COMBINATION PRODUCTS SUMMIT

COLUMBUS, OH • NOVEMBER 7–9, 2022

EU Combination Product Regulation - Challenges & Opportunities

An industry perspective

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Post-Market Changes to Device Part of Single Integral Combination Products

Background

Questions & Answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746) (EMA/37991/2019)

2.6. How does Article 117 of the MDR impact currently authorised DDCs? Rev. June 2021

Annex I to Directive 2001/83/EC, point 12 of section 3.2, as amended by Article 117 of MDR, is not intended to apply retrospectively to DDCs already authorised or to those MAAs that have been already submitted prior to 26 May 2021.

However, if after the granting of the marketing authorisation there is a change to the design or intended purpose of the device (part), or a new device is introduced, any required declaration of conformity / EU certificate / notified body opinion should be submitted as part of the appropriate regulatory procedure to EMA/NCA (see also Q2.7).

As for any other changes, the MAH should determine whether there is a potential impact on quality, safety and/or efficacy of the DDC. If the MAH determines that the change impacts the registered information, a variation application according to the variation guideline will be required. If the change does not impact the registered information but the MAH concludes that there is an impact on the quality, safety and/or efficacy of the DDC, a variation application must also be submitted. In cases where the need for a variation and/or the category of the change is unclear, it is recommended that the medicines competent authority that issued the marketing authorisation be consulted.

In line with the advice provided in the EMA Q&A for Post-authorisation procedural advice for users of the centralised procedure, given the relatively short timelines for variations procedures, the (new/updated) EU declaration of conformity / EU certificate issued by a designated notified body / notified body opinion for medical devices should be provided at the time of submission of the application to avoid any delays of the procedure.

2.7. Will I need to provide a (new or updated) EU declaration of conformity/EU certificate issued by a notified body/notified body opinion if there are changes to the device (or device part) after the initial marketing authorisation of the Drug Device Combination? Rev. June 2021

Article 117 requirement applies post-authorisation to all marketing authorisations, irrespective whether already compliant with Annex I to Directive 2001/83/EC, point 12 of section 3.2, as amended by Article 117 MDR at the time of the initial MAA, in case of changes that may affect the safety and performance of the device part or the intended use of the device. Contractual agreements between the MAH and the medical device manufacturer should ensure appropriate level of communication and action as regards changes to the device part. There are two situations where a (new or updated) EU declaration of conformity / EU certificate issued by a notified body / notified body opinion must be submitted in a post-authorisation setting of the medicinal product.

a) Addition or full replacement of the device or device part

Where a device (or device part) is replaced or a new device is added, a new EU declaration of conformity/ EU certificate issued by a notified body / notified body opinion must be provided as part of a variation or extension application.

b) Changes to the device or to a device part

Where the medical device manufacturer plans to introduce changes that may affect the safety and performance of the device part or the conditions prescribed for the intended use of the device part, there are three possible situations:

- **For devices covered under a manufacturer's EU declaration of conformity only (no involvement of a notified body):** the device part manufacturer is responsible to ensure compliance with the MDR, including changes to the device part. The EU declaration of conformity should be updated accordingly, if necessary.
- **For devices covered under an MDR EU certificate issued by a notified body:** if the assessment of changes leads to the issuance of a new/supplemented EU certificate according to the requirements established in the relevant annexes (Annexes IX, X, XI) of the MDR, the EU certificate must be provided as part of an appropriate post-authorisation regulatory procedure.
- **For devices holding a notified body opinion:** if the assessment of changes lead to the issuance of a new notified body opinion, the new notified body opinion must be provided as part of an appropriate post-authorisation regulatory procedure.

Challenge : What is the 'trigger/threshold' for a Notified Body Opinion (NBOp)?

