

## EBE-EFPIA Reflection Paper

# An Industry Perspective on Article 117 of the EU Medical Devices Regulation and the Impact on how Medicines are Assessed

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### Executive summary

With the publication of the new Regulation on Medical Devices (MDR, Regulation (EU) 2017/745) comes an important amendment to the medicines legislation, in Article 117. As part of the marketing authorisation application (MAA) for a medicinal product regarded as an integral drug-device combination product, this article requires the Marketing Authorisation Holder to provide a Notified Body (NB) opinion for the device constituent.

Within the current regulatory landscape, guidance which covers requirements for registration of pharmaceuticals such as ICH M4Q, does not sufficiently address the Module 3 considerations to ensure registration of an integral drug-device combination product. In the absence of such key guidance, it is known that location of information related to the device component, as well as specifically what level of details is submitted, is variable across companies, which was highlighted through a recent EBE reflection paper.

The MDR becomes legally enforced on May 26, 2020 and with this, the need to incorporate a NB opinion, but it is unclear how information for that assessment will be positioned against the medicinal product MAA dossier review by the Medicines Competent Authorities (CA). Moreover, what information specifically would be the focus of the NB opinion versus that of the integral drug-device combination product by the Medicines Competent Authorities is not defined. Where a device is also a component of an already marketed medicinal product, there is opportunity to leverage prior knowledge and previous NB opinion without the need for further oversight. Furthermore, and of equal importance, there is currently no understanding of how the process to support this new requirement would work or what is the proposed timing of such assessment relative to the MAA itself, which is a critical issue for manufacturers. In turn, concerns are being raised that this could impact approval timelines and unduly delay important medicines getting to market.

Following publication of a concept paper in November 2016, the EMA Quality and Biologics Working Parties are in the process of developing a quality guidance which is hoped will address many of these gaps, in conjunction with a number of Implementing and Delegated Acts being defined to facilitate interpretation and implementation of the new legislation, but the timeframe for these being available is also not currently defined.

This paper considers these technical and procedural concerns and challenges being discussed amongst industry, with a view that recommendations made are taken into consideration as guidance and



implementing acts related to integral drug-device combination products get defined. Consideration is given to the combined Advanced Therapy Medicinal Products (cATMPs) guidance on “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” which utilises a NB within the overall review and approval of cATMPs when they incorporate a medical device. With some enhancements, it is felt this procedure could be a good basis to move forward for drug-device combinations and meeting the specific requirement of Article 117. In addition, focus is given to the requirements of the NB opinion, specifically what it will cover and moreover, in relation to the CA/MAA review. Furthermore, discussion on whether Article 117 and specifically the NB opinion will include review of the manufacturers quality management system and specifically being certified to ISO 13485 is discussed.

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## List of abbreviations and definitions

AI	Autoinjector
BWP	Biologics Working Party of the European Medicines Agency
CA	Competent Authority for medicinal products
CAT	Committee for Advanced Therapies of the European Medicines Agency
cATMPs	combined Advanced Therapy Medicinal Products
CE Marking	Conformité Européenne/CE marking of conformity
Class Im	Class I measuring device, based on classification rules within Regulation (EU) 2017/745 Annex VIII, a sub category of class I, the lowest risk class
Class Is	Class I sterile device, based on classification rules within Regulation (EU) 2017/745 Annex VIII
Class IIa	Class IIa device based on classification rules within Regulation (EU) 2017/745 Annex VIII
Class IIb	Class IIb device based on classification rules within Regulation (EU) 2017/745 Annex VIII
Class III	Class III device based on classification rules within Regulation (EU) 2017/745 Annex VIII
CTD	Common Technical Document
EBE	European Biopharmaceutical Enterprises
EC	European Commission
EC Certificate	European Conformity Certificate
EMA	European Medicines Agency
ER(s)	Essential Requirement(s) (Annex I of the MDD)
EU/EEA	European Union/ European Economic Area – allowing the free movement of approved medical devices amongst countries
GSPRs	General Safety and Performance Requirements (Annex I of the MDR)
Integral DDCs	Integral drug-device combinations Article 1.9 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
ICH	International Conference on Harmonisation
ISO	International Organization for Standardization
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MEDDEV	European Commission Medical Device Guidance document
MDD	Medical Devices Directive, i.e. Council Directive 93/42/EEC concerning medical devices
MDR	Medical Devices Regulation, i.e. Regulation (EU) 2017/745 of the European Parliament and the Council on medical devices
NANDO	New Approach Notified and Designated Organisations
NB	Notified Body
NBOG	Notified Bodies Operations Group
OBI	On-body injector
PFS	Prefilled syringe
QWP	Quality Working Party of the European Medicines Agency
TEAM-NB	<u>T</u> he <u>E</u> uropean <u>A</u> ssociation <u>M</u> edical devices of <u>N</u> otified <u>B</u> odies
UDI	Unique Device Identification



## 1. Introduction

This paper provides an industry perspective on the technical and procedural concerns and challenges being raised in relation to Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use and new requirements as a result of the amendments through Article 117 of the Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices (Medical Devices Regulation, MDR) which applies from May 2020 onwards. Based on Article 117, marketing authorisation holders of products that will be regulated as medicinal products and incorporate an integral delivery device, which are intended to be placed on the market exclusively in that given combination, will be required to seek separate opinion on the device constituent by a Notified Body (NB) as part of the overall approval for the medicinal product.

In absence of any implementing acts or guidance related to integral drug-device combination products (DDCs) at publication of this reflection paper, understanding the proposed involvement of a NB remains a critical issue for manufacturers; having a defined scope, process and timing for such opinion is extremely important as it could have significant impact on the MAA review and approval timelines. The industry's concern is compounded by the increasing number of products which will fall within the scope of this requirement going forward, and questions around NB capability and capacity to perform the required assessments.

This paper puts forward recommendations and proposals, drawing on precedents and guidance already established between the Competent Authorities (CAs) for medicinal products and NBs.

It is hoped that this paper will be helpful in facilitating dialogue between regulators, NBs and industry at key regulator-industry forums in the coming months and moreover, will be taken into strong consideration as guidelines and processes are discussed and developed by the key stakeholders including the European Medicines Agency (EMA) and NB representative groups.

## 2. Challenges and Considerations with Implementing Article 117 of the EU Medical Devices Regulation

### 2.1 Regulatory Review Process

Currently, based on the principal intended action, the regulatory review process is defined by the Directive 2001/83/EC for medicinal products and Directive 93/42/EEC for medical devices (MDD), and it is required that

- i. For delivery devices that do not form a single, integral product but are presented as separate, and standalone to the medicinal product, they undergo conformity assessment according to the MDD and are CE marked (e.g. pen-injector for use with cartridges of insulin)
- ii. For delivery devices integral with the medicinal products, i.e. 'placed on the market in such a way that the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable', (e.g. prefilled syringe or prefilled auto-injector), the delivery device component will comply with the 'Essential Requirements' (ERs) outlined in Annex 1 of the MDD but this product type cannot carry a CE mark.

