EBE Reflection Paper

Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment

15 January 2018 Version 1

Developed by the EBE Biomanufacturing Working Group and its topic group on Drug-Device Combinations (DDC).

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About EBE
The European Biopharmaceutical Enterprises (EBE) represents the voice of biopharmaceutical companies of all sizes in Europe and is a specialized group within the European Federation of Pharmaceutical Industries and Associations (EFPIA). Established in 2000, EBE is recognized as the leading biopharmaceutical association in Europe.

“Industry” mentioned in the title and throughout this paper refers to EBE member companies.
Executive Summary

A working group within the European Biopharmaceutical Enterprises (EBE) focused on EU specific topics relating to those integral combination products, which are regulated as medicinal products but which contain a drug delivery device component. The EMA Quality Working Party and Biologics Working Party communicated in a recent concept paper* their intent to develop a guideline on quality aspects of the dossier requirements for Drug Device Combination (DDC) products for marketing authorization applications (MAAs), line extension applications and variations to show that the combination has been appropriately designed and controlled and can be used correctly in the intended clinical situations.

EBE developed a reflection paper with thematic mirroring the scope of the above mentioned EMA concept paper and covering as well, the impact of the Medical Device Regulation (MDR) entering into force in May 2020 and more specifically of Article 117.

The EBE reflection paper is built in five parts intending to address the following items:

- Latest harmonization initiatives related to technical requirements for DDC products, latest state of discussions within the Industry and with the regulators through Advocacy activities including a summary of main Industry comments on the EMA concept paper that help shape this paper.

- Location of device and DDC product information and example on the extent of device and DDC product information required in eCTD Module 3. The cases study considers ‘Prefilled syringe assembled with a spring loaded auto-injector’ as an example of a well-established delivery system building on Industry experience with subcutaneous monoclonal antibody products on the EU market as starting point then taking a general view addressing commonalities with chemical DDC products.

- Reflection and position on involvement of Notified Body review (scope and timing) as will be required by MDR, considering that the current regulatory pathway and review approach has not been an impediment to the review and approval of safe and effective single integral products in MAAs and variations to date.

- Reflection on a risk-based approach to classification of device post-approval change reporting level, providing ‘real-life’ examples of variation requirements experienced by Industry and discussing guiding principle for categorization of device variations while outlining and addressing the ambiguity of container closure system/device terminology and the potentially blurred interpretation of ‘single integral product’ in EU.

- Reflection on emerging technologies associated with Large Volume Devices for high viscosity biological products, electromechanical devices, and electronic add-ons to existing products (digital health).

This EBE Reflection Paper aims to encourage the discussion between the industry and the EMA on the identified issues.

* Concept paper on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product, EMA/CHMP/QWP/BWP/661488/2016, November 2016
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1. Introduction

This paper provides an industry perspective on the marketing application technical requirements (Module 3 Quality of the Common Technical Document), regulatory review process and post-approval device related change assessment for medicinal products containing a drug delivery device component.

In the context of the recent publication of the new Regulation on Medical Devices (MDR) in the European Union Official Journal, Regulation (EU) 2017/745 of the European Parliament and of the Council amending the Medicinal Product Directive (MPD, Directive 2001/83/EC) and replacing the Medical Device Directive (MDD, Directive 93/42/EEC) (1-3), the European Medicines Agency (EMA) in February 2017, initiated a call for comment (4) on its concept paper identifying the need to develop a guideline on quality data requirements for medicinal products incorporating, or used with, medical devices to address instances of inconsistent and incomplete data that are currently being submitted in Module 3 of marketing authorization dossiers, line extension applications and variations.

The EMA believes the guideline is a business need because there has been an increase in marketing authorization activity linked to drug products incorporating medical devices, henceforth referred to as DDC products.

The EMA focusses on those DDC products, e.g. prefilled syringes, inhalers, and auto-injectors that are seen as more complex than container-closure systems, due to the associated delivery and measuring or metering function. The concern is that the added complexity leads to higher potential for medication errors or Adverse Drug Reactions (ADRs).

The future EMA guideline seeks to drive consistency in Module 3 by addressing DDC product data requirements with respect to quality aspects, usability requirements and lifecycle management.

At the June 2017 Interested Parties meeting of the EMA Biologics Working Party (BWP) in London, EBE raised awareness that a number of Industry representatives were collaborating to prepare a reflection paper on this topic, with the intent of sharing some of the concerns industry are facing in the absence of focused guidance.1 Following the publication of the EMA recommendations, feedback from cross-industry review of the EMA concept paper has been incorporated into the reflection paper. See Section 2 for Cross Industry Group with EU focus.

The EBE reflection paper is now complete. It addresses special considerations for DDC products e.g. prefilled pens. It covers the many commonalities between biological medicinal products and chemical medicinal products combined with a medical device as well as some aspects specific to biologics, for example, bespoke delivery technologies.

Industry consensus and key proposals in the reflection paper are as follows:

- Location of device and DDC product information in Module 3 should remain flexible. As mentioned in Section 3 of this paper, three fundamental approaches to the distribution of information and data between 3.2.P and 3.2.R. CTD sections have been used. Location of information does not materially affect product quality; therefore, all three approaches should be equally acceptable.

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1 Previously at the July 2016 Biologics Working Party (BWP) Interested Parties meeting, BWP informed EBE that this concept paper was on their work plan and will be finalized end 2016. EBE at the time informed BWP of their intent to develop a white paper on dossier requirement for administration devices supplied as integral part of medicinal product or supplied along with medicinal product
Industry agree that a ‘Reviewer guide’ should be provided in Module 1 to help Agency reviewers locate the relevant device and DDC product information and facilitate the review.

- Industry is broadly aligned on the extent of device and DDC product information required, regardless of where it is located in the EU MAA eCTD Module 3. An example of Module 3 Dossier content strategy is provided in Section 3 for a prefilled pen, which is a DDC product. Module 3 dossier content strategy shall be built around a high level package on the manufacture and control of the medical device component in Module 3 that is focused on:
  - Manufacturing and Controls
  - Compatibility/interaction between the drug product and the device
  - Container closure integrity
  - Accuracy of dosing
  - Functional performance and
  - Usability of the product

- The enhanced requirement from MDR Annex 1 on Essential safety performance requirements (ER) are reviewed (Section 4.2).

- Involvement of Notified Body review as required by the MDR is a critical issue for manufacturers to consider. The current regulatory pathway and review approach has not been an impediment to the review and approval of safe and effective single integral products in MAAs and variations to date. The scope and timing of Notified Body review, the potential impact on development and review timings and the risk of duplicate reviews is considered in Section 4.3, which includes a summary of discussions held with Notified Bodies on this topic.

- Any new Module 3 guidance should consider the post approval impact and should align with the ICH Q12 objective of making CMC changes more predictable and efficient. The current global regulatory complexity for managing post approval changes (PACs) is increasing with varying reporting categories, documentation requirements and approval timelines as has been stated in numerous Position Papers including those from EFPIA and IFPMA. The complexity reduces the pace of innovation and continual improvement, is costly, and can lead to medicines shortages. EBE is therefore supportive of any initiative that can lead to a reduction of this complexity and clarify the variation-reporting category in EU as well as develop clearly terminology around container closure system or device. Until this ambiguity is resolved, the Industry position proposed in this paper is that the medicines category should take precedence for review of the variation by the Agency quality assessors. Section 5 of this reflection paper discusses the terminology challenges, a risk-based approach to classification of device PAC reporting level and provides ‘real-life’ examples of variation requirements experienced by Industry.

- Emerging technologies remain an open question. Industry concerns are outlined in Section 6. The main questions from a dossier content and/or regulatory review perspective are associated with Large Volume Devices for high viscosity biological products, electromechanical devices and electronic add-ons to existing products (digital health).

This reflection paper aims to encourage the discussion between the industry and the EMA on the identified issues.

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As a follow up, considering the increasing number of drug-device combination products in development and the challenges currently faced by companies as presented in this paper, a workshop with EMA, other EU regulators, Notified Bodies and Industry representatives should be strongly considered (see Section 4.4). Such a workshop would inform the development of typical requirements/guiding principles for specific DDC types, for example, for a novel medicinal product incorporating a well-characterized platform device already marketed for other products, versus a novel medicinal product incorporating a complex novel device. It is envisaged that this engagement between stakeholders would be of significant benefit, based on the consolidated Industry comments and concerns raised to EMA’s concept paper for quality requirements, and as such could facilitate and ensure a smooth and efficient transition into the new requirements of the MDR by 2020.

Along those lines, Industry would support EMA in setting up and coordinating a pilot program to explore the practical implications of MDR Article 117 implementation with complex and innovative DDC products under development. This pilot would provide a framework for informal dialogue between key stakeholders; EMA, future marketing authorization applicants and Notified Bodies intending to engage in this activity. The aim would be to address a range of procedural, technical and scientific questions in the context of the target DDC product profile, with the aim of aligning expectations and facilitating the implementation of an integrated and optimized review process.

2. Regulatory update: State of discussions within the Industry and with the Regulators

2.1 Background and Context

Drug-device combination products are growing in importance across the wider pharmaceutical industry; consequently, there has been an increase in attention from regulators. The increasing rigor and stringency of regulation and the convergence of regulatory frameworks across drugs, biologics and medical devices is also driving an increase in combination product regulation in many markets. Key examples of this are FDA’s Final Rules on cGMP Requirements and Post-Market Safety Reporting for Combination Products (21 CFR Part 4), plus the EU Medical Device Regulation. There has also been a significant expansion in guidance and other regulatory initiatives related to combination products. These are activities such as ICH Q12, a new ISO standard for device change assessment, as well as a number of guidance documents on subjects such as Human Factors and Prevention of Medication Errors. This growth appears to be a continuing trend and evidenced by the recent publication of an EMA Concept Paper on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product.