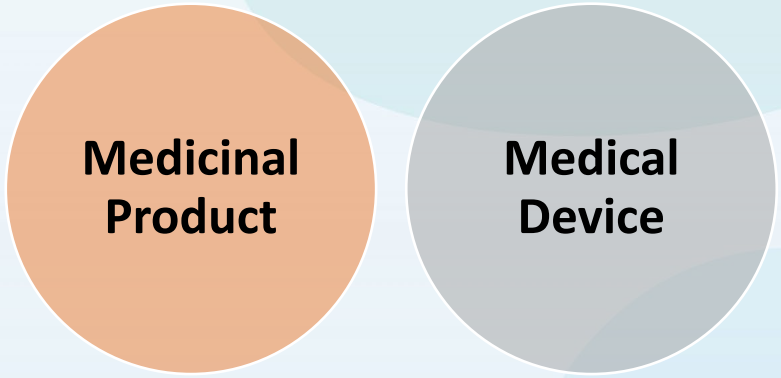
- How to interpret when a change constitutes a "change to the design or intended purpose of the device (part), or a new device is introduced"?
  - Design: change to primary function or main operating principles?
  - Intended purpose: change to route of administration, intended users, patient population, use environment?
  - New Device: new/replacement device
- How to interpret when a change constitutes a situation for *"where a device (or device part) is replaced, or a new device is added"*?
  - Same as 'New Device'?
- What are the types of changes to the device or device part that *"may affect the safety and performance of the device part or the conditions prescribed for the intended use of the device part"* such that a NBOp is required?

  e.g., device design, manufacturing process, manufacturing site, materials, software, user interface, labelling, instructions for use
- How should industry assess the need for a NBOp when supporting evidence is generated that confirms that a given change does not raise questions regarding safety and performance (ie, how is 'may' interpreted)?
- What to do if unsure whether a NBOp is needed?
  - Is enquiry with EMA the appropriate next step?
    - As single integral Combination Products fall under medicinal product regulations and changes are within scope of the EU variation framework, there is no mechanism in place by which a NB can determine whether a specific change to the device (constituent) part of would trigger the need for a NBOp. Additionally, NBs (as per their accreditation) are not allowed to consult.

Opportunity : Establish /clarify when a Notified Body Opinion is required as part of change management and subsequent MAA Variation

- **Publish framework/principles for when requirement for NB opinion would be triggered for on-market single integral Combination Products**
  - Allows MAH to make appropriate and consistent decisions during lifecycle management, as is currently the case for API and other Medicinal Product changes
- **Clarify that the trigger/threshold is one that impacts either the Established Conditions or Critical Quality Attributes of the Medicinal Product**
  - This is in alignment with the most relevant major international consensus guidance
    i.e. ICH Q12
- **Define pathway for MAH to solicit advice from EMA and other Competent Authorities on potential changes that fall outside the published framework/principles**
  - Aligned with the principle that these single integral combination products are regulated as medicinal products and not as medical devices

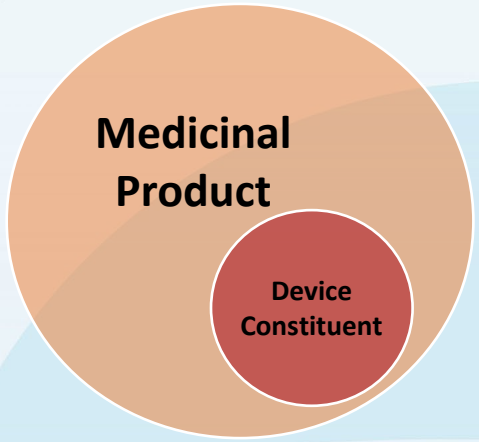
Life Cycle Management



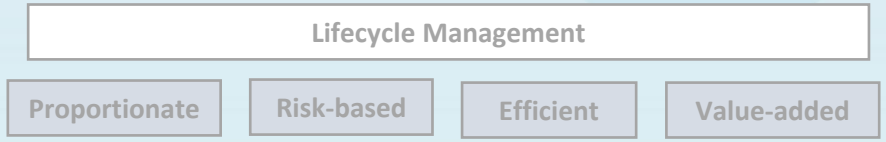
ICH Q12
Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

NBOG BPG 2014-3
Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System*

- Current guidance available is deficient in considering the breadth / complexity of single-integral combination products
- NB Opinion Report
  - is a 'snap-shot' in time, therefore does not need to be maintained
  - is an 'Opinion', it is not an 'Approval'



A harmonised approach regarding technical and regulatory considerations encompassing relevant considerations primarily from the medicinal product regulatory frameworks with the relevant medical device requirements



* MDCG - Significant changes guidance under MDR

"Endorse a framework to enhance industry's ability to manage many CMC changes effectively under the company's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation"

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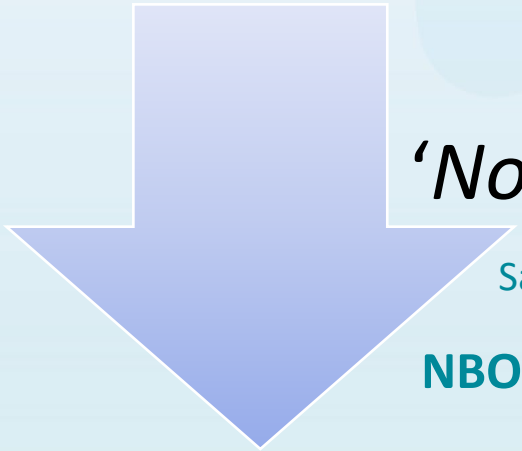
Proposal : Framework/principles should align to risk-based approach