During the regulatory review process, in (i) above, the device manufacturer will assess the safety and performance of the device component for compliance with the relevant ERs and when satisfied that all applicable ERs are met, as well as Technical File and Conformity Assessment requirements, a CE



mark is applied by the manufacturer to allow marketing of the device throughout Europe. This is in accordance with the European Commission (EC) 'New Approach' to facilitating trade throughout the EU. Based on risk classification of delivery device as defined by the MDD, for all risk classes above Class I (i.e. Im, Is, IIa, IIb and III), a third-party certification body will be involved, a 'Notified Body' (NB).

A NB within the European Union (EU) is an entity designated by an EU responsible authority to assess the conformity of medical devices before being placed on the market. The European Commission (EC) publishes a list of notified bodies with details of device product ranges, horizontal competences and conformity assessment procedures they are accredited for, in the NANDO (New Approach Notified and Designated Organisations) website<sup>1</sup>. Companies are free to choose which NB they work with, based on the device product types and competences they are accredited for.

In scenario (ii), for integral DDCs whilst conformance with the ERs is demonstrated, there is no current requirement to involve a NB in an assessment. The ER checklist summarising how the manufacturer has demonstrated compliance with the applicable requirements is often provided in MAA dossiers and has up to now been reviewed by the CA reviewing the medicinal product application.

However, the MDR requires that manufacturers of integral DDCs seek a separate opinion on the device constituent by a NB as part of the overall approval for the medicinal product. Furthermore, changes to classification rules in the MDR bring a drug-delivery device type into scope, which previously would not have required NB involvement (e.g. see MDR Rule 20 regarding device types for administering products via inhalation), in turn widening the applicability of Article 117.

### Article 117 of Regulation (EU) 2017/745

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) 2017/745 of the European Parliament and of the Council (\*), a product is governed by this Directive, the marketing authorisation 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 NB 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 NB 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 NB designated in accordance with that Regulation for the type of device in question.

Over twelve months after the publication of the MDR, how this requirement will be implemented, the expectations of each stakeholder and the process are unclear. Given the absence of Implementing acts from the Commission or guidance from the EMA, there is significant concern across the pharmaceutical and medical device industries.

Whilst engagement with a NB is considered a new requirement for integral DDCs that are regulated as medicinal products, the requirement for engagement and assessment of the medical device by a NB as part of a medicinal product approval is not new: there are some precedents that could be leveraged. Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products defines in Article 2(d) that a combined Advanced Therapy Medicinal Products (cATMP) incorporates, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices with the meaning of Article 1(2)(c) of Directive

<sup>1</sup> <http://ec.europa.eu/growth/tools-databases/nando/>



90/385/EEC. In order to ensure an appropriate level of quality and safety, those devices should meet the essential requirements laid down in the relevant Directives. A NB for medical devices may be or may have been involved in the assessment of the medical device part of a combined ATMP (cATMP). In response to this requirement EMA issued the following guidance: *“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”*<sup>2</sup>.

## 2.2 Suggested process for NB Opinion of integral DDCs

The above mentioned EMA guidance for procedural advice on the evaluation of cATMPs, which was adopted and published in 2011, was developed following collaboration between the Committee for Advanced Therapies (CAT) of the EMA, Notified Bodies Operations Group (NBOG) i.e. Member States Designating Competent Authorities for Notified Bodies, TEAM-NB (The European Association for Medical devices of Notified Bodies), and the EC.

This cATMP procedure is considered a useful and strong basis for consideration of a working process for obtaining a NB opinion for integral DDC products going forward.

Annex I of this reflection paper considers the current cATMP procedural guidance in more detail and outlines where industry considers the different sections applicable to the requirements introduced by Article 117 of the MDR, with further suggestions for enhancements to that existing procedure, mainly relating to the NB consultation for integral DDCs.

<sup>2</sup>[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](#)



Figure 1 in conjunction with the text below outlines a proposal for a process to meet the requirements of Article 117 and to include a NB opinion within the process for MAA review and approval of integral drug-device combinations.

The salient points of the industry proposal (see Annex I of this reflection paper) are summarised here:

- Whilst applicants are encouraged to perform sequential reviews and provide results of the NB opinion within the MAA itself, the procedure does allow for submission of the NB opinion after initiation of the MAA assessment. This flexibility for a parallel review may be important when finalisation of the DDC product design is close to submission date, as it is less likely to add to, or lengthen the overall timeline for review and approval of the MAA resulting in delays in important medicines getting to market.

Managing a sequential review could on the other hand prevent an effective NB opinion process due to an incomplete data package or inclusion of data from a non-final device being reviewed by the NB. The applicant would need to make the case this is still considered representative of the final, commercial presentation. If the NB does not agree with this position, it could result in delays. Therefore, a parallel review could provide flexibility and enable a review of a more comprehensive package without adding overall time to the MAA review and approval of the medicinal product application.

- Suggestions are made for documentation to be provided (although industry envisioned that specific guidance could be developed and made available by EMA in the future). Further clarification of the remit between CA and NB assessments would be helpful to ensure complementary review and minimise duplication of resource efforts.
- Utilisation of prior knowledge is important and when the DDC incorporates a platform-based device constituent that is used across multiple medicinal products, and that has been previously assessed by the NB, inclusion of this assessment along with specific compatibility aspects for the new medicinal product would be required in the MAA.
- A significant concern of industry is that if the device information resides solely within Module 3.2.R of the MAA dossier, this has potential challenges from a dossier lifecycle maintenance perspective. Industry acknowledges that sufficient information to allow the MAA assessor to understand the device and to assess the medicinal product should be contained within the MAA itself, e.g. critical delivery characteristics of the device constituent, suitability of the device with respect to product compatibility and performance must be included in Section 3.2.P.2.4. of the MAA dossier, along with sufficient information relating to device component control, materials and compliance that should be incorporated into Section 3.2.P.7. of the MAA dossier. It is further acknowledged that potential processes, roles or system required for handling the device information between the CA and NB are not clear, in the scenario of device assessment occurring in parallel. In this scenario, evidence that the separate NB assessment has been initiated could be included in MAA to achieve successful validation of the dossier.

In absence of a procedure, industry proposes that for a parallel review, the NB opinion would ideally be available by Day 80 and the latest by Day 120 (or equivalent, for a decentralised review).

- The majority of device information would not reside in the MAA and therefore not be maintained as part of the MAA dossier maintenance. When the device incurs changes, subsequent management of the device information would be separate, and, based upon the nature of the change, potentially subject to further NB assessment and a separate notification or update to the CA.

