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Lifecycle Management: 'Substantial and Non-Substantial Changes' for Drug-Device Combinations

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EMA Multi-Stakeholder Workshop

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Questions to be resolved:

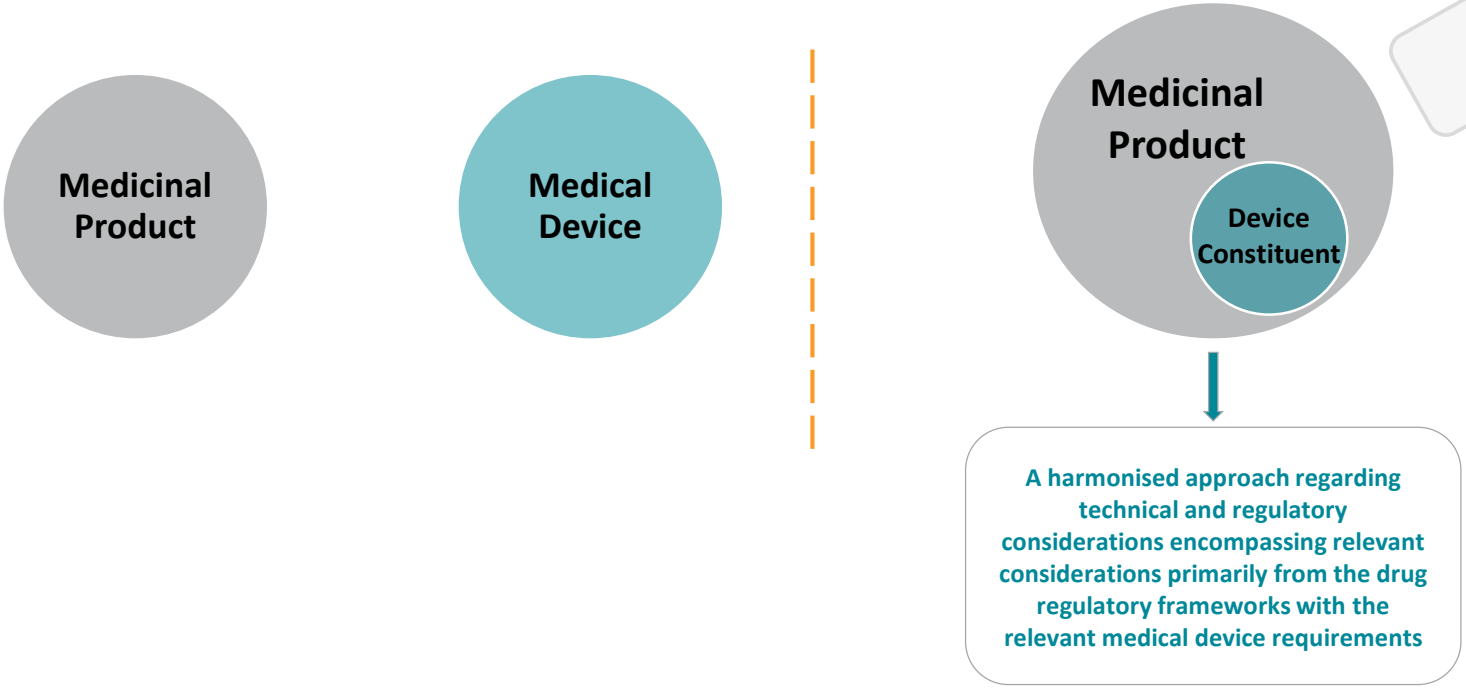
what constitutes a *'substantial change' ?*

when would a notified body opinion be required as part of lifecycle management and MAA variation application ?

As stated in CMDh Q&A (Rev 1, Oct 2019)

"Changes to the device constituent [design] ***are considered substantial*** *if the changes* ***affect the performance and safety characteristics of the device****…… It is the responsibility of the marketing authorisation holder to determine if the changes are substantial……*

MAH Assessment Guided By:



- Integral DDCs are placed on the market as medicinal products rather than medical devices therefore subject to:
  - ICH Q12 - Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
  - Variations Regulation (EC No 1234/2008 and 2010/C 17/01) for Marketing Authorisations for Medicinal Products for Human Use

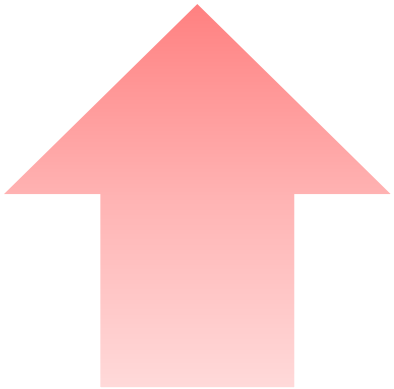
Industry Requests

1. EMA/CMDh to define framework/principles for when requirement of NBOp would be triggered for on-market integral DDCs
   - Allows MAH to make consistent decisions, commensurate with API/other Medicinal Product changes
   - Permit regulatory flexibility where appropriate, not all changes require regulatory oversight prior to implementation
2. EMA/CMDh to clarify 'a substantial change' is a change that impacts either the Established Conditions[ǂ] or Critical Quality Attributes of the Medicinal Product, thus invoking a NB assessment
   - This is in alignment with the principles of the most relevant major international consensus guidance i.e. ICH Q12 which already has DDCs in-scope
3. Define pathway for MAH to solicit advice from EMA/other Competent Authorities on potential changes that fall outside the defined framework/principles

