EBE-EFPIA Position Paper

Approach to Substantial Design Change of the Integral Medical Device Constituent Part Under Article 117: A Risk Based Approach

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Executive summary

Since the issuance of the EMA/CMDh "Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations (EU) 2017/745 and (EU) 2017/746), Rev.1", 21st October 2019, industry has open-questions with regards to what constitutes a 'substantial design change' and is requesting EMA to provide a regulatory framework upon which basis, changes should be considered and managed using a risk-based approach within the current variations guidance and process.

Given medicinal products with an integral medical device (DDCs) are governed as medicinal products under Directive 2001/83/EC as amended, the EMA/NCAs have overall accountability for these products. As such, industry is looking for guidance on a definition of 'substantial change' in respect to managing changes given the current EU variations classification guideline (EC 1234/2008, 24 November 2008) does not adequately address changes to the device constituent of an integral DDC.

Whilst the longer-term objective of the EMA should be to update the variation regulation and associated variation categorisation guideline to better accommodate single integral DDCs, the short term target to meet the 26 May 2020 MDR implementation, is to provide industry with a framework that suppports the determination of a 'substantial change' that ensures changes to the device constituent of single-integral DDCs are approached. The aim of this proposal is to achieve categorisation of device design changes in a consistent manner such that the summary of information within the market authorisation is suitably maintained to ensure that product quality and ultimately patient safety are not compromised.

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List of abbreviations and definitions

CMDh	Co-ordination Group for Mutual Recognition and Decentralised procedures – Human
CQAs	Critical quality attributes
DDC	Single-integral drug-device combination product
EC	European Commission
EMA	European Medicines Agency
GSPRs	General safety and performance requirements set out in Annex I of the MDR
ICH	International Conference on Harmonisation
ISO	International Standards Organisation
MDR	Medical Devices Regulation; Regulation (EU) 2017/745
NB	Notified Body
NBOp	Notified Body Opinion
NCAs	National Competent Authorities
MAH	Marketing Authorisation Holder
MAA	Marketing Authorisation Application
MDD	Medical Device Directive; 93/42/EC as amended by 2007/47/EC
QMS	Quality management system

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1. Introduction

The Regulation on Medical Devices (MDR, Regulation (EU) 2017/745) amends the Community Code of Medicinal Products (2001/83/EC) requiring that "*If a medical device used to administer a medicinal product is placed on the market in such a way that the device and medicinal product 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 under the medicinal product framework, Directive 2001/83/EC*", a Notified Body Opinion (NBOp) for the device constituent against the General Safety and Performance Requirements (GSPRs) of the MDR must be included within the Marketing Authorisation Application. Since drug-device combination (DDC) products are regulated under the medicinal product framework, a Notified Body Opinion (NBOp) should be issued by an appropriately designated Notified Body (NB), who conducts an assessment of evidence presented against the applicable GSPRs set out in Annex I of the MDR for the device constituent of a single-integral DDC product.

Regulatory agencies have made clear that a NBOp will be required to be provided as part of new Marketing Authorisation Applications from 26th May 2020. Additionally, the EMA/CMDh "Questions & Answers on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations (EU) 2017/745 and (EU) 2017/746), Rev.1", 21st October 2019, indicates that the Marketing Authorization Holder is obliged to submit a NBOp when:

1) "A device component is added or fully replaced", or
2) "…**with any variation or extension application describing, substantial design changes to the device component**".

Importantly, the EMA draft "Guideline on quality requirements for drug device combinations," 29 May 2019 (EMA/CHMP/QWP/BWP/259165/2019), states that changes to devices and/or device components within DDCs will require submission of a variation, that manufacturers should present the change in accordance with the relevant EU Variations Regulation and associated variation guidelines in place, and that the change should be submitted under the appropriate category. However, the variations guidance does not at present adequately manage changes for integral DDC products or incorporate the requirement for an NBOp.