Whilst some guidance is available, it is recognized that it is fragmented across countries and organizations, not comprehensive in a single-guidance and may not be aligned across regions. These growing and varied changes have done, and will continue to, place additional requirements and expectations on the combination product industry. The industry is keen to ensure combination products currently on the market and those in development meet these changing and evolving requirements to ensure patients have access to important therapies that make a significant positive impact on their lives. However, this presents challenges in terms of consistency of approach when developing combination products for a global marketplace, also having confidence that all required activities are genuinely value adding and can be shown to contribute to ensuring safe and effective products are placed in user’s hands. To address these challenges the combination product industry has been trying to work more closely together and in collaboration with regulatory agencies, legislators and other key stakeholders.
2.2 Cross-Industry Groups and Initiatives

There are a number of cross-industry groups and trade associations which are actively engaging and influencing within the regulatory environment on several hot topics and key areas of combination product development, ensuring that new requirements are better understood and advocating policy positions on regulatory issues affecting these products, and driving for a consistent approach on regulatory issues affecting combination products.

2.2.1 US Focus

The Combination Products Coalition (CPC) is a cross-industry group of leading companies from the drug, device and biologics industries. Currently their focus is covering the following main themes: marketing submissions; bridging requirements; human factors; FDA processes; post-market safety reporting and cross-labelling.

The CPC has developed an effective communication channel with FDA, including an annual meeting as a means of mutually sharing views on key topics and challenges. An example of this was a dialogue between CPC and FDA on the FDA eCTD technical Conformance Guide that FDA published in late 2015. A revised version of the guide was published in October 2016, which has helped to address many of industry’s concerns.

Additionally, CPC and FDA have collaborated in the development of programs for related conferences covering key topics relating to aspects of combination product development and requirements through the Xavier Health organization and Regulatory Affairs Professional Society.

Whilst the focus is solely on inhaled and nasal delivered drug products, the International Pharmaceutical Aerosol Consortium on Regulation and Science, IPAC-RS, have similar and many areas of overlapping focus as outlined above for the CPC. This emphasizes the evolving regulatory requirements for such products in these areas and thus the importance of driving for a consistent cross-industry approach and interpretation of the regulation wherever possible.

2.2.2 EU Focus

Within Europe, those products, which are regulated as medicinal products but which contain a delivery device and form a single integral product, are primarily the scope of the EBE working group. The group has a broad scope with emphasis being on understanding specifically technical requirements and information required to achieve successful Marketing Application registrations and Life Cycle Management filings and on the emerging requirements from Europe; certainly in light of the recast of the Medical Device Regulation (MDR). The group brings a DDC product manufacturing and control strategy perspective in addition to the device perspective and has specific expertise in Biological Products.

The EMA released a concept paper for public consultation in February 2017 in relation to the quality requirements for such medicinal products with integral device component, which EBE responded to with consolidated Industry comments.

The most significant comments are summarized below:

- Module 3 Dossier organization and content requirement.
- Per the MDR requirements and involvement of a Notified Body review for the device component of a DDC product, clarification is needed on the roles and responsibilities of manufacturers, NBs and Competent Authority (CA) assessors for different types of combinations, including cases where qualification of the device by the manufacturer may be

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3 EBE intend to publish a separate paper that should be entitled “Developing an Efficient End To End Control Strategy for a Single Integral Product”.
considered part of the Quality Management System/Pharmaceutical Quality System (QMS/PQS).

- Adoption of clear, consistent terminology is requested.
- Managing variations for DDCs aligned with ICH Q12 principles, and defining reporting categories for device changes shall be based on risk assessment.
- A means to reference device information amongst dossiers was requested, so that identical delivery devices and platform technologies are not repeatedly reviewed and approved as “medical devices”.
- Resolving conflicts and redundancies between pharmacopoeia / SmPC / labelling requirements for medicinal products and ISO standards/ essential safety performance requirements for medical devices.

2.2.3 International Focus

2.2.3.1 ICH Concept Paper

In alignment with the ICH process for new work items, there is future intent to create a concept paper that explains and justifies the need for a work item on combination products. In particular, how aspects of device information (e.g. risk management, human factors etc.) should be presented within the eCTD structure. The objective is to ensure reviewers within regulatory agencies receive the information necessary to conduct an effective and efficient review, whilst facilitating global consistency and harmonization.

2.2.3.2 ISO Technical Committee 84 / Working Group 15

Similarly, the intention behind this new standard currently in development is to provide a consistent approach for companies when assessing and managing changes to devices that are intended to administer medicinal products.

The standard applies to the product lifecycle from pivotal/registration clinical studies to end-of-life. The configuration of the device presentation within scope is inclusive of a device that is integral with, packaged with, or labelled for use with a specified medicinal product. The process defined adheres to the principles of design and development as defined within ISO 13845 [5] when evaluating a change as well as aligning with the requirements of ISO 14971 [6] with regards to risk management considerations and proposes a stepwise approach to considering a change and suggests a level of verification and validation activities to support a given change, to ensure the technical information gathered is commensurate and aligned with the level of risk and nature of change.

The adoption of a common process for the assessment of related product lifecycle changes is not intended to replace any regulatory or quality management system requirements. It is defining a common framework using a scientific and risk-based approach when considering changes to a medical device for the delivery of medicines and should offer significant value to all stakeholders; patients, caregivers, regulators, and industry. The framework does address lifecycle management and includes considerations of appropriate medicinal product guidance (e.g. ICH Q8, Q9 and Q10). Additionally this new standard has been developed to align with ICH Q12, which is also currently in development and as such could facilitate greater post-approval change and understanding variation-reporting categories.

3. Location of Information and Dossier Content Strategy for eCTD Module 3

A survey among EBE member companies outlined different approaches to the location of quality information and data on safety and performance of the device component of the combination
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product and the combination product itself. The following approaches are typically followed:

Table 1: Location of device related information in Module 3 for a DDC product

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<thead>
<tr>
<th>Location of information</th>
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<tr>
<td>Approach #1</td>
<td>Approach #2</td>
<td>Approach #3</td>
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<tr>
<td>3.2 P</td>
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<tr>
<td>All Quality information related to device component and combination product safety and performance</td>
<td>All Quality information related to combination product safety and performance</td>
<td>No information related to device component and combination product safety and performance</td>
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<tr>
<td>Compliance with MDD Annex 1 – mentioning applicable studies performed to demonstrate compliance</td>
<td>Compliance with MDD Annex 1 – mentioning applicable studies performed to demonstrate compliance</td>
<td>Compliance with MDD Annex 1 – mentioning applicable studies performed to demonstrate compliance</td>
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<tr>
<td>May or may not cross refer studies information provided in 3.2.P sections</td>
<td>Technical documentation related to device component in 3.2 P format</td>
<td>Technical documentation related to device component and combination product in 3.2 P format</td>
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<tr>
<td>May cross refer studies handled in the QMS not provided in the dossier</td>
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While the different approaches have been shown to be equivalent in fulfilling EMA/CHMP expectations with regards to location of information and data\(^4\) for the purpose of this paper, a Module 3 eCTD table of content in alignment with Approach #1 is used to illustrate the dossier content strategy for a prefilled pen.

Different approaches being equally acceptable, Industry acknowledges it is helpful to submit a reviewer guide in Module 1 providing guidance on where to find device related information in Module 3.

Regarding Module 3 dossier content strategy, it is the Industry position that Module 3 shall be built around a high level package on the manufacture and control of the medical device component in Module 3 that is focused on:

- Manufacturing and controls
- Compatibility/interaction between the drug product and the device
- Container closure integrity
- Accuracy of dosing
- Functional performance
- Usability of the product

An example of Module 3 dossier content strategy is detailed below, building on Industry experience with subcutaneous monoclonal antibody products on the EU market, taking a prefilled pen presentation (e.g. prefilled syringe assembled with a spring loaded auto-injector) as example of well-established delivery system.

\(^4\) How to shape Module 3 is influenced by tactical considerations. Module 3 granularity depends on the number of Drug Product presentations, number of dosage strengths, number of manufacturer’s, the chosen approach for the location of device and DDC related information and planned Life Cycle Management changes. In that regards, a high level of flexibility in dossier organization is needed.
Table 2: Module 3 Dossier content strategy for a DDC product – Prefilled Pen (PFP) example

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<td>NOTE: For illustrative purpose and reader convenience, device and DDC product information and data is provided in Module 3.2.P and 3.2.R according to Approach #1 but alternative approaches are equally acceptable (see Table 1)</td>
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LEGEND:
- Grey colour: Sections that contain Established Conditions according to ICH Q12 (step 2b) e.g. critical parameters
- Green colour: Sections that contain Supportive information
- No colour: Sections, which are not applicable. The guidelines quoted are frequently used and are provided for information only; alternative guidelines may be used across the Industry.

<table>
<thead>
<tr>
<th>3.2.P</th>
<th><strong>DRUG PRODUCT</strong></th>
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<tbody>
<tr>
<td>3.2.P.1</td>
<td><strong>Description and Composition of the Drug Product</strong></td>
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<td>Brief introductory information on the PFP.</td>
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| 3.2.P.2 | **Pharmaceutical Development** |
| 3.2.P.2.1 | **Components of the Drug Product** |
| Not applicable (i.e. section content not impacted by the incorporation of the device). |

| 3.2.P.2.2 | **Drug Product** |
| Not applicable (i.e. content not changed by the presence of the device). |

| 3.2.P.2.3 | **Manufacturing Process Development** |
| Brief description of the Device Manufacturing Process Development history providing comparison of material from pivotal or bridging clinical studies to the to-be-marketed PFP. |

| 3.2.P.2.4 | **Container Closure System** |
| M4Q ICH Requirements for CCS and compatibility with the formulation |
| Protection, suitability of materials, compatibility, safety |
| Performance / design system requirements of the CCS to applicable ISO/recognized standards or Pharmacopeia requirements e.g. ISO 11040 (7) for performance and ISO 10993 (8) for material safety considerations |
| Design verification for the PFP |
| e.g. Demonstrating defined performance to applicable recognized standards and/or Pharmacopeia requirements |
| Summary of risk benefit analysis aligned with suitable risk-assessment principles (e.g. ISO 14971 or ICH Q9) |
| Usability assessment |
| Substantial changes in PFP and CCS components over development |

| 3.2.P.2.5 | **Microbiological Attributes** |
| Maintenance of Container Closure Integrity5 |

| 3.2.P.2.6 | **Compatibility** |
| Not applicable (i.e. section content not impacted by the incorporation of the device). |

| 3.2.P.3 | **Manufacture** |
| 3.2.P.3.1 | **Manufacturers** |
| Manufacturer name/address for PFP assembly6, packaging, labeling and release testing operations as well as for batch release site in EU. |

| 3.2.P.3.2 | **Batch Formula** |
| Not applicable (i.e. section content not impacted by the incorporation of the device)7. |

