Your partner in progress

A Notified Body experience

An overview of the impact of the MDR (EU) 2017/745

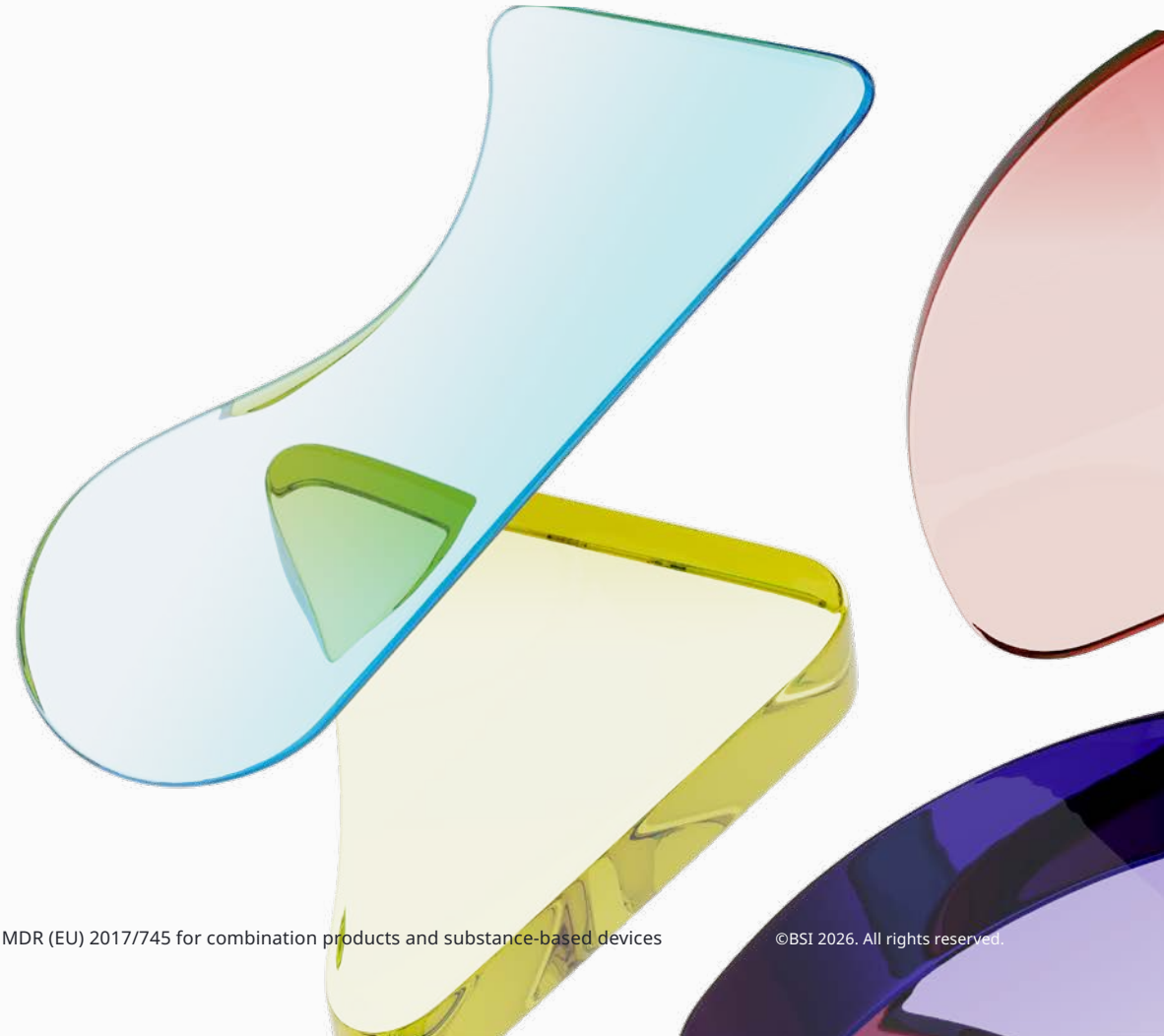
For combination products and substance-based devices

Authors

Theresa Jeary, Global Head Medicinal & Biologics, Regulatory Services, BSI

Dr. Jonathon Sutch, Principal Technical Specialist, Regulatory Services, BSI

Contents



Introduction

The purpose of this whitepaper is to provide an overview of the impact of the implementation of the MDR (EU) 2017/745 on combination products and substance-based devices. The content is based on the considerable experience gained by BSI since the enforcement of the legislation.

