

The EU Medical Devices Regulation and its Market Impact Under the Spotlight

We spoke to Nadine Kasidas-Neale [Head of Regulatory and Compliance] at Bepak by Recipharm to explore the incoming changes to EU medical device regulations. She explains their impact on pharmaceutical companies developing drug delivery devices including autoinjectors for the EU market, with reference to relevant regulatory pathways.

The global drug-device combination products market was estimated to be worth US\$ 123.5 billion in 2020 and is forecast to grow at a CAGR of 8.2% between now and 2027¹. The new combination products entering the market don't just include traditional parenterals, but autoinjectors and inhalers too, as well as other next-generation devices.

The rise of such combination products means that the integration of pharmaceutical and device regulatory requirements at the development stage is more important than ever before.

Combination products – meaning medicinal products / drugs that are fully integrated with a drug delivery device, such as autoinjectors or pressurised metered dose inhalers (pMDIs) – are governed by strict regulations in the European Union (EU) and other advanced markets. Pharmaceutical developers must demonstrate compliance with these requirements to deliver a safe and effective product to patients and trade within those territories.

Previously, in the EU, companies have had to demonstrate conformity to the essential requirements (a list of requirements outlined in the EU Medical Device Directive), by preparing drug dossiers. The intent of this directive was for individual country regulatory authorities to assess this information in the marketing authorisation applications (MAAs) that they review.

As of 26 May 2021, companies must comply with updated requirements in the new Medical Devices Regulation (MDR). The MDR is a specific regulation that all



EU Member States must comply with and changes the measures companies must take to demonstrate the safety, effectiveness, and performance of their product.

Why the Change in Regulations?

Medical devices have been regulated throughout the EU since the 1990s. Three distinct directives were initially published to regulate medical devices, covering a range of different device types. These were the Medical Device Directive (MDD), the Active Implantable Device Directive (AIMDD), and the *In Vitro* Diagnostic Device Directive (IVDD).

These existing directives require updating for several reasons. Key among these is the need to incorporate rapid product innovation, and to address recent safety issues in the market by reviewing any concerns over the assessment of product safety and performance.

In addition, it is increasingly necessary to place stricter requirements on clinical evaluation and post-market clinical follow-up, as well as improve the traceability of devices. The ageing European population is revealing new risk and health factors that must be considered to ensure devices remain suitable for the patients using them.

The new MDR is designed to strengthen the requirements included in the previous legislation and implement a life-cycle approach to product development to provide effective products that enhance the patient experience.

Until now, combination products have been regulated as medicinal products under the Medicinal Product Directive (Directive 2001/83/EC) without specific examination of the device itself by another competent authority or notified body.

This gap has existed in European regulations for many years. Companies have dealt with this by effectively providing a technical file in their marketing application that addresses the essential requirements of the directives as part of their MAAs.

The MDR specifically addresses this issue through article 117 that covers drug delivery devices and effectively amends the Medicinal Product Directive.

As a result, integral drug-device combination products, such as an autoinjector or pMDIs, must show conformity to the general safety and performance requirements (GSPRs), or Annex I of the MDR. Additionally, developers must now also find



a notified body to review the information and issue an opinion that their product is in conformance with the requirements.

Experienced combination drug developers should already be familiar with this new approach, as this has been the direction of many recent regulatory changes worldwide, such as the update to ISO 14971 in 2019.

How Has the Safety Approach Changed?

The MDR largely shares the same basic regulatory requirements as the directives it replaces; new standards build on this foundation.

Crucially, the MDR promotes a life-cycle approach to safety, backed by clinical data. This encourages policies and procedures elevating the responsibilities of companies for their products.

The intent is to improve the safety of products by strengthening the rules on placing new devices on the market, and by tightening surveillance once they are available to patients. These stricter requirements regarding the quality, safety, and performance of devices, together with steps to improve traceability of devices, are designed to provide greater transparency for both patients and authorities.

Greater emphasis is also placed on enhanced governance of notified bodies, whilst also providing them with the right to perform unannounced audits on manufacturers.

What are the Key Changes Affecting Device Development?

Under the new MDR, there are several key changes that companies need to consider for their device. These include:

- Reclassification of devices according to risk, contact duration and invasiveness.
- New requirements at the pre-marketing stage:
 - There are now common specifications that some medical devices must meet in order to comply with enhanced scrutiny for high-risk devices.