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5 After the assembly process, shipment and during long-term storage up to end of shelf life.
6 From EU GMP/Manufacturing and Importation Authorization perspective, DDC assembly falls under the definition of secondary packaging operations. The device (AI sub-assemblies) supplier is not defined as manufacturer.
7 This section is not filled in for prefilled pen. As the assembly, labeling, and packaging steps are mechanical processes, the PFP manufacturing batch size is not defined by parameters that are applied for the manufacturing of a solution for injection or an
## CTD SECTION

### SECTION TITLE

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<td>NOTE: For illustrative purpose and reader convenience, device and DDC product information and data is provided in Module 3.2 P. and 3.2.R according to Approach #1 but alternative approaches are equally acceptable (see Table 1)</td>
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### LEGEND:

- **Grey colour:** Section that contain Established Conditions according to ICH Q12 (step 2b) e.g. critical parameters
- **Green colour:** Sections that contain Supportive information
- **No colour:** Sections, which are not applicable. The guidelines quoted are frequently used and are provided for information only; alternative guidelines may be used across the Industry.

| 3.2.P.3.3 | Description of Manufacturing Process and Process Controls | High-level description of PFP assembly process and controls shall be provided. Conditions found in an assembly manufacturing process description should be those inputs, process parameters, and outputs that are necessary not to alter the product quality, container closure integrity. Since biologics are thermosensitive products, monitoring the time out of refrigeration (TOR) throughout the manufacturing process is important. |
| 3.2.P.3.4 | Controls of Critical Steps and Intermediates | Critical process steps identified as those that have the potential to impact the product and its primary function (drug delivery) impact patient safety and PFP performance. This could include incoming controls of sub-assemblies. |
| 3.2.P.3.5 | Process Validation and/or Evaluation | PFP assembly process performance qualification (PPQ) shall be completed prior to marketing authorization. Short summary of PPQ approach in the dossier. PFP shipping validation. |
| 3.2.P.4 | Control of Excipients | Not applicable (i.e. section content not impacted by the incorporation of the device). |
| 3.2.P.5 | Control of Drug Product |
| 3.2.P.5.1 | Specifications | Specifications for the PFP. |
| 3.2.P.5.2 | Analytical Procedures | Description of analytical procedures is provided for all tests in the PFP release specifications. |
| 3.2.P.5.3 | Validation of Analytical Procedures | Brief summary of method validation protocol and results. |
| 3.2.P.5.4 | Batch Analyses | Batch analysis results are provided for PFP batches used in pivotal trials, bridging clinical studies, process validation studies if available and registration stability studies. |

active ingredient. Therefore, the assembly, labeling and packaging process is independent of batch size and dosage strength as long as the commercial production parameters are applied.

8. Level of automation, numerical values and ranges for mechanical process parameters and process controls are not normally provided in the dossier.

9. Classification for critical process steps is based on a comprehensive risk assessment that includes evaluation of potential patient hazard, and the occurrence and the detectability of the failure.

10. PPQ scale shall be justified, for example it can be defined based on packaging order and maximum allowable TOR. Qualification might be done with product or placebo where justified.

11. It is sufficient to apply simulated conditions; focus would typically be on container closure integrity and only those functional performance attributes that can be affected by the transportation.

12. Typically, it can be shown in development studies that the assembly process has no impact on product quality attributes, hence warranting no release testing on the PFP. Control strategy aspects will be addressed in a separate EBE paper entitled “Developing an Efficient End To End Control Strategy for a Single Integral Product”.

13. Specific standards may apply for Functional performance method validation criteria and methodologies.
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<td>● No colour: Sections, which are not applicable. The guidelines quoted are frequently used and are provided for information only; alternative guidelines may be used across the Industry.</td>
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<td></td>
</tr>
<tr>
<td>3.2.P.5.5</td>
<td>Characterization of Impurities</td>
<td>Not applicable (i.e. section content not impacted by the incorporation of the device).</td>
</tr>
<tr>
<td>3.2.P.5.6</td>
<td>Justification of Specifications</td>
<td>Justification of specification, including justification for not conducting any testing on PFP at release.</td>
</tr>
<tr>
<td>3.2.P.6</td>
<td>Reference Standards</td>
<td>Not applicable (i.e. section content not impacted by the incorporation of the device).</td>
</tr>
<tr>
<td>3.2.P.7</td>
<td>Container Closure System</td>
<td>Details of primary packaging components and its specification as defined in M4Q ICH requirements; demonstrating compliance with Ph. Eur. and/or ISO standard requirements as appropriate. For the PFP: Illustrative drawings of the autoinjector sub-assemblies (no dimensions) Autoinjector sub-assemblies material of construction (alternatively could also be presented in P.1) Incoming controls of the sub-assemblies (alternatively could also be presented in P.3.4)</td>
</tr>
<tr>
<td>3.2.P.8</td>
<td>Stability</td>
<td>Per ICH requirements for DDC products(^{15}). Establishing shelf life(^{16}) of a PFP could consider the following: Real-time storage of the PFP and functional performance of the device constituent Real-time / accelerated testing of primary stability batches for the drug product in the primary container e.g. bulk PFS(^{17})</td>
</tr>
<tr>
<td>3.2.P.8.1</td>
<td>Stability Summary and Conclusions</td>
<td>Per ICH requirement for DDC products (PFP).</td>
</tr>
<tr>
<td>3.2.P.8.2</td>
<td>Post-approval stability and commitment</td>
<td>Per ICH guidelines for DDC products (PFP).</td>
</tr>
<tr>
<td>3.2.P.8.3</td>
<td>Stability Data</td>
<td>Not applicable (i.e. section content not impacted by the incorporation of the device).</td>
</tr>
<tr>
<td>3.2.A</td>
<td>APPENDICES</td>
<td>Medical Device</td>
</tr>
<tr>
<td>3.2.A.1</td>
<td>Facilities and Equipment</td>
<td>Compliance with the relevant general safety and performance requirements of Annex I to the MDD is stated.(^{18})</td>
</tr>
<tr>
<td>3.2.A.2</td>
<td>Adventitious Agents Safety Evaluation</td>
<td>Not applicable (i.e. section content not impacted by the incorporation of the device).</td>
</tr>
</tbody>
</table>

\(^{14}\) Performance attributes can be based on applicable engineering standards, statistical analysis of PFP batch data or literature.
\(^{15}\) The minimum ICH data requirement at time of MAA filing relates to the drug product in its primary container.
\(^{16}\) Per Ph. Eur. Monograph 2031 “Monoclonal antibodies for human use”, the expiry date is calculated from the date of sterile filtration, the date of filling (for liquid preparations) or the date of freeze-drying (where applicable).
\(^{17}\) Stress testing for PFP stability is unlikely to be required since aging of the drug product will influence the functional performing hence of little value overtime.
\(^{18}\) MDR Annex 1 enhanced requirement and Art 117 impact are discussed in section 4.
4. Industry reflections on the Regulatory review process

4.1 Reflections on implementation of Art. 117 of the Medical Device Regulation

Under the current legislation, it is the responsibility of the competent authority (CA)/European Medicines Agency (EMA) to review information and data relating to the device component of an integral product such as a prefilled pen, as part of the medicinal product application.

The current MDD makes it clear that if such a device is placed on the market in such a way that the device and the medicinal product form a single integral product intended exclusively for use in the given combination and which is not reusable, that single product shall be governed by Directive 2001/83/EC. However, the relevant essential requirements of Annex I to the MDD shall apply as far as safety and performance-related device features are concerned.

Notified Bodies are only required to review device information related to CE marked device products provided separately.

The results provided within a marketing application dossier for the DDC product is a subset of the elements necessary to demonstrated compliance with Annex I of the MDD (refer to Section 3 for the example of a prefilled pen). It is the marketing authorization holder’s (MAH) responsibility to maintain a separate full technical package. This may be managed differently in different companies.

Additionally, it should be noted that according to Article 12 of the MDD manufacturers who ‘co-package’ CE marked medical devices as part of a system or procedure pack must ensure they have verified the mutual compatibility of the devices in accordance with the original manufacturers’ instructions and within the original scope of intended use.

Although the principle of single integral product and separately supplied devices remains essentially unchanged, the new Medical Device Regulation (MDR, implementation date 26 May 2020), introduces an important amendment to medicines legislation in Article 117 (1) which requires the MAH to provide a CE marking certificate, if applicable, or a conformity assessment from a Notified Body for the device part.

For single-use integral DDC products covered under Article 117 (MDR), an EC certificate is often not available, as the medical device part is designed for the purpose to form an integral product with the medicine, hence not being a standalone device requiring an EC declaration of conformity or being

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19 PACMP can be used as a tool to facilitate approval of device related changes such as introducing a new PFP presentation when e.g. only a PFS presentation is approved, or submitting substantial PFP design changes.
covered by EC certification. Such a single integral product could be well established (e.g. prefilled syringe with needle safety device or a spring powered prefilled pen) or could be novel combinations, e.g. electronic pumps. It would be important for industry to understand EMA’s expectation in regards to the additional involvement of a Notified Body, especially in case the MAH does provide results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I of the MDR (refer to Section 3 of this document for the example prefilled pen)\(^\text{20}\).

Clarification of EMA’s perspective in regard to the ability of a manufacturer to self-assess conformity with Annex I, considering various quality management system arrangements, would also be useful. It is Industry’s interpretation that the Article 117 requirement applies to all devices except class 1 non-sterile and non-measuring.

Understanding the proposed involvement of Notified Body review is a critical issue for manufacturers; the scope and timing of obtaining a Notified Body opinion could have a significant impact on MAA review times.