The EMA/CMDh Q&A defines a substantial design change as one that affects the performance and safety characteristics of the device. Moreover, the draft CHMP guidance on quality requirements also indicates that depending on the nature of the change, the MAH should consider whether updates to relevant documentation (e.g NBOp, Declaration of Conformity, CE mark etc) associated with the device in question are required to support the change. Furthermore, the category of variation should take into consideration the impact of the change, e.g. a change that impacts DDC CQAs and/or elements(s) of the overall DDC control strategy, which maybe considered a higher category of variation. However, beyond that, there is limited guidance and it is at the discretion of the MAH to decide what constitutes a substantial design change.

In general, industry agrees the need for a non-prescriptive approach in this area, considering the potential complexity and variety of DDC types, and considers that variations could be managed through applying the principles of a risk-based approach, as was put forward by EBE in a previous reflection

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paper[1]. However, with respect to assessing when a NBOp is required for a substantial change, several challenges remain to ensure consistent implementation of the new requirements established by the MDR and further clarity is required.

1.1 Recommendations

To address these challenges, EBE and EFPIA would like to see action taken in the following areas:

- It is understood that as integral DDC products are registered as medicinal products, once authorised, the MAH is responsible for determining if a change is considered a 'substantial design change' and as such if a NBOp is required to be obtained. To realise a consistent approach to change management, it is the view of EBE and EFPIA, that the EMA/NCAs should provide a regulatory framework with guidance that defines what constitutes a substantial change and how these changes should be managed, utilising the current variations process and the categories of variation to be applied.
  This process should include the capability to consult the EMA/NCAs for advice as necessary.
  - In the guidance, EMA/NCAs should further clarify the principles by which changes would be assessed such that it would meet the definition of 'substantial change' and therefore, require the variation submission to be supported by a NBOp. Consideration of a flowchart/decision tree to support this assessment could be utilised. Such a flow chart/decision tree aligned to the principles of ICH Q12 and the designation of Established Conditions for an integral DDC product is strongly encouraged. ICH Q12 links the regulatory process and management of changes through 'prior approval' or 'notification'. Industry could envisage a 'prior approval' change being 'substantial' in nature and requiring a NBOp to support the change for the device constituent itself.
  - Given the potential challenges presented in assessing which changes meet the threshold of a substantial change, industry considers that for integral DDC, as medicinal products, it is appropriate to consult with the EMA/NCAs for advice. This is because companies would not have an on-going relationship with NBs, as is current practise for medical device companies that maintain ISO 13485 certification and assessments to CE mark medical devices. In addition to the existing pre-submission queries service for Type IA and Type IB variations, it would be helpful if Agencies (EMA/NCAs) augmented this service for device specific queries to ensure that questions from industry are appropriately or consistently addressed. For example, in providing a single point of contact or enhancing the current mailbox for device enquires.

- In the longer term, a review of the EU variation regulation and associated variation categorisation guideline should be undertaken to better reflect the new technical and regulatory paradigms of integral DDCs and to ensure efficiency in the management of changes.

1 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", January 2018

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2. Key Considerations

In order to support these recommendations, and given the immediate need post May 26 2020, when the Regulation (EU) 2017/745 comes into force, EBE and EFPIA are making the following suggestions/proposals to ensure that those managing variations for DDC medicinal products have a framework to assess against and detemine whether a NBOp is needed or not to support the variation.

2.1 Defining a substantial design change

The EMA/CMDh Q&A recognises that a NBOp is potentially required to support a variation submission, namely when a substantial change to the device component is made to a licensed integral DDC. Broadly, the Q&A requires that the change be considered relative to the safety and performance of the device constituent. Industry is proposing that evaluation of the variation category (Type IA, Ib or II) and whether the change is substantial should be performed using a risk-based approach consistent with the approach previously described in the EBE reflection paper[1], and relative to what is registered within the MAA itself for the medicinal product, including the proposed intended use and environment. In doing so, the framework as outlined in ISO 20069:2019 "*Guidance for assessment and evaluation of changes to drug delivery systems"*, could also be helpful.

In applying such measures, guiding principles for assessing the change should consider the following:

1. **Contact with the medicinal product** e.g. in direct contact and impact of a design change on the medicinal product, or impact of functionality of the device based on a medicinal product change
2. **Patient usage and appearance / patient facing materials** e.g. change in key user steps or key design change/functionality resulting in major IFU modifications
3. **Dose delivery or other performance related CQAs** e.g. impact to product release or functional specifications
4. **Changes to device components** e.g. design enhancements or changes to materials, that impact functionality of the device or patient safety or introduction/replacement of a complete new device
5. **Change in device manufacture / assembly or control strategy** e.g. changes to critical manufacturing operations

Depending on the MAH assessment of the design change, it will be determined that either a NBOp is required to support the change or it is not.