- A Person Responsible for Regulatory Compliance (PRRC) is now required for manufacturers of medical devices.
- Updates to requirements for clinical evidence, evaluation, and data as the MDR moves away from equivalence between devices. The publication of more safety and performance data is required post-market clinical follow-up as well as a Summary of Safety and Clinical Performance (SSCP).
- New transparency, traceability, and supply chain requirements:
 - Under the MDR, new medical devices and the companies responsible for them must be registered centrally.
 - Unique device identification (UDI) must be included on packaging and devices to aid traceability.
 - Increased responsibilities for authorised representatives, importers and exporters within the supply chain.
- Post-marketing surveillance:
 - The MDR requires the manufacturers of medical devices to proactively collect and review, in cooperation with other economic operators, the experience of the device they place on the market. This is intended to make it easier to identify the need for corrective or preventive actions.



- Device manufacturers are also required to report safety and clinical performance annually.
- "Grandfathering" provisions have been removed. Some exemptions may be implemented.

The most significant change for devices such as autoinjectors is that now the device is no longer considered as just secondary packaging under medicinal regulations.

For integral drug-device combination products, article 117 within the MDR requires that developers must demonstrate conformity to the GSPRs, or Annex I of the MDR. A notified body opinion is required to confirm conformance to these requirements.

This should not be a significant change for experienced developers, who would already be generating appropriate technical data to support their products under the existing MDD essential requirements. Such information includes documentation on technical and functional requirements, a detailed technical description of the device, design verification reports, and a risk management file. In addition, it should incorporate design validation through

useability and human factors and potentially a clinical evaluation report.

Failure to ensure products meet these updated requirements could mean that pharmaceutical companies are unable to market their products in the EU. Not only would this impact on their revenue, but it would also have a negative effect on the patients that rely on their treatments.

Do Changes Need to be Made to Existing Products?

Depending on the classification of the product, different approaches to compliance are needed. For medical devices, when new or CE recertification is required, compliance to the MDR is mandatory.

For combination products, Article 117 of the MDR is not intended to be applied retrospectively to products already authorised, or to those that have been submitted prior to the date the new regulation was originally due to come into force.

However, in the case of significant changes to the drug or device, or if a new EU certificate of conformity is required, then companies will have to ensure that the product complies with the MDR. A notified

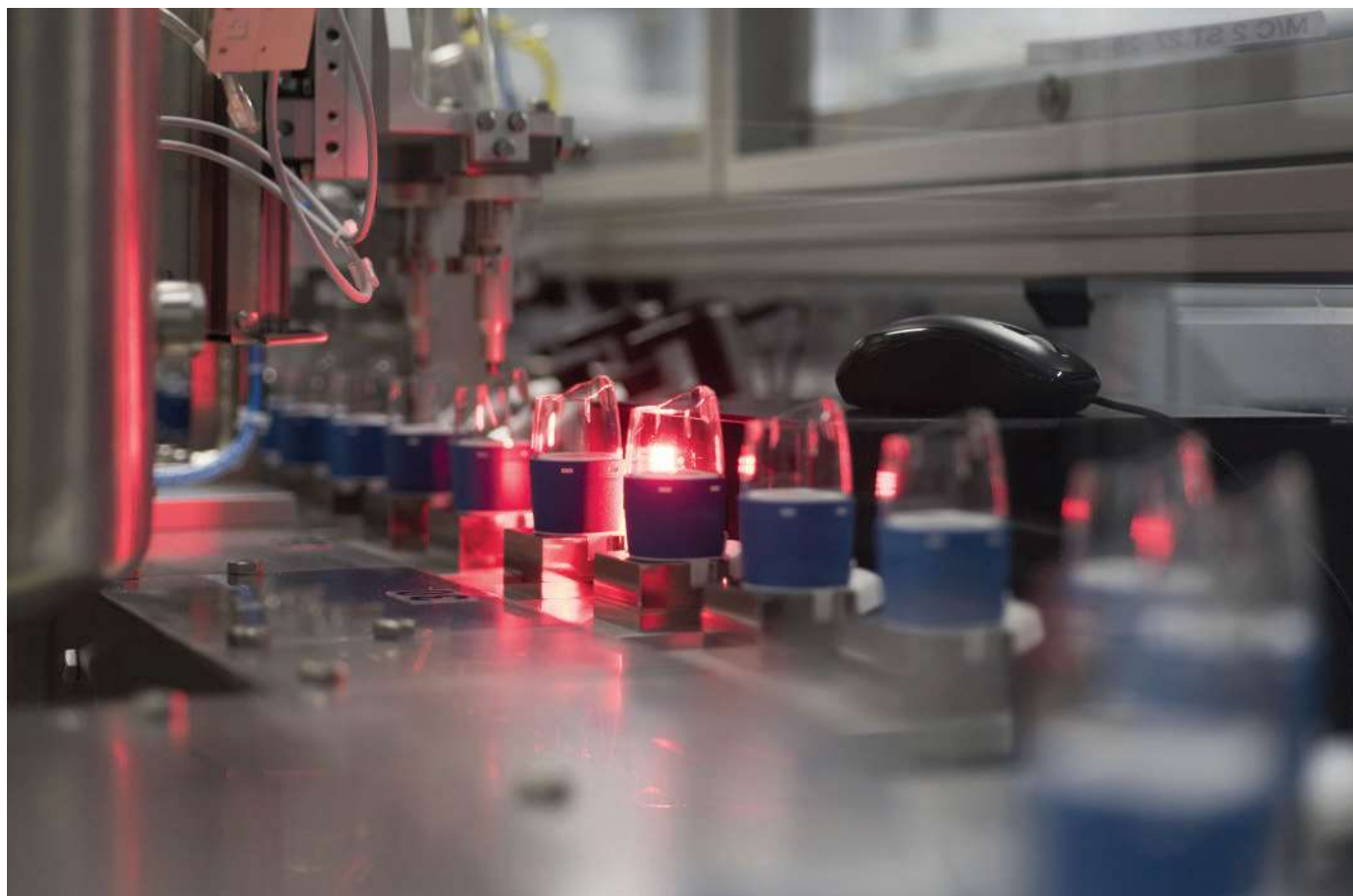
body opinion will also have to be provided as part of any change application.

