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A Notified Body's perspective on the requirements for new interactions with Notified Bodies under the MDR with respect to combination products

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Short glossary

- Article 117 of Regulation (EU) 2017/745[1] on medical devices (the MDR) describes the requirements for the device part of drug/device combinations regulated as medicines.
- Rule 13 of Directive 93/42/EEC (the MDD) specifies the requirements for medical devices containing ancillary medicinal substances under the MDD.
- Rule 14 of the MDR sets out the requirements for medical devices containing ancillary medicinal substances under the MDR.
- Rule 21 of the MDR contains additional rules for medical devices containing substances.
- Annex I to the MDR lists the General Safety and Performance Requirements that medical devices should follow as part of conformity assessment.
- Annex II to the MDR describes the documentation requirements for MDR applications.

Introduction

The term 'combination products' could apply to many medical devices and medicinal products; this article will discuss three different types of combination products:

- **Drug/Device Combinations (DDCs)**. 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, this is a medicinal product regulated under the Medicinal Products Directive (2001/83/EC)[2,3]. The medicinal product has the principal action and the device has a supportive role, often aiding delivery. Examples include pre-filled syringes, auto injector pens and pressurised metered dose inhalers.
- **Device/drug combinations**. In this case, the device has the principal mode of action and the medicinal substance has an ancillary action. Examples include drug eluting stents or wound dressings with anti-microbial agents.
- **Devices containing substances**. In this case, the substances are not medicinal products but may be absorbed by the human body. Examples include wound irrigation solutions or paraffin dressings.

Each type of combination product has its own regulatory path and regulatory challenges. The MDR, which comes into force on 26 May 2021, introduces a new requirement under Article 117 for DDCs. A Declaration of Conformity or an Opinion from a European Notified Body (NB) on conformity of the device part of the combination product needs to be included in the Marketing Authorisation Application (MAA). For device/drug combinations, the requirements under the MDR are similar to the MDD. However, slight changes to the wording (e.g. removal of the phrase 'liability to act') and changes to definitions in associated guidance documents may mean more devices fall under Rule 14 of the MDR compared to Rule 13 of the MDD. For devices containing substances, a new rule (Rule 21) has been introduced. This rule emphasises the requirements for manufacturers to demonstrate that these types of combination products are safe, in addition to all other conformity activities. This article will look at each of these requirements in turn and discuss the implementation from the perspective of a European NB.

DDCs and Article 117

Article 117 is only two paragraphs long[1] but introduces significant new requirements on DDC manufacturers applying for product licences in Europe. The requirement to demonstrate conformity of the device part of a DDC was, in fact, already there for pre-MDR DDCs as manufacturers were expected to demonstrate conformity to the Essential Requirements of the MDD. This was via self-declaration or CE certification; alternatively, compliance was assessed by the Competent Authorities as part of the assessment of the whole DDC. Article 117 of the MDR requires manufacturers to demonstrate that the device part of a DDC conforms to the General Safety and Performance Requirements (GSPRs) of Annex I to the MDR by using a CE certified product, or by self-declaration for applicable devices, or the provision of an NB Opinion (NBOp). This article focuses on the latter route.

DDCs are becoming more complex as technology progresses and the device parts can include software, applications or other active components (i.e. dependant on an energy source). As devices become more complex, the skill sets needed to evaluate their safety and performance grow, hence the introduction of NBs into the process. NBs are independent organisations designated to conduct conformity assessment on behalf of the European Union, in this case for medical devices before being placed on the market[4]. The designation process covers many different device types, grouped into different codes, and a list of NBs designated under the MDR, as well as the codes they have been designated to, can be found on the NANDO website[5]. When choosing an NB, it is important a DDC manufacturer checks the NB has the appropriate competencies for its device(s).

