THE NEW EU MEDICAL DEVICE REGULATIONS – IMPLICATIONS FOR INHALATION DEVICES

In this article, Mary Hutchens, Regulatory Affairs, Coalesce Product Development, gives an overview of some of the changes wrought by last year's introduction of the new EU Medical Device Regulation, with a specific view to its effect on inhalation devices and inhaled medical products.

INTRODUCTION

On May 5th 2017, the new Medical Device Regulations (MDR) were published in the *Official Journal of the European Union*. The MDR will replace the Medical Device Directive (MDD) and the Active Implantable Medical Devices Directive (AIMDD).

The MDR represents a major change in the regulation of medical devices in the EU and was prompted by well-publicised incidents involving breast implants and hip replacements. The development of the MDR has taken nearly a decade, with the EU Commission launching the consultation process in 2008. The new MDR is intended to provide greater scrutiny of medical devices at all stages of the product lifecycle and has implications for all parts of the medical device industry. The promotion from directive to regulation ensures harmonisation across member states by preventing alterations in local implementations.

The MDR will have a broader scope than the preceding directives, imposing greater supervision of Notified Bodies, while at the same time requiring Notified Bodies to undertake greater scrutiny of device manufacturers. Unlike its predecessors, it encompasses the whole lifecycle of a medical device and has a significant emphasis on safety, which is now mentioned 290 times. There are changes in classifications, better traceability via an improved European Medical Device Database (EUDAMED), unique device identifiers (UDIs), and more extensive requirements and scrutiny for clinical evidence and postmarket vigilance. Furthermore, there is a new requirement for manufacturers and authorised representatives to appoint a suitably qualified person to be responsible for regulatory compliance.

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Outlined hereafter are some of the key changes in medical device regulation resulting from the publication of the MDR and the implications for inhalation devices and inhaled medicinal products.

MEDICAL DEVICE OR MEDICINAL PRODUCT?

It is important to note that in the EU not all inhalers are regulated as medical devices. The Medical Device Regulation, as for its predecessor MDD, makes provision for those products that are intended to be "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" to be regulated as Medicinal Products under the Medicinal Product Directive (MPD), with the caveat that the relevant Annex 1 requirements (General Safety and Performance Requirements for MDR, Essential Requirements for MDD) are fulfilled. Such devices are not required to carry a CE Mark. Examples include certain pressurised metered dose inhalers (pMDIs) and multi-dose dry powder inhalers (DPIs).

The MDR refers to this approach in Article 10. In addition, a new requirement has been incorporated as Article 117, to amend the MPD. This article requires the involvement of a suitable Notified Body to grant an opinion on the fulfilment of the Annex I requirements, whereas historically under the MDD this could be stated by the Marketing Authorisation Application (MAA) applicant themselves, whilst holding supporting evidence.

Mary Hutchens
Regulatory Affairs
T: +44 1223 421855
E: mary@coalesce.co.uk

Coalesce Product Development
St John's Innovation Centre
Cowley Road
Cambridge
CB4 0WS
United Kingdom

www.coalesce.co.uk

Reusable devices, devices that can be used to deliver different medicaments or those devices that are not fully integrated with the drug product are regulated as medical devices, therefore they need to fulfil the full MDR and carry a CE mark. Typical examples are capsule DPIs and nebulisers. Accessories to medical devices, for example pMDI spacers, are also considered medical devices.

This article will concentrate on those inhalation devices that fall under the MDR and which require a CE Mark. The implications of the new regulations for manufacturers of such devices will be discussed.

NEW CLASSIFICATIONS

Under the MDD, devices that are non-active, that is to say devices that do not rely on a source of power other than that generated by the human body or gravity, were classified under Annex IX, rule 5, as low risk (Class I) devices. A manufacturer could formally self-certify a Class I device and apply the CE mark with no requirement for a Notified Body conformity assessment. An example would be a reusable capsule inhaler.

The MDR now incorporates 22 classification rules (including five new rules) in Annex VIII. The classification groupings are set out in Table 1.