While there is no legal definition for a “combination product” within any EU Legislation, it is a common term used to describe products that combine a medical device and medicinal product. The area applies to many medical devices and medicinal products. As indicator of the importance of this sector, in 2023 the market size for such products in the USA alone is valued at USD 47.6 Billion and is expected to grow at a compound annual growth rate (CAGR) of 7.7% from 2024 to 2030.

This whitepaper will discuss the following types of combination products, as well as provide an update on the implementation of the conformity assessment processes for substance-based devices, for which the MDR introduced a new Classification Rule and additional assessment considerations.

Each type of the below listed products has its own regulatory route and assessment requirements under the MDR. This whitepaper provides an overview of the implementation of Article 117 for IDDCs, Rule 14 for device/drug combinations and Rule 21 for substance-based devices.

Some definitions

Integral Drug-Device Combinations (IDDCs) (Article 117 MDR): when 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. It is intended exclusively for use in the given combination and which is not reusable, then this is a medicinal product regulated under the Medicinal Products Directive (2001/83/EC). The medicinal product has the principal action, and the device is intended to administer the medicinal product. Examples include pre-filled syringes, auto injector pens and pressurised metered dose inhalers.

Drug-Device Combinations (Rule 14 MDR): in this case, the device has the principal mode of action, and the medicinal substance or human blood derivative has an ancillary action. Examples include drug-eluting stents or wound dressings with anti-microbial agents.

Substance-Based Devices (Rule 21 MDR): these types of products are comprised of a substance or combination of substances that achieve their intended purpose by physical means and thereby meet the definition as a medical device. Rule 21 devices are applied to the skin or body orifices and include orally ingested devices. Examples include comfort eye drops, creams for the treatment of eczema or tablets for the treatment of obesity. These are included within this whitepaper as they are borderline with medicinal products often provided in a dosage form more often associated with medicines.

Integral Drug-Device Combinations (IDDCs) - MDR Article 117

Article 117 of the MDR introduced significant new requirements for IDDC products and the companies making marketing application for these types of medicinal product. Article 117 requires a demonstration of conformity of the device component to the MDR Annex I - General Safety and Performance Requirements, either through the use of a CE certified device, self-declaration or the provision of a Notified Body Opinion (NBOp) Report.

The requirement that the device part of these IDDCs meets the relevant requirements of Annex I of the Medical Device legisation however, is not a new requirement. Pre-MDR, the Medical Device Directive 93/42/EEC explicitly required for IDDCs compliance of the device part to the Annex I Essential Requirements of 93/42/EEC. However, the level of information required and the assessment by the Competent Authorities was not explicity stated with divergences seen in approach.

As the technology for the device part of these IDDCs becomes more complex, with on-body dosing systems and use of software to time the dosing regimens, it did become apparent that the skill set required to evaluate the safety and performance has increased. Hence, under the MDR, the introduction of the Notified Body to the process.

Data from NBCG-Med from April 2024, shown at NBCG-Med meetings and EMA meetings but unpublished, show that 17 out of 39 notified bodies that responded have issued an Article 117 opinion (NBOp) to date (see Figure 1). As a full scope Notified Body, BSI has issued over 150 NBOps since its first opinion issued in January 2020.

While Article 117 assessment process within notified bodies has become fully implemented and embedded within internal systems and procedures, for many pharmaceutical companies it may still be seen as a new and daunting process as the requirement to obtain a NBOp for affected medicinal products has only applied to New Marketing Authorisation Applications since May 2021.

