BWP/QWP Guideline

Quality of Drug-Device Combination Products: an update

Nick Lee
May 2019, Seville
Introduction

The Guideline: Core Concepts

The Guideline: Core Content

Summary Conclusions
Introduction
Scope and Definitions

Scope

Quality aspects of DDCs – overview of GL structure and content
MDR (2017), Art.117 only

Definitions

**DDC:** the term “Drug-Device Combination product (DDC)“, as used in this presentation, relates to... medicinal product(s) with integral and/or non-integral medical device/device component(s)

**NCA:** medicinal NCA (as opposed to device NCA)
Conscientia...

There are known knowns - these are things we know that we know.

There are known unknowns - these are things that we know we don't know.

But there are also unknown unknowns - there are things we don't know we don't know....”

Donald Rumsfeld

Facilis descensus Averno

Virgil
Device Legislation

MDD 93/42/EC

AIDD 90/385/EC

IVDD 98/79/EC

MDR
May 2020

IVDDR
May 2022

MDD still in effect until 2020
Confusion and Uncertainty...

For any DDC, it could be considered that...

- **Formulation challenges** tend to depend more on active substance, compatibility and method/route of administration
- **Device challenges** tend to depend more on the materials of construction, components and their design and suitability for use
- **System challenges** tend to reflect more in usability, method/route of administration and delivery
- **Medicinal products** conform to relevant legislation
- **Devices** conform to relevant standards

How they overlap/interact can be confusing.

What is required to be presented in an MAA is uncertain.
Background

Two main concerns regarding DDC dossiers

1. Variable content
2. Variable assessment

Stakeholder certainty = EMA guideline

Guideline should work for industry and regulators...

- Stakeholder feedback (CP comments, position/opinion papers, etc.)
- NCA internal guidance, assessor experience and current practice
- NB feedback (via teleconferences)
- Legal basis: MPD and MDR
Drafting Group

Ten (10) members:

- Abi Moran, UK, Rapp (QWP)
- Anna-Karin Rehnström, SE (BWP)
- Beate Maichel, AT (QWP)
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- Ilona Reischl, AT, (BWP, CAT)
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- Maeve Lally, IE, (BWP)
- Nick Lee, IE, Co-Rapp (QWP)
- Pascal Venneugues, EMA
- Veronika Ganeva, UK, (BWP)
## Timelines (...planned!)

<table>
<thead>
<tr>
<th>Month</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>May 2019</td>
<td>Internal approval to publish for public consultation</td>
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<tr>
<td>Jun 2019</td>
<td>Publish for public consultation (3M)</td>
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<tr>
<td>Sep 2019 onward</td>
<td>Collate and process comments</td>
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<tr>
<td>Dec 2019 earliest</td>
<td>Circulate revised draft for comment and approval within EMA</td>
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<tr>
<td>Jan 2020 earliest</td>
<td>Publish – final guideline and overview of comments, implementation phase</td>
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The Guideline: Core Concepts
Guideline on the quality requirements for drug-device combinations

Draft

<table>
<thead>
<tr>
<th>Draft agreed by Quality Working Party</th>
<th>&lt;Month YYYY&gt;</th>
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<tbody>
<tr>
<td>Draft agreed by Biologics Working Party</td>
<td>&lt;Month YYYY&gt;</td>
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<tr>
<td>Draft agreed by Committee on Advanced Therapies</td>
<td>&lt;Month YYYY&gt;</td>
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<td>Adopted by CHMP for release for consultation</td>
<td>&lt;DD Month YYYY&gt;</td>
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<tr>
<td>Start of public consultation</td>
<td>&lt;DD Month YYYY&gt;</td>
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<tr>
<td>End of consultation (deadline for comments)</td>
<td>&lt;DD Month YYYY&gt;</td>
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Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

| Keywords | Drug-device combination products, drug delivery, medical devices, integral, non-integral, Article 117, Notified Body opinion |
# Core Concepts #1: Scope

<table>
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<th>Out of scope</th>
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<td>Art 1(8)</td>
<td>Combined ATMPs (where devices are part of the active substance and/or the formulation)</td>
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<tr>
<td>Art 1(9)</td>
<td>Electromechanical components and electronic add-ons to existing products</td>
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<tr>
<td>Integral</td>
<td>Veterinary DDCs</td>
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<tr>
<td>Non-integral (Co-packed)</td>
<td>IVDDs</td>
</tr>
<tr>
<td>Non-integral (SmPC)</td>
<td>Device-drug combination products</td>
</tr>
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Core Concepts #2: Core Precept

“...the Competent Authority will evaluate the device specific aspects of safety and performance relevant to the quality, safety and efficacy of the medicinal product...

and that as applicable, the Notified Body (NB) will assess the relevant GS PRs”
Core Concepts #3: ATMPs

The guideline...

“...applies only to devices that are considered part of the container closure system, or medical devices that are co-packaged, or referenced in the Product Information and obtained separately.”

“Article 117 of the MDR does not apply to ATMPs.”

Section 4.4 recommends that consideration should be given to seek scientific advice
Core Concepts #4: Art. 117

Regarding compliance with MDR, Annex 1, provide...