In case an EC certificate is available, Article 117 implies that the certificate would be sufficient and the results of the conformity assessment should not be included in the dossier.

It is understood that some Notified Bodies have already been engaged with medicinal product manufacturers, providing reviews of integral devices (PFS and PPP) on a voluntary basis for several years. Good practices and learnings could be leveraged from these experiences to outline expectations for the Notified Body assessment, avoid duplication in relation to MAA review.

Similarly, since this requirement for Notified Body involvement is already established for combined Advanced Therapy Medicinal Products (cATMPs) \(^\text{9}\), clarification is requested on whether such a process could be adapted for DDC products acknowledging that both the nature and number of products affected will be very different for these types of products.

In case device components may be utilized for a number of different injectable products (e.g. PFS and prefilled pens), a system similar to the US Device Master File could be proposed in case a Notified Body review is required, e.g. where

- a general Technical file is maintained (with the optional support of the component suppliers).
- a specific section is developed for the individual combination products.

Overall, the current regulatory pathway and review approach has not been an impediment to the review and approval of safe and effective “combination products” in MAAs and variations. The future involvement of Notified Body review is a critical issue for manufacturers; the scope and timing of the review (sequential versus parallel) could have a significant impact on development and review times. Considering the increasing number of drug-device combination products in development, a workshop with interested parties could be useful to ensure smooth and efficient transition into the new requirements in 2020.

20 Interestingly, Swiss Medik only require a device conformity assessment from a notified body or an additional expert report for complex or innovative DDC products; not for the simpler one such as prefilled syringes or prefilled pen not electronically controlled. https://www.swissmedic.ch/swissmedic/en/home/news/mitteilungen/anforderungen-und-angaben-zu-kombinationsprodukten-arzneimittel-mit-einer-medizinproduktkomponente-im-formular-gesuch-zulassung-aenderung-fuer-humanarzneimittel.html
4.2 MDR versus MDD Annex 1 Requirements

For a single integral product, from 26 May 2020, compliance shall be shown in the dossier through the relevant general safety and performance requirements set out in Annex I to the MDR, as far as the safety and performance of the device part of the single integral product are concerned.

When comparing the essential safety performance requirements listed in Annex 1 of the MDD and in Annex 1 of the MDR, there is a significant increase in the number of requirements, from 14 to 23 clauses, with an additional increase in sub-clauses within the main clauses.

The key messages from the enhanced requirements of the MDR are summarized as follows:

- Emphasized acknowledgement of state of the art requirements is more apparent in the MDR. It appears in more aspects of the requirements relating to design and development, ensuring that risks have been minimized as low as possible, and that the device meets current standards with regard to safety principles, functionality and overall performance.

- Greater focus on risk management systems and more descriptive with respect to risk management evaluation for a given product, including post market surveillance requirements and control measures considered and implemented as a result. There is a greater consideration of risk profile and benefit to end users consistently throughout the requirements, with an emphasis on ensuring risk profile is as low as possible and demonstrate as such.

- More focus on substances and materials of construction relating to quality, safety, compatibility and performance based on the intended use. Increased attention to design and manufacture, considering wear and tear and impact to the above mentioned attributes.

- In addition to previous biocompatibility requirements, there is specific attention to safety with respect to chemical safety (REACH) and phthalates as well as components of CMR (carcinogenic, mutagenic and toxic to reproduction) or endocrine-disrupting substances, which applies to components/devices that have anything other than intact skin patient contacting elements. This also has specific requirements on labelling if a material or component of concern is present.

- There is greater granularity of infection and microbial contamination requirements including substances relating to sterile devices. There are enhanced requirements on components with materials of biological origin and evidence of safety, aligned with the enhanced scrutiny of raw materials and components of biological NCE’s such as traceability of origin, viral contamination and transmissible agents.

- New focus on interoperability and compatibility of multiple devices intended to be used together and minimization of risk of the ‘system’ rather than individual elements.

- New clauses with respect to software and electronic systems further to the energy source requirements of the MDD.

- Specific requirements for active implantable devices based on the combination of the MDD and Active Implantable Medical Devices (AIMD) Directives.

- Specific requirements for devices to be used by laypersons and potential associated risks, with the emphasis to ensure they are as low as possible.

- More prescriptive with respect to labelling and instructions for use, recognizing advancement in technology i.e. non-paper formats for IFUs as well as machine-readable bar codes and reduced-function devices (RFDs).
• There is more clinical focus in the MDR however it should be noted that the specific reference in Annex 1 of the MDD for ‘Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X from the MDD” has not been replaced with an equivalent requirement in the new Annex 1, Safety and Performance Requirements.

While these enhancements will have to be taken into consideration for marketing applications submitted after full entry into force of the MDR, the dossier content strategy in Section 3 reflects the current requirements for compliance with Annex 1 of the MDD.

Further to the MDR and the enhanced requirements within, there will be a number of Implementing and Delegated Acts defined to facilitate interpretation and implementation of the new legislation. There could be as many as a further eight mandatory Directives in place relating to the MDR alone. These legislative acts are being shared through the European Commission (EC) and interested parties have a period of time to comment following release.

4.3 Understanding of Notified Body Involvement based on Survey and Challenges for Manufacturers

4.3.1 Notified Body Survey questionnaire

A survey questionnaire was developed to interview Notified Bodies (NBs) as shown in Appendix 1.

As an initial survey, the view of notified bodies known to be very active in the area of combination products were sought. (Although there are currently approximately 80 medical device notified bodies in Europe, only a small number are accredited for assessment of drug device combination products). Responses were provided by two notified bodies 21 experienced with the consultation process for devices incorporating ancillary medicinal substances, as well as with informal review of integral drug delivery combination products. Both NBs are intending to be designated for this service in the future indicated that the amendment in the MDR and proposed EMA/CHMP guidance is welcome. It should clarify the expectations and set a level playing field for all manufacturers in this space.

It is believed that some NBs will make the decision to not focus on drug-delivery products, and some may not have the in-house expertise to cover these devices. NBs urge manufacturers to engage with them at the earliest stage possible to ensure that their timescales can be planned for and met.

Whilst most manufacturers provide the evidence of regulatory compliance with MDD as part of their MAA dossier without involving a Notified Body, some Notified Bodies have been conducting assessments against the requirements of Annex I of 93/42/EEC for MAHs. Dependent on the Notified Body, they may provide an assessment report outlining non-conformities and / or letter confirming compliance with the relevant Essential safety performance requirements. This assessment is on the device aspects only, as a service outside of the Notified Body operation and with no CE Certificate issued at the end of the process. The MAH may then choose to submit the assessment report as part of the MA Application submission.

It was noted that NBs are commercial bodies, with differing internal processes for reporting and

21 Their feedbacks were collected in April 2017 reflecting their views at the time, which may change over time and is unlikely to represent the view of all Notified Bodies. During NB consultation, a suggestion was also made to follow up with the notified body representation group TEAM-NB. This will be done in a follow-up EBE paper, outlining practical concerns and suggestions regarding implementation of Article 117.
EBE Reflection Paper on Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment

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approval of such reviews. Further discussion and guidance to enable efficient, collaborative working and reduce the need for clarification questions would be helpful.

4.3.2 Outcome of Notified Body Survey and Industry Position

4.3.2.1 Resources

A concern of industry is that insufficient resources are available from NBs to support their MAA due to the reasons outlined above. Given that the number of NBs remaining has reduced significantly in Europe since the joint audit process, all NBs are balancing an increased workload whilst also working on processes and procedures within the NB to ensure compliance to future MDR requirements.

4.3.2.2 Timing

The additional review by a NB will require MAH to consider and plan for additional overall review time for their dossier. The NB will need to complete its assessment to allow submission of the assessment within the MAA. The key for when an MAH can submit to the NB is when the MAH has sufficient data to demonstrate that the device component has met the essential safety performance requirements. It was suggested that this could be prior to completion of the medicinal product Clinical Trial phase of the MAA, providing other data exists to demonstrate that the device is safe to use and will perform as intended. However the final data for the device constituent part in its final presentation is often only available after the Clinical Trial phase. A defined review process with suggested timelines would support the predictability of timelines for the dossier review.

Project planning and guidance on what is considered to be sufficient data will be key deliverables for a successful MAA.

4.3.2.3 Data Requirements

The number one concern voiced by different manufacturers is how to manage the device documentation and where it should be provided in the MAA filing.

Referring to interactions with MAHs with no, or limited medical device expertise, the NBs interviewed suggested that clear, detailed guidance would be helpful - wide variances with the level of detail in documentation submitted for the device part are observed. However, MAHs should also be careful about the level of detail that they submit on the device aspects, given that changes to the MAA are subject to a variation. It could be proposed that a top-level document in the medicines dossier could be sufficient; otherwise the MAH is potentially faced with a burdensome regulatory requirement to conduct variations for all changes to the device.

The NBs’ advice to MAHs with limited device experience would be to ensure they have read the Medical Device legislation, list the essential safety performance requirements in tabulated form and then determine what data they have to demonstrate that they have met each relevant ER, detailing where that data is provided. The NBs also advise to narrate the story of the device and appreciate that it may have many impacts on the drug, and - not just consider it a simple container closure system. Considerations given to the device development should not be viewed as an afterthought to the overall product submission.

The need for pharmaceutical manufacturers and device suppliers to communicate and collaborate more closely was also expressed. MAHs are advised to engage with the expertise available at device suppliers and include them as part of the development team earlier in the process. This is often the case already and MAH’s usually have sufficient device supplier(s) control as part of their QMS.

4.3.2.4 Possible duplication of assessments
Clarification is needed in order to avoid unnecessary duplication of assessments, as the review of the device constituent part by the NB may cover data which may also be reviewed by the CA. NB views on what clinical, usability and functionality, design verification, manufacturing and controls data they should review is summarized in the paragraphs below. A means to reference device information amongst dossiers e.g. device master file as proposed in Section 4.1 above is of high interest to Industry and potentially useful to Regulators, so that identical delivery devices are not repeatedly reviewed and approved as “medical devices”.