The introduction of Article 117 means part of the review that was previously covered by the Competent Authority is now assessed by the NB. This has led to some concern within the

pharmaceutical industry that there is the potential for duplication of review[6]. However, NBs are looking at conformity of the device part to Annex I to the MDR whilst the Competent Authority retains its role of assessing conformity of the medicinal product to Directive 2001/83/EC. To ensure the implementation of Article 117 does not unduly increase the regulatory burden on manufacturers, the key stakeholders, including regulators and industry groups, have been collaborating. In particular, stakeholders have provided comments on the European Medicines Agency's Quality Working Party/Biologics Working Party guidance on quality requirements for DDCs[7]. Team-NB, the industry body for NBs, has been working to ensure the output of the NBOp is not only suitable to confirm conformity to the GSPRs but also detailed enough to (hopefully) prevent re-review by the Competent Authorities.

Whilst this is a new process for pharmaceutical manufacturers, conformity assessment is not a new process for NBs, who will be aware of the standards and solutions that can be applied for the relevant devices. It is up to the MAA manufacturer to provide evidence of conformity to the relevant GSPRs during review. Which GSPRs are relevant is arguably subjective; however, the following guiding principles should be considered:

- Data should be provided in Technical Documentation format. Annex II to the MDR describes the elements (contents) of the Technical Documentation for medical devices and is therefore a good place to start. Several NBs also provide guidance on technical documentation[8].
- Some GSPRs are more obviously relevant, or not, for example those pertaining to active devices.
- GSPRs for sterility or stability, for example, will have a lot of overlap with the Competent Authority review. It is important to remember that the NBOp is on the device part and the Competent Authority review is on the medicinal product.
- If the MAA holder judges a GSPR to be not relevant, justification should be provided rather than just entering 'not applicable'.
- The clinical data on the medicinal product is part of the Competent Authority review. The NBOp review will, again, be limited to the device part (e.g. demonstrating the device can deliver the dose as claimed in the correct patient group). This can take the form of *in vitro* or human factor studies. If specific clinical claims are made relevant to the device part, then additional clinical data may be required.
- The final DDC is licensed as a medicinal product; therefore, the labelling needs to conform to the Medicinal Product Directive rather than the MDR[3,7]. Where labelling or packaging solutions have been implemented as part of risk mitigation, these aspects may form part of the NB review.

Experience with issuing an NBOp shows that DDC manufacturers can use a range of evidence to demonstrate conformity to the GSPRs. This can include data from literature, suppliers and sub-contractors as well as in-house data. A well-structured file, following the format suggested in Annex II to the MDR containing high level overviews as well as sufficient detail to demonstrate compliance will help to facilitate the review.

For some simpler DDCs, the concept of platforms has been raised. In general, the term 'platform' is used in this context to describe a drug delivery device that can be used to deliver different medicinal substances under separate marketing authorisations. Conceptually, if the device part is the same, or very similar, the data supporting most of the GSPRs is the same and therefore should not need to be reviewed each time. Of course, there are nuances with each application, and it is these that need to be covered by a platform approach or by the NB review. One of the outstanding questions for stakeholders to agree on is an appropriate legal approach to this issue. Answers were expected after the European Medicines Agency meeting at the end of March 2020, but this meeting has been postponed due to the COVID-19 outbreak. Dialogue is therefore ongoing.

The requirements under Article 117 apply to new MAA applications submitted after 26 May 2021. They also apply to any variation applications after this date, if there are substantial changes to the medical device component. This means legacy medicinal products, for which an NBOp was previously not required, will need an NBOp as part of the variation process if this type of change is being made. Changes to the device component are considered substantial if the changes affect the performance or safety characteristics of the device[3]. This is a subjective assessment to be made by the manufacturer and will be reviewed by the Competent Authority during the variation procedure. NBs, as they are not able to act as consultants, will not be able to advise on whether a change requires an NBOp or not. Where the change does require an NBOp, the NB will likely review the GSPRs affected by the change. Again, clarification on this point was expected after the European Medicines Agency meeting at the end of March 2020, which has now been postponed.

Device/drug combinations and Rule 14

The process under the MDR for devices containing ancillary medicinal substances is largely unchanged, although the definition for ancillary substance (as covered by Rule 14) no longer contains the phrase 'liable to act'. The precise consequences of this change are still to be determined. Some industry groups argue it has been removed as it is redundant; if a component has a medicinal ancillary action it must therefore be liable to act. Other groups interpret the change as meaning any device containing a pharmacological, metabolic or immunological acting agent will now fall into Class III, regardless of the amount. MEDDEV 2.1/3[9], the borderline and ancillary medicinal products guideline, is currently

being updated, as is the classification guideline MEDDEV 2.4/1[10]. It is expected that these updated guidelines will clarify how Rule 14 is to be interpreted, as well as definitions of what constitutes pharmacological, metabolic or immunological action.