[ǂ] Acknowledging Established Conditions are not currently in the EU framework

Framework / principles should align to risk-based approach

- **All changes require internal management of change governed by MAH QMS as per EU cGMPs & ICH Q10 requirements**
- **Consider when MAA variation required and when it requires NBOp to support change and maintain registered information (ie. notification vs prior approval/Type II)**

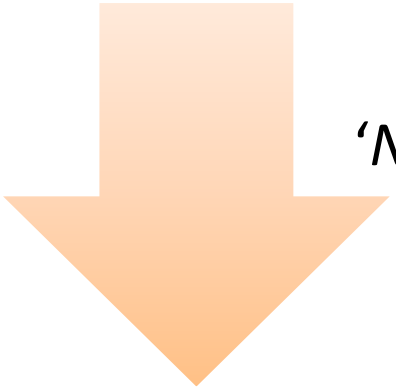


Higher-risk

‘*substantial*’ design change

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

NBOp highly likely as part of the variation



Low-risk

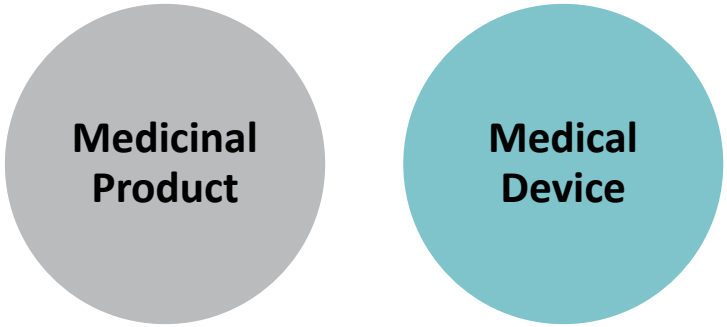
‘*Non-substantial*’ design change

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

NBOp unlikely as part of the variation

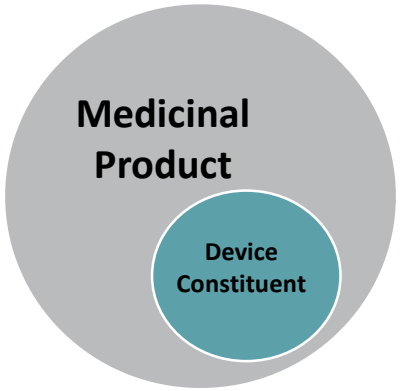
Lifecycle Management

"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"



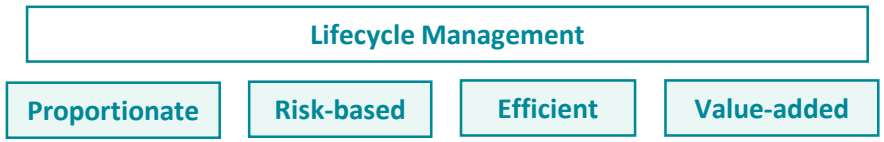
ICH Q12
Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

NBOG BPG 2014-3
Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System (+ MDCG 2020-3*)



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

- Current guidance available is not appropriate when considering the breadth / complexity of single-integral DDCs
- No ongoing NB relationship
- NBOp is a 'snap-shot' of medicinal product
  - MAH don't foresee NBOp itself needs to be maintained
  - Change assessed as to whether a NBOp also required to support MAA variation



* MDCG 2020-3 - GUIDANCE ON SIGNIFICANT CHANGES REGARDING THE TRANSITIONAL PROVISION UNDER ARTICLE 120 OF THE MDR WITH REGARD TO DEVICES COVERED BY CERTIFICATES ACCORDING TO MDD OR AIMDD

Case Studies

Representative, prior examples which present a typical change for the device constituent of medicinal product and outlines how MAH could manage such change(s) with

- **Consideration given to:**
  - What data / information required to support the change

1. Whether it would be substantial or non-substantial change
   - Are we operating within pre-defined control strategy, including device aspects? ie. Device critical quality attributes for performance

2. EU MAA variation category – category listed is per a prior MAH variation itself

- **Conclude whether a NB opinion required to accompany the variation based on nature and outcome of the change**

Change in the formulation of the medicinal product

Assumptions & Considerations

Change in formulation (higher drug concentration) results in a solution viscosity change although formulation change has no impact on the clinical efficacy and safety of the medicinal product