Article 117 requires that Marketing Authorisation Applicants provide evidence of the conformity of the device part to MDR Annex I GSPRs. While the concept of GSPRs may be new to such applicants, the following guiding principles should be considered:

- Data should be provided in Technical Documentation format, the contents of which are provided in Annex II of the MDR.
- Not all GSPRs may be applicable to the device parts for which application is made but a statement of applicability or not, with a justification for any deemed not applicable is required.
- There are some GSPRs which shall have some overlap with the Competent Authority assessment, such as stability. However, differing perspectives are taken in the assessments, the Notified Body shall ensure the device part can perform over the shelf-life of the product while the Competent Authority assessment is concerned with the chemical stability of the medicinal product over the proposed shelf-life.
- As the final integral drug-device combination is regulated as a medicinal product, the labelling needs to conform to the requirements of the Medicinal Product Directive. However, where labelling solutions have been implemented as part of risk mitigation, the Notified Body review shall include an assessment of these aspects.

From experience of conducting many NBOp assessments, the evidence used to demonstrate compliance to GSPRs may be sourced from many sources such as literature, suppliers and sub-contractors, in addition to in-house data.

Information from unpublished EMA data suggest that 25% of Market Authorisation Applications include an IDDC. Over the period reviewed, 68 IDDC applications were made. Out of these, 68 procedures, 75% had one or more NBOps currently available. The others are still to be provided prior to Committee for Medicinal Products for Human Use

(CHMP) Opinion. Only two Market Authorisation Applications provided a Declaration of Conformity (DoC) in place of a NBOp.

One of the issues raised by EMA when reviewing applications echoes feedback from the pharmaceutical industry and relates to the issue of Classification of IDDCs. Article 117 allows manufacturers of Class I devices (or to be precise, device parts of IDDCs) to present a DoC as part of their market authorisation application. For other classes, a CE certificate or a NBOp is required. There are no additional assessment requirements stated for higher risk classified device parts as part of Article 117. In addition, the Classification Rules set out in Annex VIII of the MDR are designed to classify medical devices, not integral device parts of medicinal products. The classification rules are useful in understanding the risks associated with IDDCs. For example, the degree of invasiveness, inclusion of software, the utilisation of animal tissue etc. However, beyond that exact categorisation is not required.

With respect to qualification and classification, the questions to be asked are:

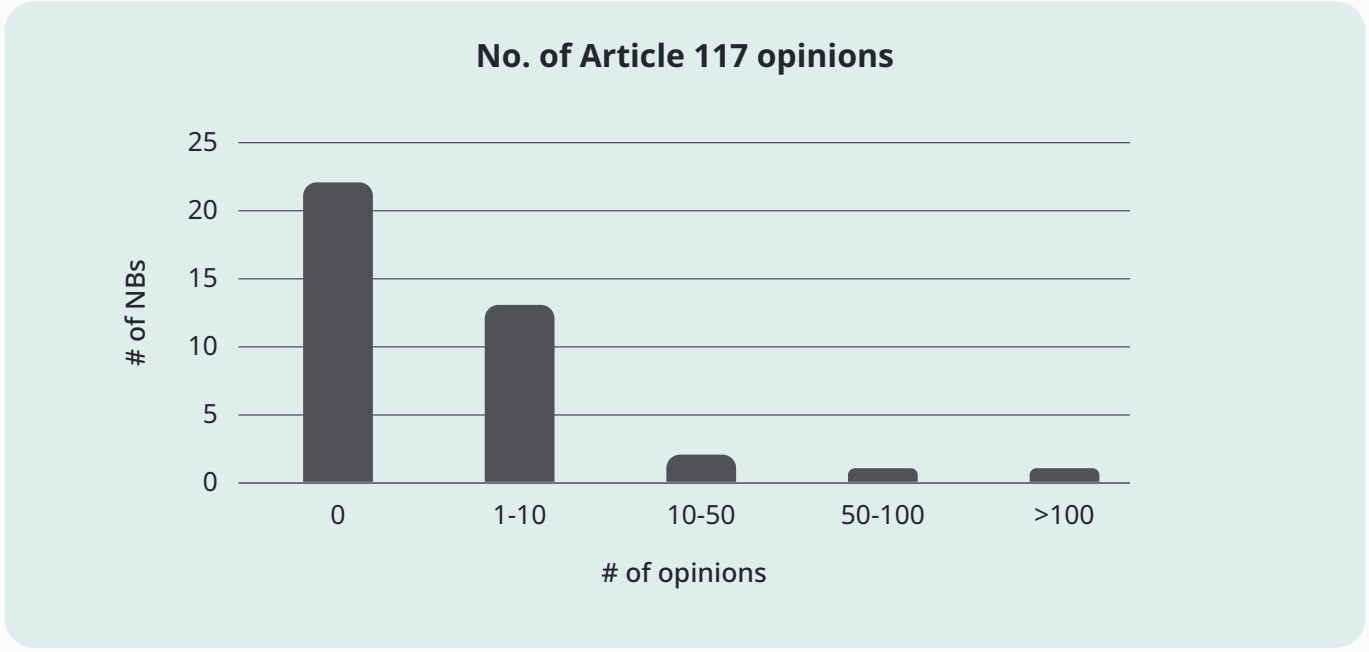
- Does the product meet the definition of an IDDC (Article 1, Section 8, second paragraph or Article 1, Section 9, second paragraph)?
- Is a NBOp required? As mentioned for all but Class I devices a NBOp is required unless a CE certificate is included. We are not aware of the latter condition being used, most likely as it is not expected an integral device part has a standalone certificate.
- Even if a CE marked device was used as part of an IDDC would the scope of the certificate and the Declaration of Conformity that sits behind it, cover the combined integral product?