- Enhancements to the current process in relation to communication are recommended, suggesting that the applicant will be made aware of all communications between the EMA, national CAs and NBs.
- The importance of good relationships and contractual agreements with third party suppliers or manufacturers of devices or device components is stressed. Making available necessary information which the applicant is not necessarily the holder of, but is potentially reliant on for approval, to either the applicant or NB as requested, as well as assessing the impact of device changes on the overall integral DDC is key.

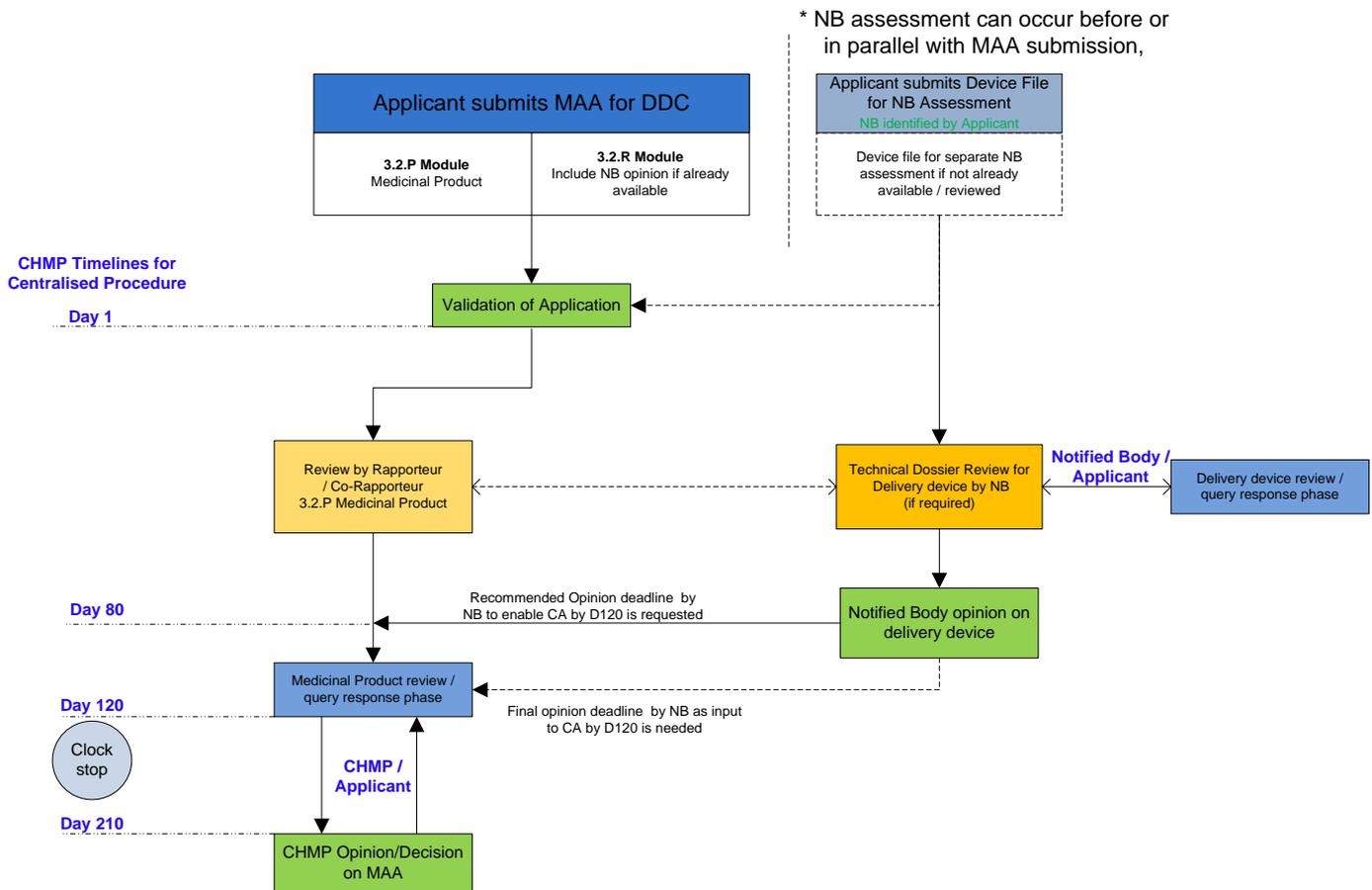
Successful adaptation and adoption of this process proposal would be a useful topic for discussion at a future workshop involving EMA, NBs, industry representatives and other relevant stakeholders, as previously suggested in the EBE reflection paper on medicinal product incorporating a drug delivery device component issued in January 2018<sup>3</sup>.

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<sup>3</sup> [EBE reflection paper on medicinal product incorporating a drug delivery device component, January 2018](#)



Figure 1- Process proposal to meet requirements of Article 117 and inclusion of a NB opinion within the MAA review and approval of integral drug-device combinations



### 2.3 Implementing Article 117 of the MDR

Based on Article 117, paragraph (1), the MAH is still required to provide an EC (European Conformity) certificate issued by a NB or a manufacturer's declaration of conformity, where applicable depending on device classification, allowing the manufacturer to affix a CE mark to the medical device. However, this only applies when the medical device is eligible to be CE marked (i.e. a stand-alone medical device). In the absence of this conformity assessment, (applicable to most integral DDC products), paragraph (2) requires the MAH to involve a NB to provide an opinion on the conformity of the device constituent part in relation to the relevant general safety and performance requirements set out in Annex I.

Clarification is also required as to products within the scope of Article 117. Certainly, when the drug-delivery device combination incorporates a Class I device which is non-sterile, non-measuring, or non-reusable surgical; as a standalone (i.e. separately used) device it would ordinarily not require a NB assessment to CE mark. Therefore, a device constituent that as a standalone device would not require a NB assessment, should not fall under the requirement of a NB opinion if it is contained within an integral DDC. It is acknowledged that some container closure systems may be used for delivery of

medicinal products; from a pharmaceutical perspective, they would not traditionally be considered a medical device nor do they carry a CE mark. Rather it could be more appropriate if they would continue to be considered as container closures and managed as such, e.g. eye drop containers. For such cases, it is suggested that the EMA QWP/BWP guidance currently in development could outline relevant expectations for these product types.

Finally, Article 117 is not descriptive as to the stage of product development the requirements apply. In the absence of clarity, we consider a NB opinion is not needed before initiation of clinical studies using integral DDCs. Confirmation of the General Safety and Performance requirements (GSPRs) set out in Annex I of the MDR that are relevant to the phase of development and the clinical study, may be a useful risk mitigation measure and a statement included in the clinical submission itself to support approval would be appropriate. The remit of Article 117 should not be an applied requirement during the clinical phase, but applicable to registration and post-approval submission stages.