- Higher viscosity solution requires change to spring component within pen-injector to retain performance (injection time & injection force)
- Design verification data supports performance of modified pen-injector; supports no change in performance from unmodified pen
- No physical usability impact; injection force remains the same
- Medium risk for patient based on intended use and medicinal product / therapy regime – updates to Patient Information required
- Managing a change to established conditions of the medicinal product but doesn't impact or change device constituent performance

Category

Type II

B.II.a.3.b.2

No NBOp required

Non-substantial design change

However, if this formulation change resulted in device changes which **also changed device performance**, could invoke a NBOp to support variation

Change in the (internal) needle dimensions for a staked prefilled syringe

Assumptions & Considerations

Internal needle dimension of staked needle is changed but route of administration remains unchanged (needle length giving SC admin)

- No change or impact to performance (dose accuracy) or on product quality demonstrated
- No change in overall patient use or interface
- Medium - low residual risk based on intended use, established technology & medicinal product
- No impact to medicinal product critical quality attributes/established conditions resulting in notification vs. prior approval submission category

Category

Type IB
B.IV.1.z[ǂ]

No NBOp required

Non-substantial design change

[ǂ] category currently does not exist in the EU Variation Classification guidelines

Withdrawal of CE Mark/Declaration

Assumptions & Considerations

CE declaration for needle safety guard used with staked prefilled syringe is no longer supported by supplier; deletion of evidence in MAA

- Update to Module 3 required to remove unsupported statements of conformance (ie. CE evidence)
- Device design remains unchanged, as does overall safety & performance for approved single-integral product
- Safety & performance of safety needle component already considered by MAH in overall conformance of staked prefilled syringe against Annex I for iDDC
- Overall no change to applicable/not GSPRs. MAH using V&V data rather from device manufacturer than relying on CE DoC/certificate as supportive evidence
- No design change to established technology. No impact to medicinal product CQA/ECs or device performance, resulting in administrative change only

Category

Type IA_{IN} B.IV.1.z[‡] (proposed)

not directly covered by B.IV.1.b or B.IV.1.c

No NBOp required
No design change

[‡] category currently does not exist in the EU Variation Classification guidelines

Example only applicable to currently approved products leveraging CE certificate/DoC evidence, new product registration would still require a NBOp to support MAA

Design Enhancement for Prefilled Pen

Assumptions & Considerations

Minor design enhancement to prefilled pen device component

- Assessment of change is shown to have no impact on safety or performance of device constituent
- The change does not affect contact of device with the medicinal product
- Performance remains within specification, incl. dose delivery
- No change in overall patient use or interface
- Low 'residual risk' based on intended use and medicinal product
- No change in device-related information or description in MAA
- No impact to medicinal product CQA/ECs resulting in no impact on MAA – internal data management only within QMS design file

Category

Non-reportable to MAA

Granularity of change not within scope of Module 3

No NBOp required

Non-substantial design change

Material Change – Metered Dose Inhaler (MDI)

Assumptions & Considerations

Change to the valve used in a pMDI for a maintenance therapy product. The material of construction of one of the components of the pMDI has been changed due to discontinuation of the current material by the manufacturer.

- The valve design is unchanged to that in the approved product and no impact to device performance
- There is no physical change to the user, no impact on usability and user interface remains unchanged
- The material of construction remains the same, although from alternative supplier
- Material safety is shown but change could incur difference in E&L profile/ drug compatibility*
- Supportive data incl. E&L would be presented in Module 3 (draft CHMP DDC quality guidance) and assessed by pharmaceutical assessor
- No impact to other medicinal product CQA/ECs or device performance

Category

Type Ib

B.IV.1.c ǂ

(proposed)

only material change which is an integrated part of the primary packaging, not device or design change

ǂ category currently does not exist in the EU Variation Classification guidelines

No NBOp required

Non-substantial design change

* B.II.e.7 change in supplier of packaging components or devices
The qualitative and quantitative composition of the packaging components/device and design specifications remain the same.

Industry Recommendations

Guidance or framework

- Targeted at device-constituent in context of single-integral DDCs (medicinal products)
- Aligns with risk-based approach /other guidance being adopted for medicinal products ie. ICH Q12
- Enables regulatory flexibility, driving consistency for when NBOp will be required & efficiency of only involving NB when needed

Alignment of stakeholders

- EMA with NB & Industry to align on expectations (Medicinal product vs. medical device)
  - Medicinal product requirements are primary for managing changes
- Alignment between EMA and National Competent Authorities

Managing MAA variations

- Alignment of EU Variations guidance with EMA CHMP Quality DDC guideline and NBOp evidence requirement
- Additional / clearer change categories for single-integral products (device constituents) reflecting advancing technologies

Industry are striving for 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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Thank you

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BACK-UP