For these reasons, the NBOp is the most common way to demonstrate conformity to the Annex I requirements of the MDR.

Of the NBOps seen by EMA, approximately 20% concerned line extensions. The majority submitted were initial NBOps, with a limited number of NBOp changes seen. The management of changes remains an area of debate and concern for the industry. There has been a lot of discussion at conferences seeking additional prescriptive guidance on the threshold for changes, or variations to an IDDC, with respect to the need for a new or updated NBOp. Theoretically, changes to the device part of a IDDC licenced prior to May 2021, would require a full new NBOp as these products would not have been previously assessed by the notified bodies. For a product authorised after this date, as an initial NBOp was provided as part of the MA Application, an updated NBOp limited to the assessment of the impact of the change to the GSPRs could be presented.

There is concern the timeline for a change to a NBOp or a new NBOp is likely to be longer than the variation review timelines for the pharmaceutical part of the device. As not many significant changes to the device part of an IDDC, that require a NBOp as part of the variation, have been seen to date, it is difficult to know the impact of this requirement. Guidance on the impact of changes on the GSPRs has been provided by Team-NB. In addition, EMA

Figure 1: *number of Article 117 opinions issued by EU Notified Bodies as of April 2024.*



discusses the impact of changes to IDDC on applications in their Q&A. This guidance can be used to help manufacturers assess the impact of a proposed variation on the device parts and therefore, the need for an updated NBOp.

Other guidance has been produced including guidance on the documentation and timelines required by the notified bodies. As might be expected, the more comprehensive the documentation, the faster the review. This includes documentation from suppliers. For example, where off-the-shelf device parts are used, the supplier's documentation of GSPR compliance is a useful piece of the conformity puzzle. Pharmaceutical manufacturers that are proactive and prepare this information in advance through suitable relationships with these suppliers and the appropriate agreements, will find faster review times.

Review times differ between Notified Bodies and are dependent on the quality of the documentation provided and number of review rounds needed to close out any open points.

Assuming the manufacturer has the evidence to support compliance to the relevant GSPRs, an opinion typically takes between 2 and 6 months to be issued. Therefore, with suitable planning, including allowing time for contractual negotiations, the NBOp should be available at the start of the Marketing Authorisation Application assessment. Early dialogue and planning with the Notified Body are key steps in ensuring conformity assessment timelines can be met.

Drug-Device Combinations - MDR Rule 14

The process under the MDR for devices containing ancillary medicinal substances is largely unchanged, although the wording in Rule 14, no longer contains the phrase “liable to act”. The implications of this change of wording caused some concerns amongst industry and notified bodies alike, as there was the potential for devices with “inactive” medicinal substances to be up classified. In fact, the correct interpretation of Rule 14 was clarified in MDCG 2022-5. This document clarified the interpretation of “ancillary action” in the wording of Rule 14. In addition, the guidance also provided improved definitions of the terms pharmacological, immunological or metabolic and therefore an understanding of the borderlines between medicinal products and medical devices. One significant clarification was that the action could “take place in or on the human body or its constituents (e.g., blood, organs, in vivo or ex vivo, gametes, exudate from a wound) and supporting the device in achieving its specific medical purpose”. Therefore, substances having a medicinal effect ex vivo, for example in blood bags, are in Rule 14 scope.