### 2.3.1 Well-established delivery technologies

For integral products that are using well-established delivery technologies such as prefilled syringes (incorporating a staked needle), spring powered prefilled pens, metered dose inhalers, a NB opinion would need to be sought with each medicinal product approval. The recommendation is that prior knowledge of current market products can, and should be utilised, in addition to a single NB opinion being leveraged across different medicinal products, if appropriate, based on similarity of delivery device, to minimise the burden. Certainly, in the latter scenario of using a single NB opinion across a range of products, the scope of the NB review could be defined so that it would appropriately facilitate that. If the risk-profile significantly changes (for example, based on a new medicinal product or specific user population), then further consultation with the NB should be sought as the applicability of the previous assessment in relation to the new marketing authorisation for the alternative medicinal product cannot be assumed. This would be a topic for discussion at a future workshop between Regulators, NBs and industry.

When the DDC incorporates a platform-based device constituent that has been previously assessed by a NB, and it is being used for the same indication and user population, there should be no need to further consult a NB for this specific device constituent in the new DDC. The previous assessment and opinion, along with specific compatibility aspects for the new medicinal product should be all that is required for the MAA. However this proposal in itself raises further questions and challenges as to how, in reality, a medical device platform assessment could be used across different companies for different DDCs. As a result, if no path forward is defined, we foresee this leading to multiple NBs looking at the same device technology and potentially coming to different conclusions and positions.

Industry is aware that SwissMedic, although still working under the MDD, has already adopted the MDR approach. Based on an announcement made in July 2017<sup>4</sup>, SwissMedic has implemented for integral or non-integral innovative and complex combination products, the requirement for an additional expert report. This could take the form, for example, of a report by a conformity assessment body (e.g. for integral combination products without CE marking) or some other type of expert opinion and/or the corresponding Assessment Report of an EU drug regulatory authority. In addition to satisfying the requirements of Annex I and demonstrating that the medical device constituent is suitable for the specific medicinal product (e.g. dosing accuracy, compatibility etc.). The requirement to provide a NB opinion would appear to be a risk-based approach: MAAs would

<sup>4</sup> [SwissMedic announcement July 2017: Requirements and information relating to combination products \(medicinal products with a medical device component\) in the form Application for authorisation / variation, human medicinal products](#)



only need to include this expert report (NB opinion) for innovative and complex integral DDCs (e.g. electronically controlled injector, chip in a tablet for monitoring patient compliance), but not necessarily for all integral products. This seems a pragmatic approach to meeting the requirements and industry strongly suggests that similar approach be implemented across all EU Member States when applying Article 117. Suggestions of how this could be put into practice are put forward in Section 2.2 Suggested process for NB Opinion of integral DDCs of this reflection paper and below.

Importantly, the EC MEDDEV 2.1/3 guidance on CA assessment of ancillary medicinal substances incorporated into medical devices also recognises that risk-based flexibility of data requirements is appropriate, and specifically states the following:

**C.3 Documentation to be provided by the NB to the Competent Authority**

*Because of the wide range of medical devices which incorporate, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative, a flexible approach to the data requirements is necessary. Nevertheless, the information should be based in principle, to the extent relevant, on Annex I to Directive 2001/83/EC, as amended.*

*It is envisaged that, where well-known medicinal substances for established purposes are the subject of the consultation, all aspects of safety and usefulness may not be required and many of the headings will be addressed by reference to literature, including standard textbooks, experience and other information generally available. Nonetheless all headings should be addressed; either with relevant data or justification for absence of data. The latter may be based on the manufacturer's risk assessment.*

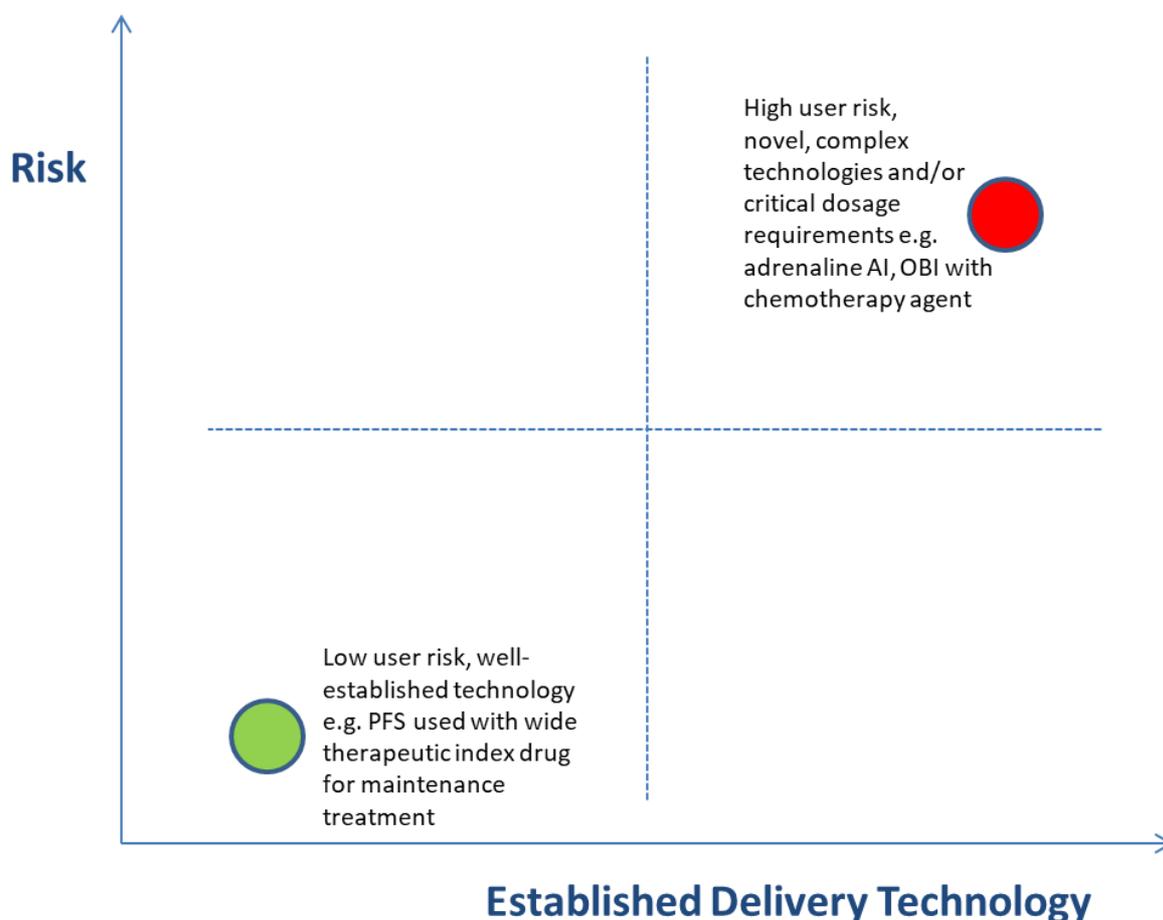
*For new active substances and for known substances in a non-established purpose, comprehensive data is required to address the requirements of Annex I to Directive 2001/83/EC. The evaluation of such active substances would be performed in accordance with the principles of evaluation of new active substances.*