4.3.2.5 Clinical data and usability data

NBs feel that some clinical data will be necessary to allow them to confirm safety and performance of the device part. This point requires further clarification as it relates to different classifications of device and intended use. However, NBs may have different approaches to clinical trials and MAH’s have also reported some challenges in meeting both medicines and medical devices requirements for drug-device combination products, so this would be another important topic for discussion and guidance.

Another example of possible duplication of assessments is usability data, which may be reviewed by EMA with the focus on dosing and medication errors, while NBs may review the same data in order to ensure that Annex I usability requirements are fulfilled.

It was suggested by one Notified Body that this is an area that could be looked at by both NBs and CAs - Notified Bodies already assess human factors data, as it is an essential safety performance requirements. However, a CA may also apply their experience and knowledge of the disease state being treated and possible conditions having an impact on the user.

4.3.2.6 Functional performance and manufacturing controls

For review of DDC product functional performance specifications and their justifications, analytical (design verification) procedures and their validation, as well as DDC product aging studies in the context of establishing a DDC product shelf life, are all key ERs – but with overlap of differing perspectives. The NB will be concerned with impacts of the drug on device performance while the CA will want to ensure the integrity of the drug and dose accuracy is not affected by device component changes.

The NBs interviewed pointed out that the PFP manufacturing information and batch data would be something that they would expect to be involved in review of, fuelling industry's concern of extended review timelines due to duplicate review efforts.

The above given examples emphasize the need for close collaboration between NBs and CAs in case a combined review is required. Clarification of the roles and responsibilities in this new area is needed with collaboration between all stakeholders and guidance written to support the Industry work through this change in approach.

4.3.2.7 Guidance

With the MDR, the NBs pointed out that all the European Commission MEDDEV (Medical Device) guidances should require amendment to reflect the changes. New and specific guidance will be needed; alternatively, Common Specifications may be a more appropriate route.

Team NB (The European Association for Medical devices Notified Bodies) is already organizing teams to discuss and debate the various elements and key changes associated with the MDR; work topics were being assigned at the time of the interview (April 2017). It was hoped that Team NBs thoughts could be considered and incorporated into future guidance from both devices and medicines
EBE Reflection Paper on Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment

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regulators, e.g. comments on the CHMP Concept paper and involvement in future guideline development.

Regarding the concluding remarks, it was suggested that the wording from the MDR could also be used, i.e. “NB has performed an assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I of Regulation 2017/745/EU. The documentation meets the requirements of the Regulation.”

Further discussion around this and what would be most useful to enable collaborative working and reduce the need for clarification questions would be helpful.

Also raised by the NBs interviewed as useful topics for discussion around drug-device combinations were:

- The impact of Class IIb active devices under rule 12.
- The “scrutiny” procedure, and
- The potential for development of Common Specifications.

4.4 Need for Cross Regulator Collaboration and Industry Proposal for Workshop and Pilot Program

It is acknowledged and very much appreciated that moves are underway to address the convergence between medicines and medical devices regulatory pathways in Europe, with establishment of a Heads of Medicines and Medical Devices Agencies initiative: the Heads of Medicines Agencies (HMA) & Competent Authorities for Medical Devices (CAMD) Working Group on Borderline and Combination Products.

It is understood that the purpose of the working group is to advise HMA & CAMD on issues relating to the Medicinal Product/Medical Device borderline and regulation of drug-device combination products, specifically

- To reach common understanding between Member States in relation to the interpretation of legislation relevant to the borderline.
- To provide a forum to discuss the classification of products to aid in decision-making.
- To agree common understandings and best practices around assessment and regulation of so-called “combination products”.
- To identify gaps in legislation relevant to these products and propose guidance to ensure consistent regulatory decision-making and protection of public health.

It is hoped that through the networks and working groups already established, European regulators and industry representative groups can work together to ensure innovative, safe and effective medical products reach patients as soon as possible.

The development of the CHMP guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product is welcomed.

It is proposed that a workshop with EU regulators, Notified Bodies and industry representatives would be an excellent opportunity to discuss the challenges faced and possible solutions in the European context.

Along those lines, industry would support EMA in setting up and coordinating a pilot program to
explore the practical implications of MDR Article 117 implementation with complex and innovative DDC products under development. This pilot would provide a framework for informal dialogue between key stakeholders; EMA, future marketing authorization applicants and selected Notified Bodies to address a range of procedural, technical and scientific questions in the context of the target DDC product profile, aligning and expectations and facilitating the implementation of an integrated and optimized review process.

5. Risk-based approach to device-related post-approval changes

5.1 Regulatory Framework for Device and DDC product related post-approval change management

The Medical Devices Directive (93/42/EEC) as well as the new EU Medical Devices Regulation requires under Annex I - “Essential Requirements” or new “General Safety and Performance Requirements” - that risks of a medical device need to be reduced as far as possible. All known and foreseeable risks, and any undesirable side-effects, shall be minimised and be acceptable when weighed against the evaluated benefits for the patient and/or user arising from the achieved performance of the device during normal conditions of use.

Furthermore, manufacturers shall establish, implement, document and maintain a risk management system, which is an ongoing systematic process throughout the life-cycle of a product for identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls.

For each medical device, the manufacturer must decide if the overall residual risk posed by the product is acceptable, after all risk control measures have been implemented and verified. In case of any remaining overall residual risk it must be evaluated if sufficient evidence is in place to support the conclusion that the medical benefits outweigh the overall residual risk and if the overall residual risk can be judged acceptable. All risk management activities should be documented in a designated file and manufacturers need to inform users of any residual risks in the accompanying information of the product. The benefit-to-risk assessment needs to be systematically repeated after production or post-production information becomes available for a medical device.

The underlying (current) harmonized standard is ISO 14971:2012 “Medical devices - Application of risk management to medical devices” which will support manufacturers to be in compliance with the Annex I requirements. The risk management process needs to be embedded as an integral part into the quality management system of the medical device manufacturer with interfaces to e.g. design control, usability engineering, manufacturing, change management, complaint management, and post-market surveillance / vigilance processes. Therefore, a risk management system within the quality management system is a key component in demonstrating regulatory compliance for medical devices throughout the life cycle of the DDC product.

It is expected that the new ISO standard ISO 20069 “Device change assessment of combination products for administration of medicinal products” currently under finalization will be useful addition on how to manage change to the device constituent of combination products intended to deliver medicinal products.

A device related change to a DDC product should be evaluated according to the quality management system and post approval changes should follow the same level of review, as would a device with the same regulatory status. Risk assessment and design verification/validation (if applicable) should be performed to ensure that the device still meets the intended user needs following the change.
5.2 Container closure system/Device and Single Integral Product Terminology

The EU device regulation does not have a specific definition for a Drug-Device-Combination (DDC) product. Due to the lack of clear terminology for a DDC product within the EU, it is challenging to determine the appropriate change-control category for submission of DDC product variations. In the context of this paper that focuses on single integral products (medicinal product with an integral device component), all the medicines related variation categories were considered.

With advances in technology, some MAHs are moving towards new administration devices that allow a larger volume of drug to be delivered in a single injection, therefore reducing the number of injections required per patient. For example, the automated mini-doser ("AMD") for use with Repatha® is a single use, on-body injector, designed to provide monthly dosing in one single injection instead of three separate injections (with prefilled syringes/prefilled pens). While this on-body injector shares many similarities with traditional PFS/PFPs, the devices differ in the way they are packaged. Unlike PFPs, where the drug container is supplied pre-loaded into the device, the on-body injector device is co-packaged with a drug cartridge. Within the EMAs variation assessment report (10) for this on-body injector, it is noted that the MAH received a major objection regarding the delivery device not being CE marked (under directive 93/42/EEC) prior to issuance of CHMP opinion. It is understood that different member states took different views on the regulation of this product.

Therefore it is vital to understand whether or not a ‘single integral product’ can consist of more than one component, if final assembly is performed by the user. In light of the above scenario, and for future emerging technologies, a clear definition of what constitutes a ‘single integral product’ would be greatly appreciated by industry.

In the EU, the variation classification guideline (11) does not provide an elaborative list of classification for Device related changes for human medicinal products. The categorization of change depends on the fact that the device component may also be classed as a container-closure system or a device, e.g. the syringe barrel of a PFS product. Therefore, there is a possibility of cross-over between the two categories.

There is a lot of confusion on device versus packaging terminology for a single integral product that would require clarification from EU regulators. Immediate packaging itself is subject to interpretation. In the EC variation guideline, immediate packaging is defined by opposition to outer packaging while in the EMA guideline on plastic immediate packaging materials (12), immediate packaging refers to i.e. packaging materials intended to be in direct contact with the medicinal product. Primary packaging seems to include immediate packaging + other packaging elements that are not in contact with the medicinal product but cannot be defined as secondary packaging elements. The industrial process that consists of assembling a device with a medicinal product is considered from a EU GMP perspective to be a secondary packaging operation as mentioned in the Drug Product Manufacturing and Importation Authorization, i.e. the same as packing prefilled pens into a carton box. However, the EU variation guideline, for a single integral product refers to “a device which is an integrated part of the primary packaging”.

In that regard, it is industry’s position that the following aspects of the product need clearer, more consistent terminology:

22 In that regards WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products (http://www.who.int/biologicals/BS2311_PAC_for_BTP_12_July_2017.pdf) gives useful definition:

"Container closure system: refers to the following components:
- A primary container closure system is a packaging component that is in, or may come into, direct contact with the drug product dosage form (e.g. vial, prefilled syringe) or components that contribute to the container/closure integrity of the primary packaging material for a sterile product."
• Components that are in direct contact with the drug product dosage form (e.g. vial, syringe barrel).

• Components that are not in direct contact with the drug product dosage form (e.g. carton, tray), including:
  o Those, which provide a function (e.g., protection from light, ensure container closure integrity).
  o Those, which do not provide a function.

• Devices, which deliver the drug product but do not come into contact with the drug product and should be considered as a secondary packaging activity.

• Devices, which deliver the drug product, but are in contact with the drug product.

