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

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19.OCT.2021
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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 NBOOp 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

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)

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

* Draft EMA guideline on quality requirements for DDC EMA/CHMP/QWP/BWP/259165/2019 of 29 May 2019 now superseded by Guideline on quality documentation for medicinal products when used with a medical device EMA/CHMP/QWP/BWP/259165/2019 22 July 2021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

**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)

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** 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

### Technical documentation

<table>
<thead>
<tr>
<th>Section 1: Introduction</th>
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<tbody>
<tr>
<td>Section 2: Documentation and Quality System Outline</td>
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<td>Section 3: Product Family and Accessories</td>
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<td>Section 4: Product Description</td>
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<td>Section 5: Claims and Classification</td>
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<td>Section 6: Responsibilities and Locations</td>
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<td>Section 7: Design Input</td>
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<td>Section 8: Risk Management Records</td>
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<tr>
<td>Section 9: Standards and General Safety and Performance Requirements</td>
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<tr>
<td>Section 10: Labeling</td>
</tr>
<tr>
<td>Section 11: Declarations (not applicable to single integral)</td>
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<tr>
<td>Section 12: Design Output</td>
</tr>
<tr>
<td>Section 13: Clinical Evaluation (not applicable)</td>
</tr>
<tr>
<td>Section 14: Design Verification and Validation</td>
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<tr>
<td>Section 15: Design Transfer</td>
</tr>
<tr>
<td>Section 16: Notified Body Documentation</td>
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</table>

### CTD content

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<th>Module 1: Product Information</th>
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<tr>
<td>Module 3 Section 3.2.P</td>
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<td>3.2.P.2.4 - Development - Container closure system</td>
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<td>3.2.P.3.5 Shipping validation</td>
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<td>3.2.P.7 - Container closure system</td>
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<td>3.2.P.8 Stability</td>
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<tr>
<td>Module 3 Section 3.2.R</td>
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**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

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

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?

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
Thanks!
Contact

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