It is proposed that the EMA or the EC take the intent of these statements into account when providing further implementation guidance regarding Article 117. Some integral DDCs that incorporate well-established delivery technologies i.e. prefilled syringe systems with or without enhanced safety features, could utilise a risk-based approach informed by prior knowledge as well as literature, or consideration of safety databases to support and demonstrate compliance with the requirements. As illustrated in Figure 2 below, those products considered a low risk by the applicant based on safety, performance and therapeutic treatment of the combination product as a whole should not necessarily be required to undergo a NB opinion, although evidence of conformance to Annex I as part of the MAA could be provided. The device component would potentially not be subjected to repeat NB assessments unless the risk of the overall DDC product was considered by the CA to warrant such a NB assessment.

It is requested that this be addressed in the EMA QWP/BWP guidance, and that agreement on the level of NB opinion required could be sought between the applicant and EMA or CA as part of a pre-submission meeting or scientific advice during development of the medicinal product, with integral DDCs with high user risks that are utilising novel or complex technologies being required to undergo a detailed NB opinion.

If however from a legal perspective the pragmatic approach of SwissMedic is not possible in the EU, and Article 117 requires a NB opinion for all integral devices, including simple pre-filled syringes with staked needle, then there could possibly be a two-tier level of NB opinions e.g. a high level review or opinion when using established devices and platform technologies, and a more detailed review of devices utilising more novel or more complex and advanced technologies.

Figure 2 - Recommended Risk-Profile Matrix for considering when a NB Opinion is required for a defined drug-device combination



PFS – prefilled syringe; AI – autoinjector; OBI = on-body injector

### 2.3.2 Consideration for Marketed or Approved Products

The expectations for integral DDCs that are already on the market or approved as medicinal products need clarification. Whilst it is recognised that for a medical device, under the provisions of the MDR, the manufacturer needs to retain ‘state-of-the-art’ status and ensure the latest regulations, standards or guidelines are being met, there is typically not the same expectation for approved medicinal products to retrospectively apply new legislation and guidelines as they become available.

The recommendation for integral DDCs would be similar to the approach for medicinal products: for DDCs that will have met the MDD and Annex I Essential Requirements, application of Article 117 should not be retroactively applied and there is no expectation that a NB opinion is retrospectively sought

ahead of May 2020 for on-market products.

Furthermore, Article 117 does not specifically address lifecycle and change management aspects, and when, based on product changes, a NB opinion would be necessary. Therefore, we propose that, when an integral DDC product undergoes a substantial change, specifically to the device constituent of the DDC, per the NBOG Guidance for Reporting Changes to a NB, the manufacturer would need to comply with the MDR requirements. It is also proposed that the NB opinion would only be required where a change is made to the device component or to aspects of the product or validated process that might impact performance, and hence a variation to the registered MAA for the integral DDC product would be required. Industry feels this approach is acceptable since there will be no change to the risk to patients in regard to marketed products as the overall safety or quality of the product has not changed. This would be a sustainable position moving forward, especially considering the increased burden to NBs if all marketed DDCs would require a NB opinion.

## 2.4. Role and Responsibilities of Key Stakeholders

The challenges of bringing together two different regulatory systems are widely acknowledged. It is useful to clarify the current differences in approach between medicinal product and medical device legislations and roles of CA assessors for the authorisation of medicinal products, compared to the role of NBs in conformity assessment procedures for medical devices.

- For medicinal product marketing authorisations under the Directive 2001/83/EC, different routes may be used depending on the nature of the medicinal product: mutual recognition of national authorisations and decentralised procedure where the CAs of each Member State approve the product in their country, or the centralised procedure where a single marketing authorisation following the scientific assessment of the MAA dossier by the EMA is granted by the EC and valid throughout the EU and EEA.

In each case, the Common Technical Document (CTD) format is followed and supported by EMA and ICH scientific and regulatory guidelines, including ICH Q9 Quality Risk Management and ICH Q8 Pharmaceutical Development; CA assessors review and issue a marketing authorisation for each individual product, based on a benefit/risk assessment of documented information on quality, safety and efficacy. Inspection of manufacturing facilities is usually performed independently of MAA procedures unless a new manufacturing site is proposed in the application. Applicable quality management systems are current Good Manufacturing Practice (cGMP) and ICH Q10, Pharmaceutical Quality System requirements.

- For medical devices, governed by the MDD, CE marking of medical devices, developed under the EC 'New Approach', allows market access throughout the EU/EEA following application of a CE mark by the manufacturer. A manufacturer of lower risk devices (Class I non-sterile, non-measuring devices) conducts a conformity assessment, makes a Declaration of Conformity themselves, places the CE mark on the product and in some cases, they may need to notify the Member State CA within their country, when placing the product on that market. For higher risk devices (Class Is, Im, IIa, IIb and III), NBs are required to verify the conformity assessment. There are a number of different conformity assessment routes available<sup>5</sup>, depending on risk classification and a manufacturer is free to choose the specific NB they wish to engage with, provided they are notified for the device type and conformity assessment procedure in question.

<sup>5</sup> [MEDDEV 2.4.1/Rev9 Guidelines relating to the application of the Council directive 93/42/EEC on Medical Devices](#)



- The NB opinion is an industry fee-for-service provision and integrally linked to the audit of the quality management system, usually ISO 13485 which includes additional responsibilities compared to cGMP for medicinal products. And, based on the risk classification of the device, a manufacturer requires formal certification. Only manufacturers of Class I devices that are non-sterile or have a non-measuring function do not require a quality management system.

Regarding the remit of Article 117 for integral DDCs, questions arose around what exactly a NB opinion would constitute, and whether it should encompass a full conformity assessment akin to current requirements for a medical device being CE marked, and thus include a review of the quality system. However, the industry's current interpretation of Article 117 suggests that only conformity of the device constituent with the relevant general safety and performance requirements as defined in Annex I of the MDR is being requested and that it does not extend to a review of the quality management system, nor does it explicitly request that certification to ISO 13485 (or similar) is required by manufacturers of integral DDCs. It is recommended that manufacturers are not mandated to obtain certification to ISO 13485 by NBs, but that they could continue to leverage the GMP quality system for medicinal products when manufacturing integral DDCs, and depending on the specific type of device, it could be complemented with relevant new documented procedures, e.g. when a device containing software is being developed.