For legacy devices (i.e., medical devices already certified under the Medical Device Directives (MDD)), re-consultations for the ancillary medicinal substances were required by Competent Authorities as clarified in MDCG 2020-12. Full documentation relating to the ancillary medicinal substance was required for this initial consultation along with a declaration from the Notified Body with respect to changes, if any, in the following:

- Ancillary substance.
- Manufacturing process.
- How the substance is incorporated into the device.
- Design, manufacturing of the device which could influence the quality, safety or usefulness of the ancillary substance, and/or
- Parts of the technical documentation related to the above aspects.

Where there were no, or only administrative changes, reduced review times were anticipated where possible. Indeed, MDCG 2020-12 states “the medicinal products authority may consider the depth of its review given the extent of the changes since the previous consultation under the MDD/AIMDD. It is at the discretion of the medicinal products authority to issue its opinion in less than 210 days. If many elements concerning the substance remain identical, the medicinal products authority is highly recommended to hasten its review.” In reality, most reviews have taken closer to the maximum permitted time. The main causes for this were:

- Change of Competent Authority: for example, all consultations performed with the MHRA over the course of the MDD were required to be transferred to an EU Competent Authority because of Brexit. Although detailed reports from the MHRA were available, these applications were managed by the EU Competent Authorities as new applications.
- Changes to the device throughout the lifetime of the certificate: significant changes or cumulative small changes may have resulted in a confused consultation history relative to the devices intended to be certified under the MDR.
- Updates to documentation including clinical evidence: although guidance is available, the quality of quality, pre-clinical and clinical documentation from device manufacturers, is highly variable. Recently, Competent Authorities have become stricter in terms of the adherence to the guidance resulting in new documentation and more thorough review.
- Competent Authority resource: not all Competent Authorities are able to support the consultations set out in the MDR, leaving a small pool to support all the European notified bodies. This has led to long lead times and delayed reviews. Due to extensive discussions with the available CAs and forward planning of MDR re-consultations, the majority of manufacturers with BSI have successfully completed this re-consultation process.

Substance-Based Medical Devices - MDR Rule 21

Rule 21 of Annex VIII, MDR, is a newly introduced rule, considered necessary as under the MDD, the rules applied to invasive devices did not sufficiently consider the level of invasiveness and potential toxicity of certain devices which are introduced into the human body. Rule 21 considers the place where the device performs its action in or on the human body, where it is introduced or applied, and whether a systemic absorption of the substances of which the device is composed, or of the products of metabolism in the human body of those substances occurs. Additionally, there was a divergence in opinion on the regulatory classification of some ingested products across the EU Member States with the same product being a medicinal product in some EU Countries and accepted as a medical device in others.

Rule 21 applies to substance-based devices that are absorbed or locally dispersed. In general, these types of devices are widely available as self-care products, often with limited medical supervision. The Rule has four indents describing the risk categorisation for different device types. It is important to note that these substance-based devices may also include a constituent that has a pharmacological, immunological, or metabolic action that is ancillary to that of the device. In this case, Rule 14 may be applicable, or the product may be regulated as a medicinal product rather than a medical device, depending on the principal mechanism of action.

Examples of these are given in MDCG 2021-24. In this guidance is noted that there is no example in the first indent. Indeed, no devices of this type have been seen at BSI and as far as we are aware, anywhere. Only devices from the first indent require a scientific opinion from one of the Competent Authorities designated by the Member States in accordance with Directive 2001/83/EC (Annex IX, 5.4(b)). However, as no such devices have been identified, this process has not been initiated. To fit under the first indent a device would need to be systemically absorbed and then

have a physical (non-pharmacological, immunological or metabolic) action to perform its intended use.

One of the most common points of misinterpretation with respect to Rule 21 relates to the term “local dispersion”, an aspect that is usually ignored, with manufacturers only justifying the non-applicability of Rule 21, only based on the lack of systemic absorption of the device. MDCG 2021-24 provides definitions of the relevant terms from Rule 21 with “local dispersion” defined as “the condition by which substances remain in a specific site without being distributed into the body via the blood and/or lymphatic system.” Therefore, topical substance-based devices are covered under Rule 21. Note: topical ultrasound gels are excluded from Rule 21, due to their complete removal following use and application as a conductive gel for ultrasound waves.