Rule 20, will have significant implications for many CE marked inhalation devices, since it states:

"All invasive devices with respect to body orifices, other than surgically invasive devices, which are intended to administer medicinal products by inhalation are classified as Class IIa, unless their mode of action has an essential impact on the efficacy and safety of the administered medicinal product or they are intended to treat life-threatening conditions, in which case they are classified as Class IIb."

Inhalers previously classified as low risk Class I devices have now been moved into a higher risk classification (Class IIa or IIb) and will require conformity assessment by a Notified Body, therefore a manufacturer will no longer be permitted to self-certify and apply the CE Mark themselves. This has many implications, some of which will be highlighted through the rest of this article.

Rules 1-4	Non-invasive devices
Rules 5-8	Invasive Devices
Rules 9-13	Active Devices
Rules 14-22	Special Rules

Table 1: MDR rules classifications.

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The Competent Authorities for Medical Devices (CAMD) has established an implementation taskforce and a roadmap has been created to guide their activities during the transition period of the MDR. Provision of "information and guidance on classification for medical devices (changes on classification rules)" carries medium priority, and guidance is expected to emerge in the coming months. Unfortunately, one key area of "guidance for combination products around appropriate level of interaction with relevant authorities" has been considered low priority.

The requirements are set out in Chapter V, Section 2, Article 52, of the MDR and the applicable procedures are outlined in Annexes IX–XI. Similar to the MDD, the MDR requires that a manufacturer has a quality management system (QMS) in

BOX 1: COMMON ABBREVIATIONS IN EU MEDICAL DEVICE REGULATION

Abbreviation	Definition
AIMDD	Active Implantable Medical Devices Directive
CAMD	Competent Authorities for Medical Devices
CEAR	Clinical Evaluation Assessment Report
CER	Clinical Evaluation Report
CS	Common Specification
ER	Essential Requirement
EUDAMED	European Medical Device Database
GSPR	General Safety & Performance Requirements
MDD	Medical Device Directive
MDR	Medical Device Regulation
MPD	Medicinal Products Directive
PMCF	Post Market Clinical Follow-up
PSUR	Periodic Safety Update Report
QMS	Quality Management System
SSCP	Summary of Safety & Clinical Performance
UDI	Unique Device Identifier

place. It is important to note that EN ISO 13485:2016 includes direct references to incorporating regulatory requirements into the QMS and is compatible with requirements of the MDR. The assessment involves auditing the QMS, the technical documentation supporting the device and an unannounced audit every five years for both Class IIa and Class IIb devices. These audits may also extend to critical subcontractors and crucial suppliers. This may affect the contractual relationships between medical device developers and suppliers. The classification and conformity criteria are based on risk, as shown in Figure 1.

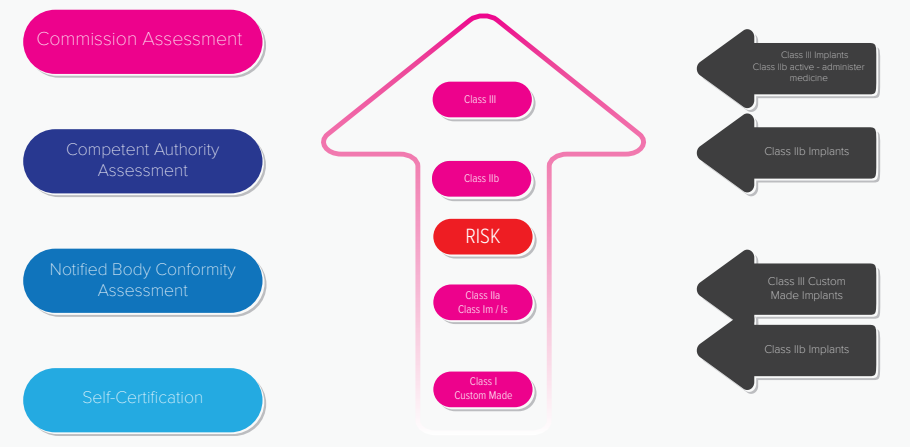

Figure 1: Classification and conformity criteria.