Confirmation is requested that demonstrating conformance with Annex I and the General Safety and Performance Requirements (GSPRs) remains the defined scope of Article 117. Furthermore, confirmation is sought that manufacturers may choose to leverage their quality management systems already governing the medicinal product. However, if they choose to adopt elements of the medical device requirements of ISO 13485 into their quality management system, which is common when working towards global development for integral DDCs, they can continue to do so without the need for obtaining certification to these ISO 13485 requirements as part of the NB opinion, as would be required for demonstrating the conformity assessment for a CE marked device according to the regulations.

#### 2.4.1 Current interactions between NB, Manufacturers and CAs or EMA for integral device-drug combinations

Although there is limited experience with the cATMP procedure referred to in Section 2.2 of this reflection paper, there is experience with Notified Bodies consulting medicines CAs or EMA on ancillary medicinal substances or human blood derivatives when they are incorporated into medical devices, i.e. device-drug combination products. These products are regulated under medical devices legislation, currently MDD Rule 13 (to be replaced by MDR Rule 14 in May 2020, as stated in Annex VIII of the MDR).

Rule 13 is further supported by detailed guidance in EC MEDDEV 2.1/3 on Borderline products<sup>6</sup>, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative medical device with ancillary medicinal substances, as well as EMA procedural guidance (EMA/CHMP/578661/2010)<sup>7</sup>.

These guidance documents outline the remit of the consultation procedure, and that the CA's

<sup>6</sup> [MEDDEV 2.1/3 Borderline products, drug-delivery products and medical devices incorporating, as integral part, an ancillary medicinal substance or an ancillary human blood derivative](#)

<sup>7</sup> [EMA procedural guidance EMA/CHMP/578661/2010](#)



responsibility is to consider the assessment of the

- Medicinal substance itself (analogous to medicinal product expectations)
- Medicinal substance as incorporated into the medical device, with data provided according to eCTD format, but only sections applicable to the medicinal substance aspects of the combination product are to be provided.

Importantly, the EC guidance recognises that risk-based flexibility of data requirements is appropriate (discussed further in Section 2.5). It is recommended that a similar approach is taken to clarify the role of NBs in consultation on device components in a DDC, i.e. the remit of the NB is to consider assessment of the

- Device component constituent parts, taking into account material safety, function, performance and shelf-life, etc
- Device component as incorporated into the final medicinal product (safety and performance when used with the particular drug formulation).

## 2.5 Technical and Quality Information Requirements

Within the current regulatory landscape, guidance which covers requirements for the registration of pharmaceuticals, such as ICH M4Q<sup>8</sup>, does not sufficiently address the Module 3 considerations to ensure registration of integral DDC products. In the absence of such key guidance, it is known that location of information related to the device component, as well as specifically what level of details is submitted, is variable across companies. This was highlighted through EBE reflection paper on medicinal product incorporating a drug delivery device component, issued in January 2018.

With the implementation of Article 117, it becomes increasingly more important that the scope of the NB assessment versus that of the CA is well defined, and consideration be given so that the assessments are not unduly duplicative in nature.

With that perspective, the following recommendation for the scope of the NB assessment and the CA is being put forward by EBE and EFPIA. In addition, it is recommended that the NB opinion should comprise a report with defined, mandated sections in order to drive consistency across NB's. This report should be filed to Module 3.2.R as a record of the compliance with Annex I, and including what specific information has been assessed, would be beneficial to the medicines assessors.

### NB opinion should be formed based upon the following:

- Evidence to demonstrate compliance with the applicable or relevant requirements of Annex I – General Safety and Performance requirements
- Technical data, where applicable, as documented evidence of the requirements and robust performance of the delivery presentation, and allowing the NB to assess whether or not the device constituent will meet those critical delivery characteristics, e.g.
  - Suitability of the device constituent with the primary container of the medicinal product and device performance is fit for intended purpose
  - Shelf life of the device constituent
  - Demonstration of appropriate performance over intended product shelf-life/use-period
  - Usability and no unmitigated risks based on intended use

<sup>8</sup>[ICH M4Q Guideline](#)



#### CA review of the MAA should focus on the following:

- Medicinal product; manufacture, quality and control
  - Compatibility of the medicinal product with the primary container (i.e. leachables, stability) as well as compatibility of the medicinal product primary container of the medicinal product with the device constituent
  - Sufficient device information to understand and to assess the medicinal product e.g. critical delivery characteristics of the device constituent
- Overall expiration of the product and associated stability data that supports the proposed shelf-life
- Based on intended use of the product in the given patient population, ensure that overall safety for the patient/user has been adequately addressed
  - Primary evidence may reside and have been reviewed within the NB assessment, but should be cross-referenced/appraised within the MAA itself
- Product labelling

#### Out of scope of the review

In addition to the recommendations for what the assessments should cover, a further recommendation is that evidence of a manufacturer's quality management system under which these products are developed, whether that be under ISO 13485 or an enhanced pharmaceutical GMP based system with specific device-related aspects, is neither a requirement nor included in either assessment. Rather, these aspects are considered, as currently the case in Europe, within the remit of GMP and separate to the MAA procedure.

Labelling for integral DDCs should not have to meet the Medical Devices requirements in full as laid out in Annex I of the MDR, including aspects such as inclusion of a Unique Device Identifier (UDI). Labelling should conform primarily to the requirements for medicinal products with the relevant labelling requirements specific to device types as it relates to safety or usability, e.g. EN 60601-1 concerning electrical safety, as well as EN ISO 11608-1 concerning needle-based injection systems, that have specific clauses regarding labeling and instructions for use which are important regarding the safe use of the device.

EBE and EFPIA put forward these recommendations as important considerations as the EMA is developing the QWP/BWP guideline "*Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product*" and request that guideline itself address the requirements for integral DDCs in the context of Article 117 and the separate assessments by a NB and CA.

### 3. Conclusions and Path Forward

This paper has focused on the challenges with integrating a NB opinion as part of the overall MAA process for review and approval of integral DDCs that are regulated as medicinal products, which will be required by the implementation of Article 117 of the MDR.

In summary, the following recommendations have been put forward:

- Develop a process that ensures flexibility on when to obtain the NB opinion in the overall MAA review and approval process. Whilst having a sequential review and the opinion available in the MAA, it is recommended that a parallel review with the MAA itself should be permitted, to assist in the overall approval without significant delay. On this basis the procedure already established for

review of cATMPS when they have a device constituent is a useful and strong basis for consideration of a working process.