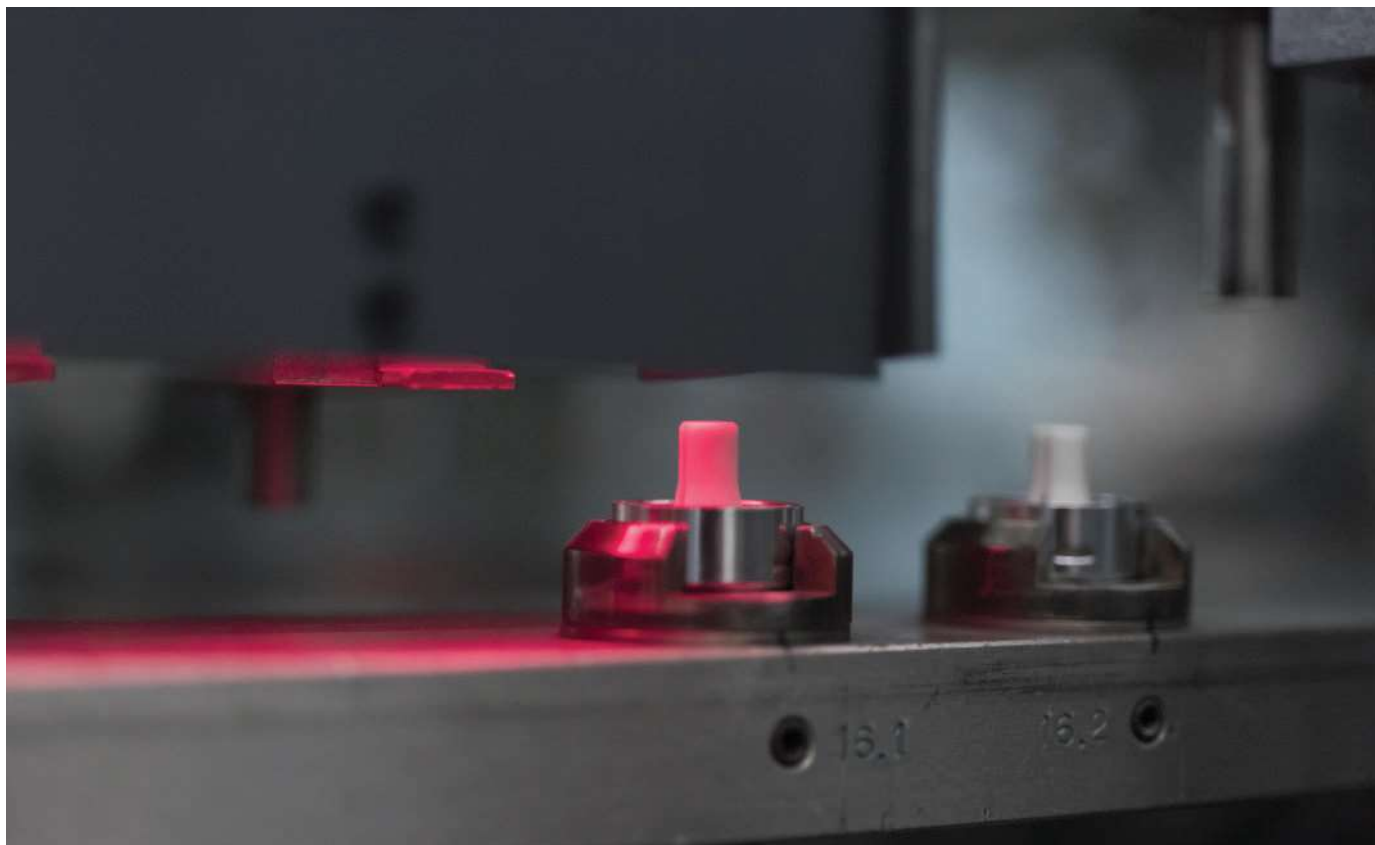
Obtaining a notified body opinion may take time that will need to be factored into any development project to ensure deadlines are met. The need to work with one of the few notified bodies already certified for the MDR may cause further delays, as many companies will be seeking their services at the same time.