5.3 Current EC Variation Guideline – Device-Related Changes

Regarding single integral products such as PFPs, device related changes can be submitted under

• **B.II.e.7:** Change in supplier of packaging components or devices (when mentioned in the dossier) –a) deletion of a supplier or -b) replacement or addition of supplier, can be submitted as a Type IA variation under certain conditions to be met by the Applicant.

• **B.IV.1.b:** Deletion of a device can be submitted as a Type IA (IN) variation. The Applicant needs to demonstrate that the drug can still be delivered accurately.

• **B.IV.1.c:** Addition or replacement of a device, which is an integrated part of the primary packaging: can be submitted as a Type II variation category. This is the most commonly used category used for single integral devices when not negotiated as a 'z' unforeseen variation. This highest risk category requires Module 3 update and supplementary usability studies depending on the type of device/change. Some examples include:
  o Change in the type of PFS with significant change to the design and functionality that does not fall within a drug immediate container variation category (B.II.e.4)
  o Addition or change of a pen-injector - where the pen-injector is for single use and integral to the medicinal product; some examples may include – adding a new pen-injector device where a PFS was first registered, significant change in design of the pen-injector where the delivery function directly related to the usage by the patient/caregiver e.g. changing from a mechanical spring-based to an electromechanical device.
  o A major change to the functionality and design of an integral device component that is in direct contact with the immediate packaging, but itself is not the complete administration device, and would have an impact on use.

• **Extension applications** (13) - This category is used when there is a major change to the presentation of the device or pharmaceutical form e.g. moving from vial to a PFS, or from a simple prefilled syringe to a prefilled pen. As per this guidance document ‘pharmaceutical form’ is defined slightly differently and is a representative of ‘presentation seen by the patient’ rather than pharmaceutical forms defined by pharmacopoeia standard terms.

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- A secondary container closure system is a packaging component that is not, and will not be, in direct contact with the dosage form (e.g. carton, tray).
- A functional secondary container closure system is a packaging material that is not in direct contact with the product that provides additional protection or serves to deliver the product.”
In addition to the medicinal device related changes, the EU variation categorization guideline includes the following categories where changes to the device part sometimes overlap with changes to container-closure system:

- **B.II.e.1**: Change in immediate packaging of the finished product; composition of packaging material or change to/addition of a new container. This variation may apply to changes to a syringe-based container closure system that would also be classified as an integral administration device.

- **B.II.e.2**: Changes in the specification parameters and/or limits of the immediate packaging of the finished product.

- **B.II.e.3**: Change in test procedure for the immediate package of the finished product.

- **B.II.e.4**: Change in shape or dimensions of the container or closure (immediate packaging).

- **B.II.e.6**: Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)).

Such scenarios where a change could be classified under a container/packaging variation or a device variation, consultation with the EMA is often necessary considering the lack of clear definitions above mentioned. The Industry position proposed in this paper is that the medicines category should take precedence for review of the variation by the EMA medicines assessors. This is notwithstanding any need for a Notified Body assessment.

In the scenario where there is no appropriate category for the variation, an application under Type IB variation comes under ‘unforeseen’ variation as per Article 5 of the variation guideline 1234/2010. CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human) published a Q&A document on this topic (14).

### 5.4 Example of Device-Related Changes and their Reporting Categories

Currently there are no example of device related changes and their unforeseen variation category in CMDh Q&A meaning that individual MAHs have relied on self-assessment or consulted EMA to confirm the relevant variation category.

The possibility of reporting any such change will depend on the risk-assessment performed by the manufacturer to decide if any changes for design improvement with no direct impact on the usage (device functionality or user interface) or contact with the medicinal product are to be reported. Such a change assessment should be maintained in the company Quality Management System for any future audit. Real life examples of device related changes that required regulatory reporting as foreseen or unforeseen variation or did not require regulatory reporting are provided in Appendix 2.

The device changes must be considered in the wider context of the summary of product characteristics, labelling and package leaflet (jointly referred to as ‘the product information’). The EC variation guideline states that if a variation leads to a revision of the product information, this change is considered part of that variation. It is recognized that certain device component changes may have a consequential impact on the product information, for example a change to the instructions for use. In this situation the EMA variations guideline would be applied and the highest change category would take precedence. It is noted that any substantial changes to the product information would default to a Type II variation, as described in section C Safety, efficacy and...
pharmacovigilance changes of the EC variation guideline \(^\text{23}\).

### 5.5 Guiding Principles on Deciding Variation Categories

Based on the above examples, guiding principles for risk-based categorisation of device related changes were derived. The risk category should be further correlated with the EU Variation categorisation guideline to establish an appropriate variation category. This risk-based approach allows decisions on reporting to Competent Authorities as a variation. Moderate to high-risk changes would be submitted as variations, whereas low-risk changes would not require CA notification.

The guiding principles for risk-based categorisation of device related changes are as follows:

- **Contact with medicinal product**: How the medicinal product is integrated within the device to establish possibility of contact between the device component and medicinal product:
  - If there is a direct contact between the device and medicinal product then the change to the device design has to be established based on whether the change may impact dose delivery and patient usage (categories 2 and 3). These types of changes could fall under a moderate to high-risk category and would typically be managed as Container Closure System changes.

- **Dose delivery**: Changes to parameters that impact dose delivery function due to device design change, such as extractable volume or injection time would likely require device re-verification for compliance to the essential safety performance requirements.
  - If there is potential impact on device functionality that is controlled by the DDC release specification, the change may be moderate to high risk (e.g. over- or under-dosing by change to deliverable volume, injection-site pain or reaction due to change in injection time) and managed according to the Variations guidance under Control of Finished Product or Medical Devices depending on any actual impact on the DDC specification.
  - If there is potential to impact on a device delivery parameter that is not controlled by the DDC release specification, the change may be of moderate risk. Verification that the device still performs as claimed, would be recommended. A variation may be submitted in accordance with the medical devices section of the EU-variation guidelines.

- **Patient usage and appearance**: If the change in device design may have an impact on appearance and usage function of the device, especially if this will impact with device-user interface:
  - If no impact for the patient regarding appearance or usage, nor product contact, nor dose delivery, then this type of change could be classed as low risk. This includes minor appearance changes that would not be immediately detectable.
  - If appearance is changed without changes to the usage, further consideration should be given if changes to the Patient Information Leaflet (PIL) and the CTD registered detail e.g. 3.2.P.7 Container closure system- Moderate risk (change category to be decided based on the EU-variation guideline)
  - If the appearance and usage of the device has altered then this design change could be classified as major (change category to be decided based on the EU-variation guideline)

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\(^{23}\) C.I.4 Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data are submitted as Type II.
Changes to device components:
- Like-for-like changes: these are generally considered as low risk, however, categories 1, 2 and 3 should be considered in Table 3 below.
- Modified components: Categorisation based on principles under points 1, 2 or 3 in Table 3 below.

Change in device manufacture/assembly and control strategy:
- Like-for-like change to details that are not mandatory in Module 3 (e.g. change in manufacturing equipment), could be classed as low risk
- Changes to registered details within Module 3: these changes most likely fall under a moderate category (change category to be decided based on the EU-variation guideline)
- Changes that may have direct impact on functionality of the device; these changes should be categorised based on points 1, 2 and 3 in Table 3.

Table 3: Risk factors to consider in evaluating device related change reporting category

<table>
<thead>
<tr>
<th>No</th>
<th>Category</th>
<th>Definition of the change</th>
<th>Risk categorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Contact with the medicinal product</td>
<td>Direct contact between the device and medicinal product then the change to the design has to be established based on how the change may impact functionality (also consider categories 2 and 3)</td>
<td>Moderate to High</td>
</tr>
<tr>
<td>2</td>
<td>Dose-delivery function</td>
<td>Direct impact on the dosage functionality (also consider category 3)</td>
<td>Moderate to High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No impact on DDC release specification</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Impact on DDC release specification</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Patient usage and appearance</td>
<td>Readily detectable appearance change:</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Without changes to the usage procedure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Usage of the device usage has changed</td>
<td>High</td>
</tr>
<tr>
<td>4</td>
<td>Changes to device components</td>
<td>Like-for-like changes</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Modified components</td>
<td>Categorisation based on principles in category 1, 2, 3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Change in device manufacture/assembly and control strategy</td>
<td>Like-for-like change to details that are not mandatory in Module 3 (e.g. change in manufacturing equipment)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Changes to registered details (e.g. new assembly site or change to IPCs, or change to specification) within Module 3</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Changes that may have direct impact on functionality of the device</td>
<td>Categorisation based on principles in category 1, 2, 3</td>
</tr>
</tbody>
</table>

* should be considered in conjunction with EU-variation categorisation guideline.

6. Emerging Technologies

New delivery technologies are being developed, driven by the properties of biological medicinal products, required dose and frequency of administration and patient compliance considerations. With the growing interest in large volume, electronic, biolistic, needle-free and alternatively...
powered devices, increasingly with associated software, several issues need to be considered to enable consistent, risk-based and efficient regulation of these emerging technologies.

6.1 Large Volume/High Viscosity Biological Products

Currently with a subcutaneous administration volume of 1 mL as a standard of care, monoclonal antibodies often need to be formulated at high concentrations, e.g. 100 mg/mL. When the required dosing exceeds 1 mL, the requirement of multiple injections raises concerns of patient non-compliance and inconvenient dosing. Self-administration of subcutaneous injection volumes superior to 1 mL can be delivered by disposable large-volume syringes, large volume (2.25 mL) prefilled syringes, large-volume auto-injectors, and on-body injectors. Reflecting this, a new ISO standard on bolus injectors is in development, 11608-6, as an extension to the series on “Needle-based injection systems for medical use – Requirements and test methods”.

With large volumes to be administered there are scientific and technical challenges to be overcome such as increased pain upon injection, high subcutaneous back pressure, leakage due to large volume and injection site reactions. Potential risks for the patients may include needle breakage due to mechanical fatigue, inability of users to sustain in injection force until the product is fully administered, and incomplete injection due to injection pain [15]. Suitable risk remediation shall be addressed in device development cycles and usability studies, main industry concern being related to avoiding duplication of advices or assessment and potential inconsistencies from Competent Authorities and Notified Bodies on those technical considerations (Refer to Section 4.3.2.4).