Higher-risk

'Substantial' design change

Safety or performance is no longer within prior approved established conditions / critical quality attributes

NBOp highly likely to be required to support variation



Low-risk

'Non-substantial' design change

Safety or performance remains within prior approved established conditions / critical quality attributes

NBOp unlikely to be required to support variation

- In situations where NBOp is not considered necessary, variation still likely to support the change and maintain registered information (i.e. notification level vs prior approval/Type II)
- In all situations, internal management of change within MAH QMS is still required

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Summary of Industry Proposals

Guidance or framework

- Targeted at device part of single integral Combination Products (medicinal products)
- Aligns with risk-based approach /other guidance being adopted for medicinal products i.e. ICH Q12
- Enables consistency for when NBOp will be required

Alignment of stakeholders

- EMA and NB to align on expectations (medicinal product vs. medical device)
  - Medicinal product requirements should take precedence
- Alignment between EMA and National Competent Authorities

Managing MAA variations

- Alignment of EU Variations guidance with EMA Quality Combination Product guideline and including NBOp evidence
- Additional / clearer device-related change categories for single integral combination products reflecting advancing technologies

Industry are seeking a solution that allows the **timely** and **efficient** introduction of CMC changes important for drug quality, safety, ensuring continued **availability of medicines to patients**

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Combination Product Regulation in Europe

Fit for the Future

Challenges in Europe

Increasing importance of Combination Products

- These novel products are key to driving new therapies and consequent enhanced patient outcomes

Increasing complexity of Combination Products

- e.g. Novel drug delivery technologies, incorporation of software and electronics

Increasing pressure on current regulatory framework

- Challenges to the regulatory boundaries and interfaces of Medicinal Products and Medical Devices

e.g. clarity of regulatory pathways, obtaining timely and relevant scientific advice on a 'whole product' basis

- European situation is not unique
- Similar challenges exist in other regions
- Work underway by legislators and regulators in other regions to address these challenges

Opportunity : Revision of the General Pharmaceutical Legislation

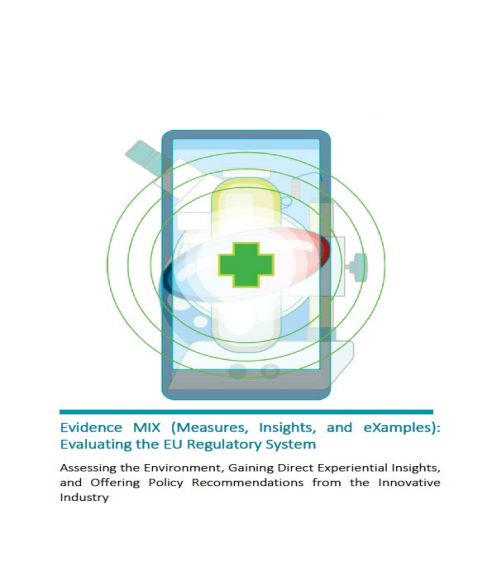
European Commission

Pharmaceutical Strategy for Europe*
(November 2020)

Revision to Variations Regulation

Intention to revise and replace Medicinal Product Directive (2001/83/EC)

Proposals Submitted to Public Consultation



** https://ec.europa.eu/health/medicinal-products/pharmaceutical-strategy-europe_en*

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efpia

Key Proposals to enable future streamlined assessment framework for Combination Products

Ensuring clarity that EMA has overall accountability for assessment of Combination Products that are regulated as Medicinal Products

- The intersection between devices and medicines is becoming ever more important for an optimised use of innovative medicines. The EU must be prepared for this as it is crucial to ensure that European patients can benefit from these innovative medicines in a timely manner

- Aim to simplify, streamline and accelerate clearer decision-making for combination products
  - Approx. 25% of products in the current industry pipeline

- Clarity that EMA has accountability for the regulatory assessment of the entirety of the combination product is needed to give the predictability and certainty in the EU that is currently not present

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Key Proposals to enable future streamlined assessment framework for Combination Products

Create a new legal definition for those combinations of medicines and medical devices that are regulated as medicinal products in the EU