CLINICAL REQUIREMENTS AND POST MARKET CLINICAL FOLLOW-UP

Clinical Evaluations and Investigations are covered in Chapter VI (Article 61) of the MDR and Annexes XIV and XV (Clinical Evaluations and Clinical Investigations, respectively). The MDR enhances the requirements currently outlined in the MDD and now defines the term "Clinical Evaluation".

Under the MDD there was a requirement for a manufacturer to produce a Clinical Evaluation Report (CER). Under the MDR, this CER must, in addition to a review of the clinical data available, include the results of clinical investigations, and must also refer to conclusions on the safety and performance of the device and a risk/benefit analysis.

The CER should also now be considered a "live" document, and thus should remain active throughout the lifetime of the device, with regular reviews and updates based on postmarket clinical follow-up (PMCF) and postmarket surveillance (PMS).

Not only have there been changes to the requirements, but also to the scrutiny of clinical evaluations and investigations. The MDR sets out a clear requirement for scrutiny of the CER by a Notified Body, and for Notified Bodies to produce a clinical evaluation assessment report (CEAR) for a device as part of a conformity assessment. The manufacturer will typically need to generate and provide more in-depth clinical data to prove their safety and performance claims and equivalency standards will be tighter.

The MDR introduces new mandatory requirements relating to post-market clinical follow-up (PMCF). A PMCF must be prepared as part of the overall clinical evaluation and must form part of the technical documentation of the device. It will also be reviewed as part of the conformity assessment by a Notified Body.

The requirements for a PMCF are set out in Annex XIV, Part B of the MDR. The PMCF is a continuous process that updates the clinical evaluation. When conducting a PMCF study for a CE marked device, the purpose of the data generated is to:

- Confirm the safety and performance of the device during its lifetime.
- Identify previously unknown side effects and monitor identified side effects and contra-indications.
- Identify and analyse emergent risks.
- Identify possible systemic misuse or off-label misuse.

POST-MARKET SURVEILLANCE

In the MDR, Chapter VII is dedicated to post-market surveillance, vigilance and market surveillance, in addition to sections 1.1 and 1.2 of Annex III. A postmarket surveillance system must be prepared for each product as part of the QMS. Postmarket surveillance activities must include a PMS plan, a PMS report and periodic safety update reports (PSUR). The requirements for a PSUR are set out in Article 86 of the MDR.

Class III, Class IIa and Class IIb devices will require PSURs, which must be updated annually for Class III and Class IIb devices. For Class IIb devices the PSURs should be updated when necessary and at least every two years. Accidents, injuries and deaths will need to be reported, and patients will have access to more safety-related information. Non-fatal incident reporting has been relaxed from 15 days to 30 days.

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

The MDR replaces the Essential Requirements (ERs) of the MDD and AIMDD, with General Safety and Performance Requirements (GPSRs). The general principles of the ERs remain in the GSPRs, although there are more GSPRs, partly due to the combining of the two directives (Figure 2).

Annex I of the MDR sets out the GSPRs in three chapters:

Figure 2: MDR General Safety & Performance Requirements.