6.2 Digital Health

There are valuable opportunities to utilize digital technology to aid in adherence to dosage regimes or share treatment information with healthcare professionals and thus optimize therapy outcomes.

However, not only is it a challenge from the perspective of understanding how the current directives apply to digital medical products, it is also a challenge to submit appropriate data under the existing eCTD structure. These products are often designed as independent design files and are not always a direct component of the container closure system.

Taking a simple example of software associated with a PFP, i.e. a cap with Bluetooth, clarification would be useful as to where this should be captured and assessed - in the eCTD or NB opinion? Moving forward, software related to AI/PFP may be more relevant as the medical device technical documentation reviewed by the NB.

6.3 Electromechanical Devices

Currently, when developing electromechanical driven injectors, in addition to the requirements of ISO 11608 – 1 Needle-based injection systems for medical use: Requirements and test methods - Part 1: Needle-based injection systems [16], consideration is also given to ISO 11608-4 ‘Pen-injectors for medical use —Requirements and test methods for electronic and electromechanical pen-injectors’ [17]. This standard provides performance requirements for the critical product attribute aspects of the design; notably at the same time ensuring that variations of such injectors are not unnecessarily restricted.

In addition, it will be important to include in the overall product risk assessment consideration to international standards relating to electrical safety, electromagnetic compatibility and environmental testing. Where applicable, specifically the requirements of IEC 60068-2 Environmental Testing of Electronic Equipment [18] and IEC 60601-1-X [19] standards, known as collateral standards, will apply, which cover general requirements for safety for a range of electrical medical devices (EMD),
For risk management assessment, battery reliability and life may be critical, depending on the nature of the medicinal product to be delivered; testing under challenging conditions is required and will need to be considered in shelf-life setting of the overall medicinal product.

Suitable disposal of devices and injectors with an electrical component also need to be considered in the risk management evaluations, as well as the instructions for use and product labelling. In order to be compliant with Directive 2012/19/EU on waste electrical and electronic equipment (WEEE) (20), it is important to ensure the battery or other electrical based components are disposed of appropriately, in a similar way to consumer goods.

Considering the number and range of applicable standards for these electrochemical devices components, the medical device quality management system and review by Notified Bodies would be more appropriate than inclusion in an eCTD. This would allow for the controls and flexibilities necessary for frequent updates to the risk analysis and compliance with current regulatory expectations, including cybersecurity.

6.4 Future of Emerging Technologies Regulation

The regulatory challenges of emerging technologies described in this section have been recognized by FDA in their usage of the term “complex products” to describe products where complexity or uncertainty concerning the approval would benefit from early scientific engagement. It is hoped that through the networks and working groups already established, European regulators and Industry representative groups can work together to ensure innovative, safe and effective DDC products reach patients as soon as possible.

7. Conclusions and Path forward

The development of a CHMP guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product is greatly welcomed. During the public consultation phase of the EMA concept paper, EBE shared their main comments and proposals with EMA/CHMP and this process helped to shape this EBE reflection paper.

This paper reflects industry consensus and key proposals on the EU Marketing Application technical requirements, regulatory review process and post-approval device related change assessment for a medicinal product containing a drug delivery device component. Its scope is intentionally broad and covers the following items in a consistent manner:

- Location of device and DDC product information that should remain flexible and example on the extent of device and DDC product information required in eCTD Module 3.
- Reflection and position on involvement of Notified Body review (scope and timing) as will be required by MDR, considering that the current regulatory pathway and review approach has not been an impediment to the review and approval of safe and effective single integral products in MAAs and variations to date.
- Reflection on a risk-based approach to classification of device post-approval change reporting level, providing ‘real-life’ examples of variation requirements experienced by industry and discussing guiding principle for categorization of device variations while outlining and addressing the ambiguity of container closure system/device terminology and the potentially blurred interpretation of ‘single integral product’ in EU.
EBE Reflection Paper on Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment

15 January 2018

- Reflection on emerging technologies associated with Large Volume Devices for high viscosity biological products, electromechanical devices and electronic add-ons to existing products (digital health).

EBE members have a broad range of experience in drug delivery device technologies and relevant manufacturing and control experience and would be keen to share that expertise in collaboration between EMA, CAs, industry and academia.

This reflection paper aims to encourage the discussion between the industry and the EMA on the identified issues and challenges. As a follow-up, considering the increasing number of drug-device combination products in development, a workshop with interested parties should be strongly considered. Such a workshop would inform the development of typical requirements and guiding principles for specific DDC types, for example, regulatory building blocks required for a novel medicinal product incorporating a well-characterized platform device that is already marketed for other products, versus a novel medicinal product incorporating a complex novel device. It is envisaged that this engagement of stakeholders would be of significant benefit, based on the consolidated industry comments and concerns raised regarding the EMAs concept paper for quality requirements, and, as such, could facilitate and ensure a smooth and efficient transition into the new requirements of the MDR by 2020.

Along those lines, industry would support the EMA in setting up and coordinating a pilot program to explore practical implications of MDR Article 117 implementation with complex and innovative DDC products under development. Such a pilot would provide a framework for informal dialogue between key stakeholders: EMA, future marketing authorization applicants and Notified Bodies intending to engage in this activity. The aim would be to address a range of procedural, technical and scientific questions in the context of the target DDC product profile, with the aim of aligning perspectives, expectations, and facilitating the implementation of an integrated and optimized review process.

8. Acknowledgements

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9. Conflict of Interest Declaration

The authors declare that they have no competing interests.

10. Glossary of Terms and Definitions

Single Integral Product: Article 10 in Chapter 1 Scope and definition of the MDR gives the definition of a single integral product: “if the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended
exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable

AIMD: Active Implantable Medical Device
ADR: Adverse Drug Reactions
AQL: Acceptance Quality Limits
AI: Auto-Injector
ATMP Advanced Therapy Medicinal Product
CAMD: Medical Device Competent Authorities
CCIT: Container Closure Integrity Testing
CMDh: Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
CPC: Combination Product Coalition
CQA: Critical Quality Attribute
eCTD: electronic Common Technical Document
DDC: Drug Device Combination
DP: bulk Drug product (prefilled syringe or sealed cartridge)
EMD: Electrical Medical Device
ER Essential Requirement (of the MDD)
HMA: Heads of Medicine Agencies
IFU: Instructions for Use
IPC In-process control
MAH: Marketing Authorization Holder
MDR: Medical Device Regulation
MDD: Medical Device Directive
MEDDEV: European Commission Medical Device Guidance document
NB: Notified Bodies
NBOG: Notified Bodies Operations Group
PFS: Prefilled Syringe
PFP: Prefilled Pen
PIL: Patient Information Leaflet
PQS: Pharmaceutical Quality System
PV: Process Validation
REACH: Registration, Evaluation, Authorization and Restriction of Chemicals
RFD: Reduced Function Device
Team-NB: The European Association for Medical devices Notified Bodies
11. References


In Annex I to Directive 2001/83/EC, point 12 of Section 3.2.

Where applicable and if needed, a CE marking which is required by Community legislation on medical devices shall be provided is replaced by the following:

- 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 authorization 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.


(4) Concept paper on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product, EMA/CHMP/QWP/BWP/661488/2016, November 2016

(5) ISO 13845 Medical devices - Quality management systems - Requirements for regulatory purposes,

(6) ISO 14971:2012 Medical devices - Application of risk management to medical devices

(7) ISO 11040-4 Prefilled Syringes Part 4: Glass barrels for injectables and sterilized sub assembled syringes ready for filling

(8) EN/ISO 10993 - Biological evaluation of medical devices
Procedural advice on the evaluation of combined advanced therapy medicinal products and the consultation of Notified Bodies in accordance with Article 9 of Regulation (EC) No. 1394/2007

EMI/140771/2017, Committee for Medicinal Products for Human Use (CHMP), Assessment Report on extension of Marketing Authorisation, Repatha, International non-proprietary name: evolocumab, Procedure No. EMEA/H/C/003766/X/0002

2013/C 223/01 Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures


CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/Art_5_Recommendations/CMDh_172_2010_Tracking_Table_Article_5.xls


International Electronic Commission Standard IEC 60601-1-X Medical Design Standard for Power Supplies

Appendix 1: Notified Bodies Questionnaire

Notified Body Interview (carried out in April 2017)

Regarding

1. MDR introducing changes to medicines legislation Directive 2001/83/EC

REGULATION (EU) 2017/...
OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of ...
on medical devices, amending Directive 2001/83/EC, ......

Whereas:

(10) Products which combine a medicinal product or substance and a medical device are regulated either under this Regulation or under Directive 2001/83/EC of the European Parliament and of the Council. The two legislative acts should ensure appropriate interaction in terms of consultations during pre-market assessment, and of exchange of information in the context of vigilance activities involving such combination products. For medicinal products that integrate a medical device part, compliance with the general safety and performance requirements laid down in this Regulation for the device part should be adequately assessed in the context of the marketing authorization for such medicinal products. Directive 2001/83/EC should therefore be amended.

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/... of the European Parliament and of the Council++, a product is governed by this Directive, the marketing authorization 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...+, 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.

2. EMA/CHMP/QWP/BWP/661488/2016 Committee for Human Medicinal Products (CHMP)

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


Questions to Notified Bodies:

MDR and Article 117

1. Are you aware of the background as to why this amendment has been introduced? Also, how has the term ‘combination product’ crept into the final version of the MDR, when it is widely acknowledged that there is no definition of this term in the EU (unlike the US)?
2 Considering the enormous changes ahead with implementation of the MDR, do you think that some NB’s will specialize in drug-device combination products and others will not develop this kind of activity? Is it part of your priorities to support review of device components for MAA submissions? Do you believe this will require additional accreditation and would a formal application/contract be needed, as for medical devices?

3 How often have you already assessed an integral device component (of a medicinal product) against the relevant device Essential Requirements for safety and performance? Could you explain a little about how that currently works?

