from manual to automatic assembly line

Same key steps

Same control strategy and limits

→ Minor process change (type IB variation); No New NBOp required



Example 2: new Bluetooth connectivity on a CE marked electronic device

Same user interface for administration steps

No new review by a Notified Body

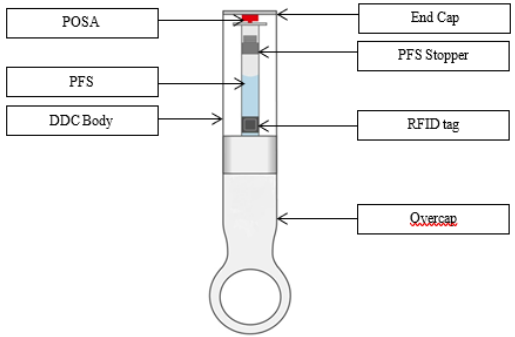
→ Same CE certificate

→ Updated CE declaration of conformity

Variation due to minor Summary of Product Characteristics edits (not affecting instructions for use) (type IB variation)

Case study for borderline presentation : is the dose-dispenser cartridge eligible for NBOp?

Dose-dispenser Cartridge



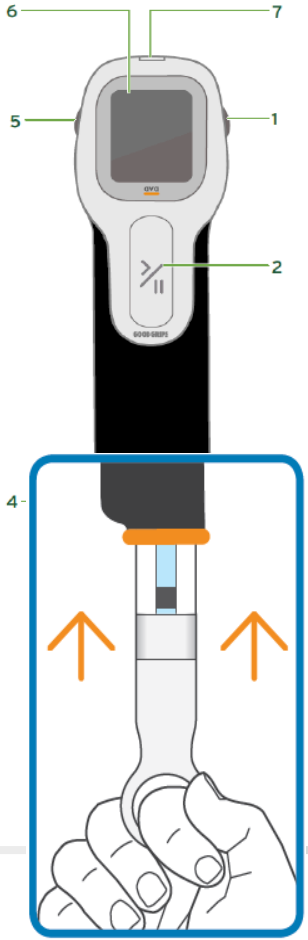
Fits the Pre-filled Syringe into the e-Device
Not suitable for administration (not meant to administer the Drug Product)
Not a medical device in itself

Documentation:
Technical File of e-Device
MAA file (Common Technical Document)

Variations that affect design, performance, quality, safety or efficacy
→ subject to Notified Body review

CE certificate ensures adequate review by Notified Body

e-Device



Thanks!

Contact

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