- This will put the EU on par with other regions (US, Canada, Japan, China) and recognise that such combinations generate unique regulatory and legal issues. The change can be anchored in legislation (upcoming revision of Directive 2001/83/EC), while maintaining flexibility to evolve with science. This solution would provide more leeway to adapt the definition to accommodate future technological advancements.
- The new legal category will be a driver for an extended EMA remit to coordinate and arbitrate in relation Combination Products. These would remain regulated as medicinal products and this will not change the distinct regulatory pathways for medicines and medical devices in Europe. The new category should reflect the scope of the recent EMA quality guideline (June 2021) that has been vetted with Member States.
- Opportunity to leverage the European Commission proposal for the EMA to provide a coordinating role during future health crises. The proposal covers both medicinal products and medical devices.
- In order to provide an integrated scientific advice pathway for Combination Products (and Companion Diagnostics), the technical expertise of Notified Bodies (NBs) may in some situations be required. NB's review timelines need to be reinforced and aligned with the ones from medicine regulators. While ensuring that the EMA Scientific Advice Working Party (SAWP) has access to device expertise (national competent authorities/expert panel), the legislation should also clarify that NB participation in EMA scientific advice and qualification procedures is permissible and does not constitute consulting

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Thank You

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EMA Perspectives on Lifecycle Management of Integral Drug Device Combinations

Pascal Venneugues

European Medicines Agency, Human Medicines Division

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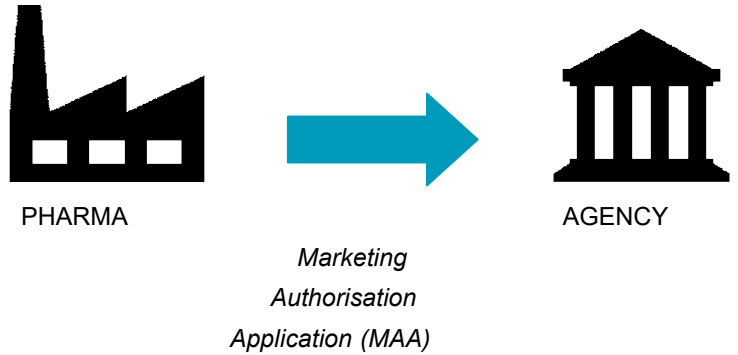
Article 117: General principles

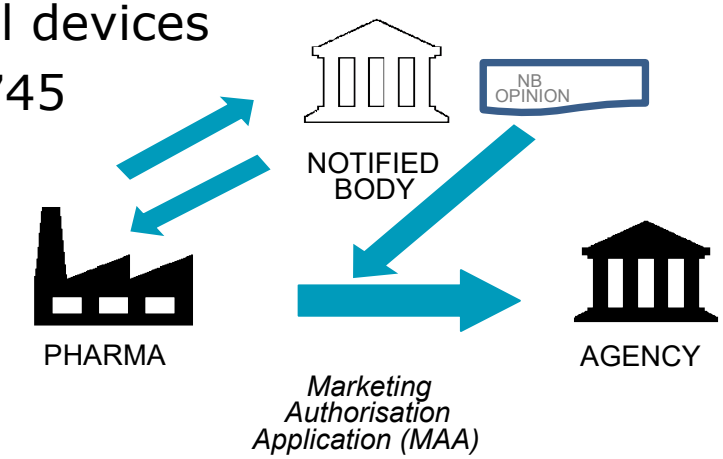
- **MAAs submitted before 26 May 2021**
  - EMA/NCAs in charge of evaluation medicine + integral device (relevant Essential Requirements from Directive 93/42/EEC)
  - Compliance with Regulation 2017/745 optional



- **MAAs submitted after 26 May 2021**

  Notified Body involvement to confirm compliance of integral devices above Class I with the relevant GSPRs from Regulation 2017/745

  ➔ Notified Body Opinion (NBOp) or CE certificate



Objective: strengthen regulatory oversight and increase confidence in the system

- **Also relevant for line extensions and variations** when applicable: new or "substantially" changed device
- **Not applicable to combined ATMPs**

Article 117: Role of EMA/NCAs vs Notified Bodies

- **Core precept of CHMP guideline on drug-device combinations:**

  EMA/NCAs: evaluate device specific aspects relevant to quality, safety and efficacy of the medicinal product

  Notified Bodies: assess the relevant GSPRs for the medical device

Guideline objective: To minimise overlap between EMA/NCAs and Notified Body reviews

- Several GSPRs may impact quality, safety and efficacy of the medicinal product
  - But different perspectives, expertise
  - And it does not change the fact that **GSPR compliance check, content and review of an application for new or revised NBOp fall outside EMA/NCA remit**

What is a significant change* to a device?