4 How do you think it will work with the new MDR requirements? Do you envisage that it will be best for MAHs to engage NBs as early on in development as possible and work towards complete review for inclusion in the MAA submission when the design of the final combination product is established? Any other thoughts?

5 Do you find that different MAHs have different approaches (if any) to how they maintain the technical documentation on non-CE marked device components? Do you have any advice on procedures that make it an easier and a more efficient process for the notified body assessment?

6 Do you think it will impact the way that pharma companies and device suppliers work together vs today – are there opportunities for suppliers to better support Pharma manufacturers?

7 It is expected that the opinion of the notified body will be based on the safety and performance of the medical device as used in the finished product, since the device may be affected by different drug formulations and physico-chemical properties.

   a. Could it work to have a general ‘Technical File’ for the device components and then an abbreviated TF that is more specific to the device when integral to the medicinal product?

   b. Would a Technical File as such be required or useful for all device components?

8 From experience with medical devices containing ancillary medicinal substances, notified bodies find it helpful to have a detailed report from the medicines CA, outlining the aspects that have been reviewed and commenting on particular areas of concern that may be relevant for future changes to the product. Do you think such a report would be useful for inclusion in the ‘Opinion from the notified body’ for submission in the MAA?

9 Would a suitable conclusion for the opinion of the notified body be something along the lines of: Based on information reviewed [LRQA] are able to verify that the solutions adopted by <manufacturer X>, satisfy relevant essential requirements of the MDR as far as safety and performance-related device features are concerned such that <device Y> is safe and effective for administration of <drug Z>?

10 The ATMP regulation already requires input from notified bodies in the review of device components of cATMPs. Have you been involved in these procedures and are there are any learnings about good practice, challenges or potential for improvements in communication from these experiences?

11 Who do you think will be responsible for reviewing the human factors/usability engineering aspects of the device component – would this fall within the remit of the notified body rather than the medicines competent authority?
12 Who do you think will be responsible for reviewing the clinical evaluation aspects of the device component – would this fall within the remit of the notified body rather than the medicines competent authority?

13 Who do you think will be responsible for reviewing DDC product functional performance specifications and their justifications, analytical (design verification) procedures and their validation, DDC aging studies in the context of establishing a DDC shelf life?

14 As a case study (very detailed for the purpose of the survey, not what would be submitted in a Module 3), process of assembling the auto-injector components with bulk prefilled syringe containing the product is controlled by automatic controls, which monitor the process online and continuously. This comprises cameras as well as a test of the assembled auto-injector to ensure that the prefilled pens are accurately assembled and that no manufacturing faults adversely affect the correct functioning. CPPs (critical process parameters)/CIPCs (critical in-process controls are derived from a comprehensive risk assessment which is based on the patient hazard, the occurrence and the detectability of the failure. Potential process risks are identified with e.g. failure mode and effect analysis (FMEA) encompassing a variety of sources of information, e.g. design requirements, experience with similar products, knowledge of potential hazards, etc. Who do you think will be responsible for reviewing this information package and batch data?

15 What do you think will be the role of the new entity at the EC: the Medical Device Coordination Group (MDCG), consisting of ad hoc experts, versus notified bodies, versus EMA/CHMP?

Guidance and CHMP Concept paper on developing a guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product

16 Do you think it would be helpful to have guidance on this new requirement included in an updated MEDDEV 2.1/3, along the lines of guidance on consultations for devices incorporating ancillary medicinal substances/human blood derivatives, in order to facilitate a consistent, transparent approach?

17 Following on from this, do you have any positions or thoughts about the content of the concept paper from CHMP and will you be commenting on it?

18 With the impact of the new MDR text on medicines legislation, do you think that notified bodies will be invited to have a greater role in development of the guidance, perhaps through bodies such as the NBOG (Notified Bodies Operations Group) or TEAM-NB?

19 FDA, via the Office of Combination Products, have been putting a lot of effort into improving education and collaboration between medicines and device reviewers – do you think that something similar would be useful in EU for discussion, relationship building and clarification of roles and responsibilities? Perhaps something for the new HMA (Heads of Medicines Agencies) / CAMD (Medical Device Competent Authorities) Borderline and Combination Products Working Group?

20 Do you think there is the possibility of working towards greater harmonization of requirements for devices used in combination with medicinal products, e.g. through ICH or ISO standards such as ISO 20069 on Change assessment of devices intended for administration of medicinal products (in development)?

21 Finally, any other comments/thoughts?
### Appendix 2: Real-life example of regulatory reporting requirements for device-related changes

<table>
<thead>
<tr>
<th>Summary of the change</th>
<th>Justification variation category</th>
<th>Submission strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A single-use, disposable, variable dose drug delivery device made to deliver the required dose of a medicinal product had a design change to mitigate modifying the dose delivery settings. This was achieved through changing the torque force with no impact on the injection time or delivery rate.</td>
<td>The marketing application did not include the level of detail regarding the medical device for the parts of the device impacted by the change and there were no changes to the IFU, product information, labelling or artwork.</td>
<td>No variation submission was required since there was no change to registered details within the MA and no changes to use or user of the device.</td>
</tr>
<tr>
<td>Introduction of a new PFP presentation (same pharmaceutical form, same route of administration)</td>
<td>B.II.e.1.b).2. Change in immediate packaging of the finished product, Change in type of container or addition for sterile medicinal products.</td>
<td>Type II variation</td>
</tr>
<tr>
<td>Prefilled syringe (PFS) with staked-in needle, where only the needle dimension changed.</td>
<td>B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging) b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product.</td>
<td>Type II variation B.II.e.4.z (Unforeseen change)</td>
</tr>
<tr>
<td>Change in needle shield system to make it ‘safe-sharp’. There was no change to the design of the device/needle or the delivery aspect of the device. There is no contact with product and no change to the IFU or product literature</td>
<td>B.II.e.6 - Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)</td>
<td>Type IA change</td>
</tr>
<tr>
<td>Change to the design of the device where the delivery function was automated, without any change to the medicinal product compartment (cartridge)</td>
<td>B.IV.1.c classified as a major change</td>
<td>Type II variation</td>
</tr>
<tr>
<td>Device design changes to improve use with no or minor (readily observable by user) external appearance change.</td>
<td><strong>Conditions:</strong> No change to registered detail. No anticipated impact of product quality, safety or efficacy. No change in sterilisation status – no revalidation of sterilisation procedure required. No change to user interface or IFU. Intended to resolve expected root causes of complaints (continuous improvements).</td>
<td>Non-reportable change</td>
</tr>
<tr>
<td>Changes or additional vendors for device components (excluding batteries and adhesives if composition changes) where the vendor is not the supplier of the finished device.</td>
<td><strong>Conditions:</strong> No change to registered detail. No anticipated impact of product quality, safety or efficacy. No change in device use, performance or appearance. No change in specification of device components.</td>
<td>Non-reportable change</td>
</tr>
<tr>
<td>Summary of the change</td>
<td>Justification variation category</td>
<td>Submission strategy</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Change of the supplier of the needle for PFS</td>
<td>Assessed to be ‘non-reportable’ under EU variation categories</td>
<td>Non-reportable change</td>
</tr>
<tr>
<td>Change in the needle dimensions not in the registered detail for a PFS</td>
<td>There is no category defined within the EU variation classification guideline.</td>
<td>Type IB B.IV.1.z</td>
</tr>
<tr>
<td></td>
<td>However, given the impact of the change due to possible product contact especially for formulations that are high in viscosity or suspensions, this may be classed as Type IB with classification- B.IV.1’z’ (unforeseen change).</td>
<td>Supported by batch data to show accuracy of dosing and data to show that the delivery function is not changed. Competent authority must be contacted to obtain confirmation of classification.</td>
</tr>
<tr>
<td>Change in the assembly process of the device; that is not in direct contact with the medicinal product</td>
<td>If the assembly operation is reported within the dossier, then this could be classed as ‘minor change in manufacturing processes’. However, this must be carefully assessed on dossier content and the impact of the change within the manufacturing process.</td>
<td>Type IA change under category- B.II.b.3.a</td>
</tr>
<tr>
<td>Addition or replacement of site responsible for assembly operation of the device and product. The product is not in direct contact with the device and there is no change to the assembly operation, or device functionality</td>
<td>The device assembly process is considered as ‘secondary packaging’ operation. Hence this change was submitted as Type IA change.</td>
<td>Type IA change under category B.II.b.1.a</td>
</tr>
<tr>
<td>Change in glass syringe siliconisation process using new equipment at the vendor site. The new process allows for a better distribution of the silicone layer in a reproducible manner with continuous IPC monitoring on 100% of the syringes.</td>
<td>Conditions: The quality and quantity of silicone oil, syringe specifications and associated drawings remain unchanged. There are no changes to registered details. This change has no impact to the quality of the product (e.g. visible and sub-visible particles, purity attributes) and has a positive effect on Glide Force consistency at bulk PFS level or delivery time consistency at release and upon aging at PFP level without any impact to the bulk PFS/PFP control strategies and specifications.</td>
<td>Non-reportable change</td>
</tr>
<tr>
<td>Change to Auto-injector front and rear subassembly plastic components, designed to minimize internal frictions ensuring more consistent drug delivery, and to facilitate the mechanical subassembly process</td>
<td>Conditions: There are no changes to the supplier, to the material of construction, specifications, outer design of the prefilled pen once assembled; hence there are no changes to the design of the product-</td>
<td>Type IB B.IV.1.z</td>
</tr>
</tbody>
</table>
EBE Reflection Paper on Medicinal product incorporating a drug delivery device component: An Industry Perspective on the EU marketing application technical requirements, regulatory review process and post-approval device related change assessment

15 January 2018

Version 1

<table>
<thead>
<tr>
<th>Summary of the change</th>
<th>Justification variation category</th>
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</tr>
</thead>
<tbody>
<tr>
<td>patient interface. A design verification study has been performed supporting that the proposed changes have no unintended impact to the functionality of prefilled pen, including delivery and dose accuracy. All sub-assemblies sub-components illustrations in P.7 are impacted by the changes.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Co-packaged CE marked medical devices are excluded from this list

Tables

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