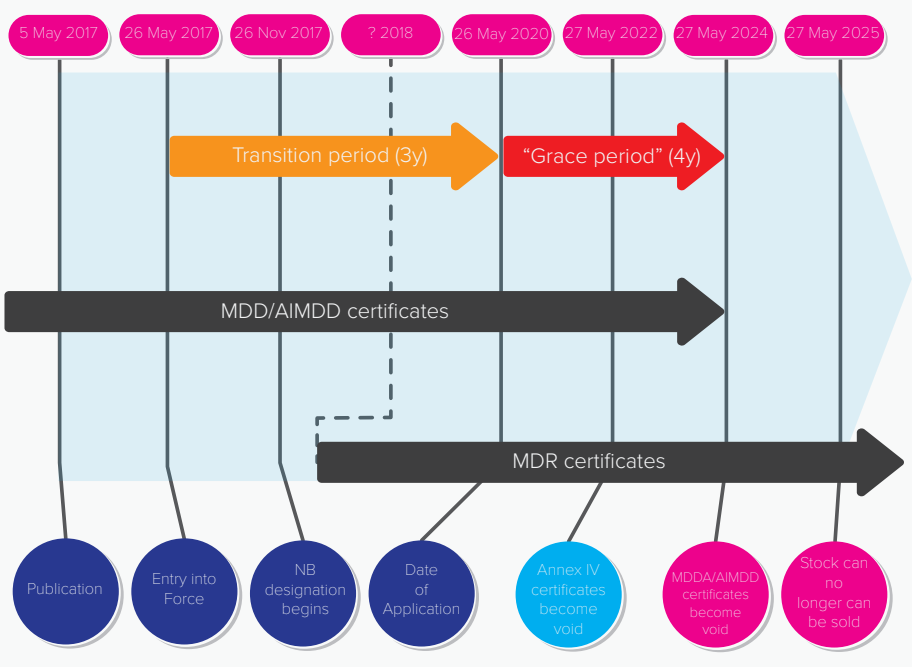

Figure 3: MDR timeline.

1. General Requirements (GSPRs 1-9)
2. Design and Manufacture (GSPRs 10-22)
3. Information Supplied with the Device (GSPR 23).

When compared with the ER lists, the new GSPRs have some numbering and organisational changes, expanded areas on risk and labelling, and some topics have been moved into annexes. Manufacturers with existing CE marked devices will need to conduct a gap analysis comparing the ER of the MDD with the GSPRs of the MDR to ascertain what additional data will be required.

PERSON RESPONSIBLE FOR REGULATORY COMPLIANCE

Article 15 of the MDR requires that a manufacturer must have a person responsible for regulatory compliance available within their organisation. However, given that many device manufacturers are small enterprises where having a suitably qualified individual within the organisation would be difficult, the MDR allows micro and small enterprises to have the person "permanently and continuously at their disposal". A similar arrangement is allowed for EU representatives.

The individual must have a degree in a scientific or technical discipline and at least one year's experience in medical device regulatory affairs (RA) or QMS, or at least four years' professional experience in medical device RA or QMS (two years for custom-made devices).

UDI AND EUDAMED

A UDI is used to help track devices through the supply chain and will be required on labelling. In Article 27, a definition of the UDI is given. The UDI comprises:

- a UDI device identifier (UDI-DI) specific to a manufacturer
- a UDI production identifier (UDI-PI), the unit of device production.

The basic UDI-DI is the primary identifier of the device and will be stored in EUDAMED and will be referenced on labels and declarations of conformity. EUDAMED will allow access to the information stored about the device.

TRANSITION TIMELINES

The MDR came into force on May 26th 2017, following publication in the *Official Journal of the European Union* on May 5th 2017. There is a three-year transition period during which the MDD and AIMDD will still operate, meaning that devices will still be certified under the directives. Certificates granted during this period will still be valid under a "grace" period for four years. However, after this period, ending on May 26th 2024, the certificates will become void and the devices will have to conform to the MDR. Devices receiving certification after May 26th 2020 will need to conform to the MDR (Figure 3). There will be no "grandfathering" of pre-MDR devices. This means that at the end of the transition process, all CE marked devices will have to be compliant with the MDR.

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ABOUT THE COMPANY

Coalesce Product Development develops medical and drug delivery devices for global markets. The company has ISO 13485 certification for the design and development of medical devices. Coalesce's experienced team encompasses mechanical engineering, electronics, analytical science, industrial design, human factors, project management, regulatory affairs, and quality assurance. Its facility in Cambridge, UK, is equipped with a state-of-the-art design centre, an analytical science laboratory, an ISO Class 7 cleanroom, and an engineering development and testing suite.

ABOUT THE AUTHOR

Mary Hutchens is in charge of Regulatory Affairs at Coalesce Product Development. She graduated as a biologist and began her career working in the agrochemical industry. Having specialised in regulatory affairs, she moved into the medical device field in 2000. She has experience in the regulation of medical devices in a variety of global markets, particularly in the EU and US.

Ms Hutchens has worked for companies ranging from large multinationals to small start-ups. She has developed regulatory strategies for new products, encompassing the creation of Design History Files and compilation of Technical Files to satisfy essential requirements. She has also commissioned clinical trials for innovative products.