Additional requirements as result of Rule 21 includes a review of the quality and safety of devices in respect of the requirements not covered by this Regulation, in accordance with the relevant requirements laid down in Annex I to Directive 2001/83/EC for the evaluation of absorption, distribution, metabolism, excretion (ADME), local tolerance, toxicity, interaction with other devices, medicinal products or other substances and potential for adverse reactions (MDR Annex IX 5.4(a). For substance-based devices where it can be shown that there is no absorption, the ADME portion aspect is typically covered under the biological safety review of the MDR and ISO 10993-1, as is tolerance and toxicity. Commonly used constituents of substance-based devices are also well characterized and often also used in either medicinal or cosmetic products as excipients. The use of literature to support their safe use and ADME characteristics is a widely accepted approach.

The potential for interactions with concurrently used medical devices, medicinal products or other substances are expected to be covered in the risk assessment, but in accordance with GSPR 12.2, additional scrutiny on these aspects is required to be assessed for these devices.

There are also additional labelling requirements for these devices as detailed in GSPR 23.2(r) and GSPR 23.4(t), with a requirement to include qualitative and quantitative details of the device composition. This requirement is commonly misinterpreted with manufacturers reticent to divulge their proprietary formulation information. However, while qualitative information is required for the device, the quantitative information is limited to the main constituent or constituents responsible for achieving the principal intended action.

Borderline cases and classification disputes

One of the challenges for manufacturers and regulators alike, is ensuring correct qualification of devices with respect to the different legislation. Common borderlines include medicines versus devices or devices versus cosmetics, especially since the introduction of Rule 21. Guidance is available, for example MDCG 2022-5, MDCG 2021-24 and the Borderlines Manual. However, it is not possible to cover all scenarios in these guidelines. Note: manufacturers are responsible for the appropriate qualification of their product.

Important questions to ask to help determine the qualification and classification are:

- Are medical claims being made? Do these have appropriate clinical evidence (MDR Article 2(1))?
- Is the principal mechanism of action physical or pharmacological, immunological or metabolic? Is there evidence to support this?
- What claims are being made around the ingredients? Note: if the manufacturer shows that the substance does not have any action ancillary to that of the device, no claims of benefits about that substance may be made on the IFU, labelling, packaging, advertising and websites.

A common area for additional scrutiny during the application stage is the use of constituents/ ingredients which may also be commonly used in foods or cosmetics. When used in medical devices their action must be understood including any potential pharmacological, immunological or metabolic action. Examples include CBD or menthol. When ingredients could have an action on the body, for example anti-microbial or anti-inflammatory, evidence for the mechanism of action must be provided and their reason for inclusion in the formulation should be understood.

Where classification disputes cannot be resolved between a manufacturer and a Notified Body, Article 51(2) allows for the dispute to be resolved by the Competent Authority where the manufacturer resides (or their European Representative) and the Competent Authority where the Notified Body is located. At the current time, we have seen a limited number of cases that have required escalation via the arbitration process. The difficulty for those that have needed arbitration, is in the variability in the Competent Authority procedures and timelines. Potentially, any European Competent Authority could be involved in the dispute process (based on manufacturer or EU Representative). However, despite it being part of the Regulation, not all Competent Authorities have a process in place to deal with such cases. In addition, the Regulation does not clarify how the two Competent Authorities should communicate or provide an overview on timelines. Our experience shows this can add considerable time to a conformity assessment procedure.

Conclusion

The aim of the MDR is to improve and future-proof the regulatory framework for medical devices in the EU and to improve the Integral Drug-Device Combinations assessment process by involving device expertise to the process, with increased patient safety at the core. The MDR has strengthened the cooperation across differing specialisms, with Notified Bodies now part of the assessment process for Integral Drug-Device Combinations. While Medicine Competent Authorities continue to support Notified Bodies in the assessment of medical devices with ancillary medicinal substances, the introduction of Medicine Competent Authorities in the assessment, is necessary for substance-based medical devices, under certain conditions.