- Change affecting design, performance, safety characteristics, intended purpose of the device part
- Impact on QTPP, DDC CQAs, DDC overall control strategy, delivery, instructions for use
- **But no legal definition of a significant/substantial/major change to a device part of an integral DDC**

  Applicability of MDCG 2020-3*, ISO 20069 or TeamNB guidance?

  ➔ Not directly relevant for EMA since written from a device perspective

- It is expected that a new or revised NBOp will be linked to a variation (or line extension)
- But a "significant" change from EMA point of view may imply a Type II variation (or line extension), not necessarily a new or revised NBOp

Different perspectives on the importance of a change

- Does a change in intended use (e.g. new paediatric indication) always qualify as a substantial change?
  - ➔ EMA: it depends!
- New supplier for integral device (same material and specifications)
  - ❖ Not a substantial change from Notified Body perspective
  - ❖ But new device from EMA perspective
- Does a change in formulation always qualify as a substantial change?
  - ➔ EMA: it depends! For example, is viscosity affected, impacting device performance?
- Extension of shelf life not in line with stability protocol
  - ➔ May be considered a substantial change by a Notified Body but new/revised NBOp not necessarily expected by EMA

Challenges

- EMA can advise on changes requiring a variation (or line extension)
- Feedback from Notified Bodies and Pharma Industry:

  Notified Bodies cannot advise on any change, even when a NBOp is already issued:
  - Consulting / providing regulatory advice is excluded from their legal mandate
    - ➔ Notified Body's role is to review conformity against regulations not to advise on how to achieve compliance
  - Liability concerns from Notified Bodies in case of divergent views with EMA
- **Interpretation of Notified Bodies' role is not within EMA remit**
- In practice, **EMA can support applicants, on a case-by-case basis**, on changes considered to require a new or revised NBOp.
  - ➔ But it is not a long-term solution

General recommendations for integral device changes

- Liaise with EMA well before the intended submission date
  - Need for new or revised NBOp based on a risk assessment
  - 3 scenarios:
    - Variation + NBOp
    - Variation only
    - No variation and no NBOp
    - NBOp only not foreseen
- New or revised NBOp, <u>if required</u> in the EMA submission, should:
  - Correspond to the (new) claimed intended use
  - Preferably be submitted with the initial submission to reduce the risk of delay
- If no NBOp is provided, a justification is expected in the dossier (3.2.R) for transparency reason, even if already agreed during pre-submission
  - No specific guidance but should be based on a risk assessment

Partial compliance with relevant GSPRs

The NBOp is binding to CHMP

- **Lack of <u>full</u> compliance with the relevant GSPRs impacts the approvability of the MAA, line extension and variation**
  - CHMP cannot bypass the NBOp conclusion
  - CHMP cannot follow-up on deficiencies identified in the NBOp
    - But issues affecting quality, S&E can be raised without referring to GSPRs
- In case of partial compliance, the applicant should always liaise with the Notified Body to address the deficiencies and provide a revised NBOp <u>before</u> CHMP Opinion

Activities and initiatives

- ICH Q12 example to define Established Conditions for a prefilled syringe/pen
  - List of changes and expected reporting change categories (IA, IB, II or not reported)
  - Should inform the revision of the Classification guideline (Pharma Strategy)
  - Expected to be agreed by end of 2022 or Q1 2023
- EMA guidance on classification of minor device changes
  - Should address the lack of granularity of the Classification guideline on variations for device changes (until the guideline is revised)
  - Expected to be agreed by end of 2022 or Q1 2023
- Update of the EMA Q&A on the MDR implementation
  - Expected to address issues faced by EMA since publication of current version (June 2021)
  - Will require discussions with the Commission. No clear timelines yet.
- CMDh Small Group meetings to share experience and harmonise handling of device queries/issues across EMA and the NCAs

Area of further cooperation for medical devices

Core Recommendation:
Create an integrated evaluation pathway for the assessment of medical devices, *in vitro* diagnostics and borderline products

- Establish stronger ties with medical device stakeholders to explore involvement in development, authorisation and lifecycle management
- Examples of considerations:
  - Multi-stakeholder scientific advice for medicinal products used in combination with medical devices
  - Development of joint EMA-Notified Body guidance on device changes

Any questions?

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