How to Address Regulatory Changes in the Development Process?

Regardless of the nature or classification of the product, it is crucial to set a clear regulatory strategy at the outset of a project. This is essential to guide the development process and generate the required documentation to meet new MDR requirements; this is an approach that experienced developers should already be taking.

An effective strategy will consider the resource required to collate clinical and technical evidence to support MDR compliance. It will also involve in-depth analysis at the beginning of the project to understand where additional work is needed to generate the required information.





The responsibility for collating the required data for combination devices on the market lies with the pharmaceutical company, and not with third parties, such as device partners. However, when selecting the best partner, the ability to work collaboratively and support the integration of the drug and device into the overall system application is critical.

The MDR also defines specific post-launch requirements for products. To comply, pharmaceutical companies must take a proactive approach in the management and in the regular assessment of their products.

How to Work with Development Partners to Ensure MDR Compliance

There is a considerable amount of information that needs to be generated and collated, not just from within the pharmaceutical company, but from suppliers as well. It is crucial that development of the regulatory strategy includes close collaboration between the pharmaceutical company and their device development partner.

Not all third-party providers will be able to meet the required level of collaboration, so it is important to choose the right device partner. Experienced device development partners will not only be able to support

in the design and commercialisation of the device, but they will also be able to enhance useability for patients which can optimise the regime compliance.

The right partner will be able to support drug developers in establishing and realising their regulatory strategy and advise on what information needs to be collated to comply with the MDR requirements and support its generation.

Most importantly, an expert development partner can provide support beyond the MDR compliance, encompassing global regulations for key markets. Pharmaceutical companies should talk to their device partners now, to understand fully the assistance they can offer to ensure regulatory compliance.

Time to Act

The upcoming changes to the regulatory environment for medical devices have been in development for some time, and companies across the industry should already have taken steps to ensure their current and future projects meet the new requirements under the MDR.

As global regulatory frameworks develop and evolve, we can expect more enhancements over the coming years. By working closely with expert device partners,

pharmaceutical companies can be confident they have the support they need to meet the stringent requirements of new regulations, not just in the EU, but in all key markets across the globe.



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Nadine is the Head of Regulatory Compliance at Bepak by Recipharm. In her role, Nadine combines her experience as a research and development scientist and global regulatory professional, leading the Bepak by Recipharm teams to deliver new products and ensure full lifecycle regulatory and scientific product development strategies. She has also led the implementation of new strategies to meet global regulatory landscape changes across multiple product portfolios and business units, including compliance with the new European Medical Device Regulation. With over 17 years of experience in the diagnostic, medical device and combination product industry, Nadine brings a wealth of experience to the Bepak by Recipharm team.