Combination Products continue to be an important area of growth, with Integral Drug-Device Combinations offering many innovative solutions to assist self-care at home and improve patient compliance for medications. Drug-Device Combinations continue to support the use of the device and provide state-of-the-art healthcare solutions.

For substance-based devices, the inclusion of a specific Rule within the MDR was necessary to ensure appropriate scrutiny, given the challenges and risks associated with devices having this level of invasiveness, potential toxicity and the potential self-care nature of these products.

What we have learnt during the implementation phase of the MDR is the importance of continued dialogue between all stakeholders and for them to work together to provide additional clarification on requirements and expectations and to increase harmonisation.

Why choose BSI?

- BSI has been the first Notified Body issuing a NBOp under MDR Article 117.
- We conducted > 80% of all NBOp submitted to EMA.
- We received more than 170 Article 117 applications and isssued up to150 NBOp to date.
- The top 10 global pharma companies relied and choose BSI to issue a NBOp.
- BSI has over 190 ongoing applications under MDR Article 14, covering both ancillary medicinal substances and ancillary human blood derivatives.
- BSI supports the majority of top 10 medical devices manufacturers under MDR Article 14.
- Out of 180 applications received for MDD to MDR consultations, the 98% have been submitted to Medicines Competent Authorities. The 60% of the total has already completed reconsultations.
- BSI already issued 112 CE certificates under Article 14, through MDR conformity assessment.

Get in touch

Whether you are starting the certification process, looking to transfer or need to discuss your options, we can guide you through the process.

Talk to us

References

Grand View Research. (2022). *U.S. drug device combination products market size, share & trends analysis report by product (infusion pumps, transdermal patches, orthopedic combination products, photodynamic therapy devices, drug-eluting stents) and segment forecasts, 2024 - 2030.* **Grand View Research**.

TEAMNB. (2020). *Position paper for the interpretation of device-related changes in relation to a Notified Body Opinion as required under Article 117 of Medical Device Regulation (EU) 2017/745.* TEAMNB.

European Medicines Agency. *(n.d.). Questions & answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the regulations on medical devices and in vitro diagnostic medical devices.* **European Medicines Agency**.

European Medicines Agency. *(n.d.). Questions & answers for applicants, marketing authorisation holders of medicinal products and notified bodies with respect to the implementation of the regulations on medical devices and in vitro diagnostic medical devices (Regulations (EU) 2017/745 and 2017/746).* **European Medicines Agency**.

BSI Group. *(n.d.). MDR article 117 drug-device combination products application process*. **BSI Group**.

European Commission. (2022, April). *MDCG 2022-5 guidance on borderline between medical devices and medicinal products under regulation (EU) 2017/745 on medical devices.* **European Commission**.

European Commission. (n.d.). *MDCG 2020-12 guidance on transitional provisions for consultations of authorities on devices incorporating a substance which may be considered a medicinal product and which has action ancillary to that of the device, as well as on devices manufactured using a substance which may be considered a medicinal product.* **European Commission**.

European Medicines Agency. (2010). *EMA/CHMP/578661/2010 rev. 1 European Medicines Agency recommendation on the procedural aspects and dossier requirements for the consultation of the European Medicines Agency by a notified body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in medical devices.* **European Medicines Agency**.

European Commission. (2021, October). *MDCG 2021-24 guidance on classification of medical devices.* **European Commission**.

European Commission. (2022, September). *Manual on borderline and classification in the community regulatory framework for medical devices.* **European Commission**.

European Commission. (2019, May). Manual on borderline and classification in the community regulatory framework for medical devices (Version 1.22). **European Commission**.

Disclaimer

Your partner in progress

BSI Assurance UK Ltd (0086)
Kitemark Court,
Davy Avenue, Knowlhill,
Milton Keynes MK5 8PP
United Kingdom

+44 345 080 9000

BSI Group The Netherlands B.V. (2797)
Say Building,
John M. Keynesplein 9
1066 EP Amsterdam
The Netherlands

+31 20 346 0780

BSI Group America Inc.
150 Opportunity Way,
Suite 900
Reston, VA 20190
USA

+1 800 862 4977

Find our services at
bsigroup.com/medical

Email us at
medicaldevices@bsigroup.com

Find us on
LinkedIn