- Utilisation of prior knowledge of current, marketed products should be allowed, as well as permitting the leverage of platform technology and NB opinions across medicinal products. If the platform technology has previously been assessed for the same indication and population, no further NB opinion should be required, and the compatibility of the device constituent with the new medicinal product should be managed in the MAA itself.
- Furthermore, the implementation of Article 117 and expectation for approved or marketed products should be that this revised approach and a NB opinion be required when a substantial change is made to the device constituent of the integral DDC, post the effective date of the MDR, May 2020.
- Article 117 does not apply within clinical-development and that, whilst the device should show conformance to Annex I, a NB opinion would not be required. Article 117 would only be applicable to registration and lifecycle of integral DDCs.
- A risk-based approach could be implemented for cases when a NB opinion would be required. In other words, integral DDCs that incorporate well-established technologies in conjunction with low use risk medicinal products, could utilise prior knowledge and should not be required to solicit a separate NB opinion.
- The manufacturer of integral DDCs does not require a device quality management system (QMS) or certification to any associated QMS standard (e.g. ISO 13485) and could leverage the GMP quality system for medicinal products.

Global submission requirements for integral DDCs are becoming more detailed and divergent across regions. The potential for harmonization of requirements through ICH merits consideration.

This paper has put forward a proposal that industry feel is a suitable approach with regards to adopting a process and clarifying when specifically, NB engagement and a formal opinion are required, recognising that a risk-based approach could in some instances be adopted. Applicants have a strong view that being able to utilise prior knowledge and NB opinions for platform or well-established technologies is important with regards to flexibility and being able to meet these new requirements, without there being an impact or delay to medicines reaching the markets and, more importantly, not compromising safety to patients. There are many questions being raised by industry in various forums regarding the practicalities of how this will work. This paper puts forward recommendations and proposals, drawing on precedents and current guidance already established between the CAs for medicinal products and NBs, with some enhancements that could be readily adopted for integral DDCs.



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## Annex 1: Potential adaptation of the guidance “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” to be applicable to Article 117 of Medical Device Regulation (EU) 2017/745

The following text has taken the headings of the EMA/CAT procedural guidance into consideration and makes a proposal, including explanatory comments, on how EBE and EFPIA consider the EMA guidance may be adapted and utilised as a basis for the procedure to solicit the NB opinion required for integral drug-device combination products, as required by Article 117 of the MDR. The recommendations put forward by EBE and EFPIA are clearly identified and placed in a green box within each section.

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## 1. Introduction

The current EMA/CAT 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<sup>9</sup> is considered in the context of Article 117 of the new Medical Device Regulation, EU 2017/745<sup>10</sup>.

The cATMP procedural guidance was developed following collaboration between EMA/CAT, Notified Bodies Operation Group (Medical Device Agencies), TEAM-NB (Notified Bodies representative group) and the European Commission<sup>11</sup>.

Also taken into consideration is the procedure for notified body consultations according to the current Rule 13 of the medical devices directive MDD (Rule 14 of the Medical Device Regulation applicable from 26 May 2020) and outlined in European Commission guidance MEDDEV 2.1/3 on Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative<sup>12</sup>.

**EBE-EFPIA comment:** It is envisioned that the current EMA/CAT cATMP procedural guidance could be readily adapted to DDCs, within the context of developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product.

## 2. Scope

The proposed scope of guidance would be Integral medical devices, initial submission for NB opinion.

### Out of scope

As per cATMP guidance and the CHMP Concept paper, the guidance would only consider the initial application as referred to in Art 117; further guidance on post-approval procedures could be developed at a later stage, taking account other related developments.

**EBE-EFPIA comment:** This section could be adapted to the scope outlined above.

## 4. Specific considerations

### 4.1 Applicant

Consistent with the cATMP procedure,

- The Applicant of a drug-device combination product regulated as a medicinal product would be the MAH responsible for submitting a Marketing Authorisation Application (MAA) for the medicinal product to a national Competent Authority or to the European Medicines Agency (EMA).
- The Applicant would be responsible for any fee payment direct to the NB for the work performed by the NB.
- It is envisioned that any interaction between the EMA/CAT and the NB(s) will be done in conjunction with, or via, the Applicant.

<sup>9</sup> [EC No. 1394/2007](#)

<sup>10</sup> [EU 2017/745](#).

<sup>11</sup> [PROCEDURAL ADVICE ON THE EVALUATION OF ADVANCED THERAPY MEDICINAL PRODUCT IN ACCORDANCE WITH ARTICLE 8 OF REGULATION \(EC\) NO 1394/2007](#)

<sup>12</sup> [MEDDEV 2.1/3](#)



## 4.2 Data requirements

Similarly to the cATMP guidance, it may be expected that evidence of conformity with general safety and performance requirements of the MDR could follow IMDRF guidelines, currently '2008 Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)': <http://www.imdrf.org/docs/ghrf/final/sg1/technical-docs/ghrf-sg1-n011-2008-principles-safety-performance-medical-devices-080221.pdf>, but similar non-STED formats could also be deemed acceptable, including a checklist to demonstrate how the general safety and performance requirements are met.

It is proposed that there should be some flexibility in the amount of supporting data provided to demonstrate conformity with the GSPRs depending on the type of integral device, whether it has been reviewed previously and the risk-profile of the overall DDC, taking into account the indication and intended use. This is consistent with ICH Q9 Quality Risk Management and the EC MEDDEV Guidance MEDDEV 2.1/3 on devices incorporating ancillary medicinal substances, Section C3 'Documentation to be provided by the Notified Body'.

### Notified Body Opinion report

The cATMP guidance proposes that NBs would ideally use a standardised format based on principals of the NBOG guidance on Design – dossier examination and Report Content<sup>13</sup>.

However, it may also be useful to adapt the format further, in order to provide relevant information to medicinal product assessors, regarding

- what data has been reviewed,
- how it has been demonstrated that the GSPRs have been met
- any particular critical features that would be important to focus on in the case of changes to the DDC.

Specifically, the report should look to include:

- Unique document number (to enable referencing)
- Name of NB
- Name of applicant
- Product name
- Design version (to support later change and notification management)
- Scope of assessment
- Criteria against which the assessment has been made (also see opinion criteria, below) – typically those relevant safety and performance requirements of Medical Device Regulation (EU) 2017/745, Annex 1
- Clear statement of opinion outcome – e.g., “Positive”, “Granted”, or similar
- Date of issue
- Expiry date (if ultimately deemed applicable)
- Name of individuals performing the opinion assessment
- Signature of responsible NB representative

It should be clear there no CE-mark can be applied to the product and on this basis, it may be beneficial to delineate clearly between the look of an NB's CE-marking certification and any Art.117 opinion report/document.

<sup>13</sup> [NBOG BPG 2009-1 Guidance on Design-Dossier Examination and Report Content](#)



Furthermore, it is suggested that the use of a standardised format for provision of information from the notified body to the CA may facilitate efficiency and consistency of review. It is expected that any reports or evaluations conducted by the NB will be confidential and only shared with the Applicant and CAs.