If a classification is not clear from the guidelines on Rule 14 and if the manufacturer and NB do not agree, there is a new classification dispute process in the MDR (Article 51(2)). It is important to note this procedure cannot be performed out of context; it must be as part of the conformity assessment activities of a device. This is to ensure NBs are not acting as classification consultants; their role is to assess the rules are being applied correctly. Under the new procedure, classification disputes will be escalated to the Competent Authority of the manufacturer and the Competent Authority of the NB for arbitration. Once agreement has been reached then the Competent Authority of the manufacturer will notify the Medical Device Coordination Group (MDCG) and the European Commission. In this way, it is expected there will be more consistency in classification for borderline cases.

The consultation procedure for ancillary medicinal substances has not changed between the MDD and MDR. All Class III Rule 14 devices will be expected to have a medicinal dossier, in Common Technical Documentation (CTD) format, on the ancillary medicinal substance. The NB then consults a Competent Authority on the usefulness, risk and benefit of the medicine in the device. For legacy products, which had a consultation under the MDD, this may involve a repeat consultation or a gap analysis by the Competent Authority before positive advice is provided allowing certification under the MDR.

One area where there may be a change with respect to the consultations is as a result of Brexit. Manufacturers who have a consultation with the UK Medicines and Healthcare products Regulatory Agency (MHRA) under the MDD will need to 'transfer' their consultations to a European Competent Authority. At the time of writing, there is no European process for this as transfer of consultations was not envisaged under the MDD or MDR. Individual Competent Authorities are developing processes, which may involve a review of MHRA reports and transfer or a re-consultation. NBs will need to guide manufacturers through this process as the consultation is between the Competent Authority and the NB.

Devices composed of substances and Rule 21

This is a new rule for the MDR and introduces new requirements on manufacturers of these devices and on the NBs. The purpose of Rule 21 is to ensure the safety of a substance introduced into the human body is considered by analogy to the principles of Absorption, Distribution, Metabolism and Excretion (ADME) outlined in Directive 2001/83/EC. Rule 21 (*below*) classifies devices with substances according to risk:

'Devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body are classified as:

- class III if they, or their products of metabolism, are systemically absorbed by the human body in order to achieve the intended purpose;
- class III if they achieve their intended purpose in the stomach or lower gastrointestinal tract and they, or their products of metabolism, are systemically absorbed by the human body;
- class IIa if they are applied to the skin or if they are applied in the nasal or oral cavity as far as the pharynx, and achieve their intended purpose on those cavities; and
- class IIb in all other cases.'

For all Rule 21 devices, the technical documentation as described in Annex II to the MDR should include detailed information on the test design, complete test or study protocols, methods of data analysis, and data summaries and test conclusions. Studies should be conducted in relation to:

- ADME;
- possible interactions of those substances, or of their products of metabolism in the human body, with other devices, medicinal products or other substances, considering the target population, and its associated medical conditions;
- local tolerance;
- toxicity.

In addition to the requirements described above for Class III Rule 21 devices, if they or their products of metabolism are systemically absorbed by the human body in order to achieve the intended purpose, there is a new Competent Authority consultation procedure. As this is a new process, there is little guidance from the Competent Authorities on how it will run but it is expected the data described above will be provided to the Competent Authority for review. As stated in the MDR, the opinion of the Competent Authority consulted shall be drawn up within 150 days of receipt of all the necessary documentation.

Conclusions

The MDR has brought in some new requirements for the various combination products described in this article. For NBs, some of these requirements are brand new, requiring close collaboration with other regulators to ensure correct and consistent implementation. Other MDR requirements are similar to those under the MDD. The European Commission is developing further guidance to ensure

fair and consistent application of these requirements across different NBs and Competent Authorities. Although there are challenges with a developing regulatory landscape, which is to be expected, NBs are well placed to ensure patient safety through conformity assessment.

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