EBE paper: Industry Perspective on the marketing application technical requirements and regulatory review for medicinal product containing a drug delivery device component

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Context for developing an EBE paper on single integral product

- Call for comment on 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
  - EBE/EFPIA/Vaccines Europe member companies consolidated comments send to EMA on May 15, 2017

- Recent publishing of the new Regulation on Medical Devices (MDR) (EU) 2017/745:
  - Art 1 (9): 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. In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part of the single integral product are concerned.
Context for developing an EBE paper on single integral product

- Recent publishing of the new Regulation on Medical Devices (MDR) (EU) 2017/745:
  - Art. 117: If the [MAA] dossier does not include the results of the conformity assessment [CE marking] and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required …, 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.
Key value propositions of EBE paper

- **Update on harmonization initiatives** related to technical requirements for single integral product, latest state of discussions within the Industry and with the regulators,

- **Main industry comments on EMA reflection paper** on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product

- **Industry perspective on what CMC / Device information and data shall be provided in a complete Module 3 at time of MAA filing for a single integral combination product**
  - Case study for Prefilled pen e.g. prefilled syringe assembled with a spring loaded auto-injector as example of well established delivery system.
  - Identification of enhancement requirements from Annex 1 of MDR versus Annex 1 of MDD
  - Companion guidance covering for end to end analytical control strategy from components to the finished product
Key value propositions of EBE paper

• **Industry perspective on the future regulatory review** process under Article 117 of the MDR based on interviews of Notified Bodies/Team-NB and Regulators.

• **Risk based approach to single integral product LCM**
  - Example of variation reporting category commensurate with risk for device related changes

• **Key points to consider on technical requirements for emerging technologies** addressing:
  - Large Volume Device,
  - electromechanical driven injectors,
  - single integral product definition issue with co-packaged products
Key value propositions of EBE paper

- **EBE position paper covers commonalities between biological medicinal products and chemical medicinal products** containing a drug deliver device components as well as the aspects specific to biologics such as:
  - Impact of drug properties (e.g. viscosity), primary packaging and device component variability and syringe siliconisation on drug delivery time, dose accuracy and pre-filled product (PFP) functioning,
  - New delivery technologies driven by the properties of biological medicinal products, required dose and frequency of administration and patient compliance considerations
EBE Paper layout

1. Problem Statement................................................................. 4
2. Regulatory update, state of discussions within the Industry and with the regulators........ 5
3. Single integral product established conditions and related Module 3 dossier content strategy 9
4. Industry position on the regulatory review process................................................................. 15
5. Single integral combination product Life cycle management – a risk based approach........... 20
6. Key points to consider with emerging technologies................................................................. 20
7. Conclusions and path forward ................................................................................................. 21
8. Acknowledgments................................................................................................................... 21
9. Conflict of Interest Declaration.............................................................................................. 21
10. Glossary of terms and definitions......................................................................................... 21
11. References............................................................................................................................. 22

Appendix 1 : Prefilled pen assembly process flow chart with process controls ......................... 22
Appendix 2: Notified Bodies questionnaire................................................................................. 27
Appendix 3: Developing an efficient end to end Control Strategy for Single Integral Product...62
Module 3 dossier content strategy

• **EBE paper will reflect Industry consensus reached on Module 3 dossier content strategy** built around a high level package on the manufacture and control of the medical device component focused on:
  - Compatibility/interaction between the drug product and the device
  - Container closure integrity
  - Accuracy of dosing
  - Functional performance
  - Usability of the product

• **EBE paper will reflect three different approaches in location of device information across 3.2.P and 3.2 R** shown to be equivalent in fulfilling EMA/CHMP expectations
  - 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.
Main Industry comments on EMA Concept Paper

* Should apply to vaccines

* Should not apply to legacy products

* Should give clear, consistent terminology to describe the different situations where a DDC product is considered combined and recommend defining “single integral product”

* Should outline data requirements as well as requirements for submission of these data (in e.g. IMPDs, MAAs, line extensions, and variations):
  - For medicinal products with delivery system (single integral product, not re-usable) as described under Article 117* of the new EU MDR.
  - For stand-alone CE marked medical devices (co-packaged) to be used with a specific medicinal product.