If the change is shown to impact either safety or performance based on the above guiding principles, then it would be considered a substantial design change and the MAH should ensure a NBOp for the device constituent accompanies the MAH variation. However, a NBOp should not be required for changes that are not shown to impact safety or performance of the device constituent in the context of MDR Annex 1 (2017/745) and thereby positioned as 'low risk' and considered 'non-substantial'.

Nevertheless, even if a change is considered 'non-substantial' in relation to Article 117 by the MAH, a variation could still be required on the basis of patient safety and product efficacy for the integral DDC and maintenance of module 3 of the MAA.

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Obtaining an NBOp is a lengthy process (projected 4-to-6-plus months). Therefore, it is of critical importance that regulators provide unambiguous guidance confirming the specific changes in the EC Variations Guidance, which would constitute a substantial design change under the EMA/CMDh Q&A document and enable the MAH to plan for a NBOp. If this situation is not clarified, MAHs may face significant delays if unanticipated requests for NBOps are made by Regulators either when an application is being validated or under review.

Notwithstanding the principles and examples outlined above, assessing which changes will meet the threshold of a substantial change and require a NBOp is recognised as complex and Agencies should take steps to ensure that questions from Industry are appropriately and consistently addressed. For example, by ensuring a suitable framework to which they can refer, so that questions on these matters are dealt with consistently via specific Agency contacts or mailbox.

2.2 Governance and assessment of change following issuance of a notified body opinion

As outlined above, EBE and EFPIA understand and welcome that it is the responsibility of the MAH to determine the classification of change and whether a change is substantial. However, there will be cases where the classification of a change (substantial or non-substantial) may need clarification and in such situations, the pathway for obtaining such advice needs further definition and guidance.
One potential approach implied by the updated EMA/CMDh Q&A, is for MAHs to liaise with the Notified Body (NB).

However, this is problematic for several reasons:

- The experience of NBs regarding notification and assessment of changes as they relate to the Variations Regulations and Guidance for medicinal products is limited, given the separate regulatory frameworks for medicinal products and medical devices.
- The relationship between the MAH and the NB for integral DDCs is different from that between a NB and the manufacturer of a medical device. In the case of integral DDCs, the engagement with an MAH and NB is not continuous and only triggered by the requirement to obtain a NBOp or any potential subsequent revision, whereas for medical devices, the NB and Manufacturer have an on-going relationship given the role of the NB in the certification process of the medical device itself as well as the company's Quality Management System (QMS). Consequently, the ability to liaise with the NB to determine a substantial change for an integral DDC will be challenging and may well not be possible.
- NBs are required to remain independent and impartial, they not permitted to be involved in consultancy activities to ensure no conflict with their independence of judgement[2,3]. This is evidenced by EFPIA member companies who have reported that several NBs have indicated that they do not consider that they are appropriately placed to determine whether a change is substantial or otherwise.

It is proposed that MAHs should discuss with EMA/CAs and not NBs, regarding clarification of changes.

2 MHRA issued Guidance on legislation Requirements for UK notified bodies, November 2013
3 Annex VII: (EU) 2017/745; Clause 1.2

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With regard to the absence of a specific detailed guidance on the definition of substantial changes, it is likely that MAHs, Notified Bodies and EMA/NCAs may look to either (1) the EC variation categorisation guideline which is already recognised as deficient for integral DDC medicinal products or (2) guidelines issued under the current Medical Device Directive (MDD) that will be superseded by the MDR, such as the NBOG-BPG 2014-3 *("NBOG's Best Practice Guide: Guidance for manufacturers and Notified Bodies on reporting of Design Changes and Changes of the Quality System")* or the NB-MED/2.5.2/Rec2 Guideline *("Reporting of design changes and changes of the quality system", 2008),* to try to determine whether a device constituent change is 'substantial'.