1. **EU Declaration of Conformity (device manufacturer) or a Certificate of Conformity (NB) to allow a CE mark**

2. **If the above information is not available:**
   
a) **Devices that, if used separately, do not require the involvement of a NB, the applicant’s confirmation that the device part meets the relevant GSPRs, or**

   b) **If the conformity assessment of the device, if used separately, would require the involvement of a NB, a NB opinion (NBOp) on the conformity of the device with the relevant GSPRs, issued by an appropriately-designated NB**
Core Concepts #5: Dossier content

Information on the device follows eCTD format

Information to be included - specific sections of M1 and M3

M3: appropriate information on the manufacture, control and usability of the DDC as defined for the intended patient population

3.2.P: product-specific quality aspects of the device relevant to quality, safety and efficacy of the medicinal product

3.2.R: relevant information related to demonstration of compliance with MDR Annex 1

Platform technologies: are not excluded and should be discussed and justified, with references provided
Core Concepts #6: Other

Standards

“Compliance relevant Ph. Eur. chapter(s) or monograph(s) should be demonstrated. Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards.”

Scientific advice

Guideline is not exhaustive; thus, the importance and utility of obtaining scientific advice should be recognised

“Consideration should be given to seeking advice within the EU Competent Authority network early in development, particularly for new and/or emerging technologies.”
The Guideline: Core Content
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Integral: Product Information

Defines expectations, e.g.

- SmPC Section 6.5: the type of the device(s) and its (their) component material(s) should be listed

- For a device that has a CE mark, the CE mark may be included on the device itself but should not be included on the labelling for the DDC as this may be interpreted incorrectly as referring to the DDC as a whole
Integral: Module 3

Defines expectations regarding information to be presented in the dossier, and its location in the dossier

Key sections are...

- 3.2.P.2.4/3.2.P.7 (CCS), 3.2.P.3.3 (MoM), 3.2.P.5.1 (Control) and 3.2.P.8 (Stability)
- 3.2.A Device (Adventitious Agents Evaluation)
- 3.2.R Device (Compliance with MDR Annex 1, usability (human factor) studies and platform technologies)
Integral: Module 3.2.R

Regarding compliance with MDR, Annex 1, provide...

1. EU Declaration of Conformity (device manufacturer) or a Certificate of Conformity (NB) that allows a CE mark to be displayed on the device

2. If the above information is not available:
   a) If class I (excluding Im, Is, Irsi), applicant’s confirmation that device part meets relevant GSPRs, or
   b) If class Im, Is, Irsi, IIa, IIb or III, an NBOp on the conformity of the device with the relevant GSPRs, issued by an appropriately designated NB

3. For devices used as CCS for ATMPs:
   a) EU Declaration of Conformity (device manufacturer), or
   b) Certificate of Conformity (NB), or
   c) Evidence that GSPRs are met provided by the applicant (e.g. checklist)

Note: a suggested template for NBOp is provided in an Annex
Non-Integral (Co-Packed)

“...Information to be provided will depend on the specifics of the device and the risks thereof to the quality, safety, and or efficacy of the medicinal product”

Reduced level of information:

- Primarily P.2 and P.7
- Evidence of conformity
Non-Integral (SmPC)

(Further) reduction in the level of information presented in the dossier

“The impact of the specific device on the medicinal product (when used together) should be addressed using a risk-based approach, with consideration to the need for a usability study.”
Bridging (Development to Commercial)

Integral DDC:

“...data to bridge the different device designs from a quality, safety and efficacy perspective may be required in Module 3.”

- Risk assessment should describe the changes, batches used and trial(s) affected, and how the impact on product quality was mitigated

- Scope should be limited to potential impact of changes to device during pivotal clinical trials in terms of potential impact on quality, safety and efficacy of the medicinal product
Life-Cycle Management

Core expectation...

- Apply variation guidelines, submitting under appropriate category
- Where the need for a variation is unclear and/or the category of the change is unclear, consult with medicines CA that issues the MA to agree the category prior to submission of the variation application

Regardless, consider scope and impact of the change...

- A change to a device that impacts any DDC CQA(s) and/or any element(s) of the overall DDC control strategy may warrant a higher category of variation
- What updates to relevant documentation are required e.g. NBOp, Declaration of Conformity, CE mark etc.?
Emerging Technologies

- Where utilising emerging technologies, engage with medicines CAs in a timely manner, e.g. by formal scientific advice, or through Innovation Offices, etc.
- Engage in discussions with a NB in a timely manner
- Alternative documentation approaches for emerging technologies could be acceptable, if adequately justified
- Samples aid assessment and minimise queries relating to hands-on, practical aspects of its use
What can you do to help?

• Provide consolidated feedback as an industry

• Provide a priority-list rather than a wish-list
  – Focus on what can be changed!
  – Be pragmatic

• Take the opportunity to talk to regulators
Summary

Guideline progressing through EMA process to be published for consultation

- Publication in Jun 2019
- 3M consultation period

DG intent is for GL to be published in final form prior to May 2020

Scope of any implementation plan tbc
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