* on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product
Main Industry comments on EMA Concept Paper

- **Should elaborate on the appropriateness of notified body assessments**, depending on the type of combination product as possible interpretation of Article 117 of the Medical Devices Regulation (MDR).

- **Should clarify cases where NB involvement** is required and also the roles and responsibilities of manufacturers, NBs and CA assessors for different types of combinations, including cases where qualification of the device by the manufacturer may be considered part of the Quality Management System/Pharmaceutical Quality System (QMS/PQS).

- **Should give guidance on the types of device change** that require reporting to the medicines agency would be welcome, along with procedural information on how the medicines agency and Notified Bodies will work together for variation approval.
Main Industry comments on EMA Concept Paper

- Should ensure reporting risk based categorization of device changes aligned with ICH Q12 principles, with most device changes managed in the PQS.

- Should allow to cross reference device information amongst dossiers so that identical delivery devices are not repeatedly reviewed and approved as “medical devices”.

- Should solve some conflicts and redundancies between pharmacopoeial/SmPC/labelling requirements for medicinal products and ISO standards/Essential Requirements for medical devices

- Should align with the US FDA guidelines on submission requirements, human factors and minimization of medication errors to harmonize standards and avoid creation of market-specific dossier and study requirements.
Comparison of Annex 1 of MDR vs Annex 1 of MDD – Key points

- **Significant increase in the number of requirements**, from 14 to 23 **clauses** with an increase in sub-clauses within those also

- **Few examples of enhancement requirements:**
  - **A greater consideration to risk profile and benefit to end users** consistently throughout the requirements, with an emphasis to ensure it is as low as possible and demonstrate as such
  - **In addition to previous biocompatibility requirements**, specific attention to **safety** with respect to **chemical safety (REACH) and phthalates** as well as components of **CMR** (carcinogenic, mutagenic and toxic to reproduction) and/or **endocrine-disturbing substances** which applies to components /devices which have anything other than intact skin patient contacting elements.
  - **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 RFID
  - **New clauses with respect to software and electronic systems** further to the energy source requirements of the MDD
Regulatory review process for licensing single integral product

• A survey questionnaire (20 questions) was developed to interview Notified Bodies via the representative group Team NB

• The survey cover the following areas
  - Notified body (NB) resources and current involvement in integral device assessment
  - Timing for NB assessment
  - Learning from device assessment by NB in the context of MAA filings for combined ATMP (e.g. medical + cell/tissue part)
  - Data to be assessed by NB versus Competent Authorities
    ▪ Human factor/usability engineering of the device component
    ▪ Clinical evaluation aspects of the device component
    ▪ Functional performance specifications and their justification
    ▪ Analytical (design verification) procedures and their validation
    ▪ Aging studies in the context of establishing a DDC shelf life
    ▪ Assembly process, CIPC and their justification
Position Paper development - milestones

- **April 6, 2017** F2F EBE topic group workshop in Paris
- **May 18, 2017**: Two weeks team review of EBE paper draft V.3.3
- **June 14, 2017**: EBE Talk at BWP IP meeting
- **Mid-End June, 2017**: 3 weeks EBE/EFPIA/VE review (if consensus reached during team review)
- **Q3/early Q4 2017**: Publishing in scientific journal e.g. PDA J of Pharm Tech
- EMA/CHMP/NB workshop on data requirement and review process for single integral product
Topic Group members

- Serge Mathonet, Sanofi, Global Regulatory Affairs CMC Biologics
- Janine Jamieson, JCombinations AB Consultant, IPQ publication editor
- Amanda Matthews, Pfizer, Regulatory CMC
- Feuerstein, Ulrike, Abbvie, Primary Packaging Development for parenterals ex CMC Submission groups for prefilled pens
- Carolin Gordon, Astra Zeneca, Regulatory CMC
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