Moreover, guidance documents on significant changes related to MDR implementation have also been prepared by specific NBs, but they have clearly articulated these are focused on medical devices and not intended or appropriate to be applied to device constituents of integral DDCs. Consequently, conflicting conclusions for whether the device change is, or is not, substantial could be received; thus resulting in either failing to include an NBOp or unnecessarily providing a NBOp in a variation submission.

Considering the complexities of the situation, it is the EBE and EFPIA Member companies' opinion that when the MAH requires advice, the EMA/NCAs would be best placed to advise if planned changes should result in the issuing of a NBOp to support the modified device constituent. This is aligned with integral DDCs being regulated as medicinal products (e.g. where clarification is sought via EMA mailboxes for Centrally Authorised Products). Moreover, this approach is consistent with the general expectation for MAHs to document compliance with the relevant GSPRs of the MDR within the MAA, as evidenced by the NBOp. The role that NB opinions has in this process is recognised and as such it will be important that any framework and considerations for the definition of substantial changes are established and in alignment between Regulatory Agencies and Notified Bodies.

Once defined, it would be helpful for Agencies to publish examples of those changes which would be considered to result in a NBOp to support a variation and the appropriate variation category. For example, by addition of annexes to the current EMA/CMDh Q&A or the quality guideline for DCCs.

2.3 Variations regulation and guidelines

The changes in regulations and approach introduced by the MDR and requiring a NBOp to support a MAA for integral DDC products, were not envisaged at the time the Variations Regulation (1234/2008/EU) and Variations Guidelines came into force. As the guideline is limited with respect to device changes, certainly as part of integral DDCs, this currently presents significant challenges, and often the majority of changes can default to a 'z' categorisation. This is in contrast to container closure system changes, which are more specifically defined and consider the appropriate level of risk. Furthermore, the variations guidance requires that 'substantial changes' of the finished medicinal product are classified as major Type II variations , but that may not in all cases be appropriate since 'substantial' changes as defined under Article 117 may not equate to 'substantial' changes as defined in the Variations Guideline. Using risk-based approaches it can be justified that many changes designated as 'substantial' under Article 117 should not result in major (substantial) variation categories but could be Type IA or Type IB minor variations.

It is EBE and EFPIA position that the review of the variations framework and associated guidance is

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warranted more generally. This would also provide the opportunity to fully evaluate the further impact of the MDR and other developments in the technical and scientific development of single integral DDCs on the Variations Regulation, and if there are further opportunities for efficiency in the management of changes. For example, through the inclusion of additional and clearer device- related change categories.

Moreover, if the opportunity is presented by opening the EC variations guidance, it would be appropriate to have the requirement for a NBOp written into the required documentation for the appropriate variation categories. As part of the recommendation to update the variations guideline, consideration should be given to aligning with the principles and framework of ICH Q12 and utilising a risk-based approach for evaluating what changes would qualify within scope of a variation submission. Furthermore, what changes would be considered substantial such that a NBOp would be expected to support the change.

3. Conclusions and Path Forward

Industry is responsible for determining whether a change to a device constituent of an integral DDC is considered 'substantial' and in doing so, is requesting guidance from EMA/NCAs to enable a consistent approch to manage changes for these products. Given integral DDCs are regulated as medicinal products, it is proposed that the MAH should discuss with the EMA/NCAs and not NBs regarding clarification. To facilitate this, industry is requesting that a suitable framework is available which could include specific Agency contacts or mailbox being set-up.

Based on the projected lengthy process to obtain a NBOp, potentially equivalent or longer than the overall review and approval of a variation submission itself, MAHs are requesting that in the near-term, there is clear guidance developed to assist with assessing changes so variations are not deficient of NBOps based on certain types of changes being made. Given the breadth of different change types that could occur over the different presentation types of single DDCs, industry is suggesting that a risk-based approach should be implemented when defining a 'substantial change'. Other changes outside of this would not require a NBOp to support the change and could be managed through a lower reporting category.

In the longer term, a review of the variation regulation and associated variation categorisation guideline should be undertaken to better reflect the new technical and regulatory paradigms of DDCs and to ensure efficiency in the management of changes.

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