### Location of device information in the MAA

The cATMP guidance instructs that information on the device part of the combined ATMP and the NB assessment, if available, should be submitted in Module 3, section 3.2.R of the CTD under the “medical device” section.

This provision of a distinct module of information pertaining to the device component is analogous to the procedure for medical devices incorporating ancillary medicinal substances, where a distinct section on the medicinal substance component is provided and available for review by both notified bodies and medicines CAs, including detail on

- the ancillary medicinal substance alone
- the ancillary medicinal substance as incorporated into the device

This could be adapted to provision of

- a common Technical file for the device(s) alone, which could be a file made available by third party device manufacturers, where applicable and used for multiple products
- it may be useful to consider including in this general TF results of testing safety and performance of device components with a range of products of different viscosities, pH etc
- a specific file for safety and performance requirements of the device incorporated into the medicinal product or into a medicinal product ‘system’ consisting of multiple device components. This specific file may include specifications for device components that are deemed critical for the individual DDC ‘system’ and supported by confirmation that appropriate supplier agreements are in place

**EBE-EFPIA Comment:** The original EBE Reflection paper suggested a potential flexible approach to MAA data requirements, which it is hoped will be taken into account in development of EMA guidance. The use of a standardised format for the NB opinion may facilitate efficiency and consistency of review by the EMA/CA. NB opinions on general compliance with ERs/GSPRs for device components used with a range of medicinal product formulations may be useful to consider – these could be obtained and offered to customers by device manufacturers; for higher risk/more complex DDC products a NB opinion on the finished product as intended for market would be required.

### **4.3 Consultation of a Notified Body**

This section envisions that, if an opinion from the NB is not provided, CAT will decide whether a consultation is required.

The original text relating to Article 117 foresaw a similar process for DDCs, with the option for medicines CAs to decide, on the advice of their experts for medical devices, that an NB opinion was not necessary. However, the text was subsequently amended, to withdraw this option.

Thus, it is understood that, if an opinion from the NB is not provided at the time of submission, and if the device by itself would require review by a NB for CE marking, then such an opinion will be requested by EMA/CAs.

The purpose of the consultation, as outlined in the cATMP guidance is to deliver an opinion on compliance with the general safety and performance of the device when used for the specific intended purpose with the particular ATMP/medicinal product.

**EBE-EFPIA comment:** to note in this section, the cATMP guidance strongly recommends a pre-submission meeting at the EMA. Considering the expected much greater volume of DDCs in development compared to



cATMPs, this is not likely to be possible for all DDCs. Thus, clear and practical guidance on the procedure and data requirements will be immensely helpful for all involved. It is suggested that this could be a useful topic for a regulator-industry workshop to be held in early 2019.

#### 4.4 Identification of a Notified Body

It is required that the Applicant

- identify an NB in the MAA form (section 2.2.4)
- should ensure the identified NB is appropriately notified for assessment of the equivalent type of medical device under the MDR (i.e. Class Im, Is, IIa, IIb or III)

**EBE-EFPIA comment:** It is expected that both of these requirements will be applicable to DDCs, thus it will be helpful to include an updated link to the NANDO (New Approach Notified and Designated Organisations) website.

This would also be a useful topic for discussion at a workshop dedicated to this new procedure, to include notified bodies intending to offer this service.

#### 4.5 Access to data concerning the medical device component and confidentiality

This section clarifies that the EMA/CAT can request at any time during the evaluation procedure, the Applicant to provide any information related to the device component. The Applicant is responsible for the content and timely submission of such information and any clarifications requested.

The Applicant should also ensure necessary agreements are in place between themselves and third party suppliers for access to any data relating to the medical device that may be requested in the procedure and that *“These agreements should include provisions to allow the exchange of information on a continuous basis so that the Applicant is fully aware of any changes of the medical device component or safety issues related to the device which may have an impact on the combined [product] Benefit Risk assessment.”*

It is also mentioned that post-approval, the EPAR (European Public Assessment Report) published by EMA may include some information regarding the device part, but as per normal procedure, the Applicant will be requested to comment on published information prior to publication.

**EBE-EFPIA comment:** Appropriate supplier agreements would already be in place, but it may be useful to clarify how exactly confidential information from the device supplier will be provided to the NB/EMA/CA. Maybe the NB could comment on whether appropriate supplier specifications are in place to control critical device component functionality?

## 5 Procedure to consult a Notified Body

### 5.1 Timetable for the consultation of a NB when the results of the assessment of the medical device(s) have not been provided

EMA encourages cATMP Applicants to provide the results of assessment from the NB in the MAA but allows for the option to provide an NB opinion later in the procedure, which may be useful for the DDC procedure.

Therefore, this section could be adapted to DDCs as follows:

Day 1 It could be identified at validation stage that an NB opinion has not yet been provided but will be provided by Day 80/120 of the procedure. The proposed NB should be identified and verified for suitability against the NANDO website list

Day 80 If,

- an NB opinion was not provided, or

- there are questions remaining about the device after the review of the NB opinion
- an explicit list of questions (LoQ) will be provided to the NB via the EMA Project Team Leader (PTL),
- the Applicant is informed of the LoQ, and when the NB response is sent back to EMA
- Note: in the cATMP guidance, there is also the possibility that a different NB may be sought - clarification on why this was envisioned would be useful.

Day 120 If the responses from the NB are not provided by Day 120, the request is added to the LoQ and the clock stopped until a response is received from the NB through the Applicant.

If additional questions are identified following the receipt of the NB's responses, a third (and exceptional) consultation with the NB may take place.

Day 170 If the responses from the NB are not provided by Day 170, the request is added to the List of Outstanding Issues (LoOI), and the clock is stopped until an appropriate response is received from the NB.

## 5.2 *Timetable for the consultation of a Notify Body when the results of the assessment of the medical device(s) have been provided*

This timetable is envisioned for when it is considered necessary to consult an NB when additional information is required on the medical device part of the cATMP/DDC.

Day 80 Additional information may be requested by the NB in the LoQ, sent to the NB in collaboration with the Applicant.

Day 120 If responses are not provided by the NB by Day 120, the request is added to the LoQ; or if additional questions are identified following the receipt of the NB's response, a second consultation with the NB may take place.

Day 170 As Day 170 above.

**EBE-EFPIA comment:** The possibility of submission of the NB procedure at a later stage in the procedure would be welcomed, taking into account that the final presentation and associated labelling, both of which will be necessary for NB review, may not be available until close to submission date. Submission by day 120 is suggested.

Regarding the procedures outlined for cATMPs, there are some concerns around the number of DDC submissions requiring NB consultation and resource issues with engaging notified bodies.

Again, in order to minimise the number of rounds of questions at each stage of the MAA procedure and facilitate efficiency, clear and practical guidance on the data requirements and content of the NB opinion would be helpful.

