Integrating Medical Devices into Pharmacovigilance Portfolios Part II

How to Carry Out Post-Marketing Safety Surveillance of Medical Devices and Drug-device Combination Products in the EU And USA.

Understanding medical device and drug-device combination (DDC) product regulation is essential when integrating medical devices into pharmacovigilance (PV) portfolios. This article dives deeper into the reporting essentials and obligations associated with the post-marketing safety surveillance of these products both in the EU and U.S. markets.

The article discusses the current trends and challenges in the industry, offering insights into best practices and regulatory expectations, including how to navigate the complexities of safety surveillance and ensure compliance with international standards.

Global DDC Trends

DDCs are on the increase. The number of combined product submissions to the FDA increased from 317 in 2014 to 518 in 2019.[1] The global combination product market continues to grow at a CAGR of 7%,[2] with an estimated value of £139 billion by 2025.[3] One of the biggest areas of growth is implants, which may have a software component to them, increasing their complexity.

With increasingly complex drug delivery systems, combined products become more common. This complexity impacts all parts of the product life cycle, from technical development to product quality and supply chain integrity. If we look specifically at the regulatory environment, identifying the most efficient regulatory pathway for complex product configuration depends on several factors, including its primary mode of action, regulatory precedents, and market experience with current products.

As awareness of product experience and risk increases, we are also gaining an understanding of the practical challenges we need to address. These include changes and inconsistencies in the classification of devices. This can be anything from software added to a device to products not described in the guidelines. Ambiguity regarding classification makes it necessary to seek clarification on how elements will be classified in the future.

Other key challenges include:

- Device classification issues and the impact on the Notified Body (NB) opinion requirement.
- Lack of full compliance with relevant general safety and performance requirements (GSPRs) impacting the approvability of the Marketing Authorisation Application (MMA).
- A lack of a clear definition of a "substantial change" and how much additional documentation is required.

To overcome those challenges, we need to increase our understanding of the differences between drug and device safety surveillance and how to integrate medical devices into drug safety portfolios. We must also build effective interfaces between the Quality, Surveillance, and Regulatory departments and establish entity ownership interface agreements.

An Overview of DDCs in the EU and USA

There are four essential types of DDC in the EU based on the authorisation or certification these documents receive. The biggest differentiator is the regulatory pathway and how these products are going to be handled in the future. The four main product categories are:

- integral DDCs
- non-integral DDCs
- devices with an ancillary medicinal substance
- devices intended to administer medicines

An example of an integral DDC is a prefilled syringe or an inhaler that cannot be taken apart. The Marketing Authorisation holder, in this instance, would apply to the European Medicines Agency (EMA) or the National Competent Authority, which might require input from a NB. The output would be Marketing Authorisation with an NB opinion.

In contrast, non-integral DDCs such as dry powder inhalers co-packed with medicine capsules are each approved separately. Here, we would have Marketing Authorisation for the medicinal product and a CE certificate for the delivery device, handled as two distinct products.

For devices with an ancillary medicinal substance or devices intended to administer medicines, you get a CE certificate, sometimes with consultation from a competent authority for medicinal products, or a CE certificate without anything else. The approval documentation determines how these products are handled for safety reporting.

The U.S. concept is similar. Drugs follow drug regulations, which are 21 CFR 314; biologics follow biologics regulations, which are parts 600 and 606; and devices follow 803 and 806. In addition, 21 CFR Part 4 applies to combination products.

Reporting Essentials

Reporting obligations concerning combination products depend on how the product is approved. In the U.S., it is the application and applicant type, while in Europe, it is the regulation pathway. The product's status defines how the safety reporting will be handled.

In Europe, medical device reporting timelines are two days for serious public health threats, 10 days for serious incidents and 15 days for any other reportable incidents. Until the vigilance module of EUDAMED becomes available, national reporting procedures remain in place. Reporting forms for medical devices include a Manufacturer Incident Report, Field Safety Corrective Action, Periodic Summary Report, and Trend Report.

With reporting of combination products in the USA, drug and constituent drug parts have a reporting timeline of 15 days, while device constituent parts have a timeline of 30 days. Safety reporting timelines can get more complex, especially when you have a product available on the market in both the USA and Europe.

In the U.S., the traditional approach allows for separate reporting of regulated

components. A streamlined approach will enable us to leverage some common elements in good manufacturing practice and address the provisions that would be different for each device, drug, or biologic. This is an attractive option because it prevents duplication of efforts. However, there can be challenges. For example, if each component is manufactured by a different entity, the device manufacturer may end up with multiple quality management systems. Even though the last entity, the applicant, is ultimately responsible, using a streamlined approach may not be practical if you are dealing with different entities.

Any procedure for reporting DDCs must be able to provide objective evidence that three main areas are covered:

1. There are defined processes to ensure individual device-related adverse events are reported to regulatory authorities as required.
2. Advisory notices are reported to regulatory authorities and authorised representatives when necessary.
3. There are appropriate records of individual device-related adverse events and advisory notices.

Complaint Handling and Vigilance Procedures

Complaint handling is an essential component of any quality management system within the medical device domain. It is described in full detail in ISO 13485 and includes a broad definition of a complaint to cover Quality and Vigilance in all areas. It also includes recording an awareness date to meet vigilance timelines and forms that may differ from device to device.

It is common practice for forms to differ from one device to another and cover the relevant risks. This is different from drugs, where the forms used to collect adverse events tend to be the same.

There also needs to be a process for determining the reportability of events. With medical devices, this might include malfunctions that did not result in patient injury. A clear description of the escalation process must exist to facilitate communication between all relevant parties. When, for example, a PV department is checking on the portfolio of an acquired company, the interfaces between individual economic operator roles and internal departments can get very complex. It is always important to understand who is responsible for the product itself.

The vigilance procedure covers the applicable vigilance regulations for covered geographies, including definitions. It needs to cover not just the timelines and instructions on how to complete the report but also any investigation and follow-up. This creates a need for interface with the Quality Management Department and, potentially, PRRC.

Post-Marketing Surveillance, Vigilance and Handling

There are some similarities between the post-marketing surveillance, vigilance and handling requirements in the USA and Europe. For example, in both there must be an adequate system for the medicinal product to comply with obligations on the recording or reporting of adverse reactions and with post marketing surveillance requirements.

One of the key differences, however, is that vigilance in the USA for post-market safety reporting is driven by application and applicant type. Application-based reporting is supplemented with specific reporting elements for each of the constituent parts of the combination product. Similar reporting requirements also apply if a reportable event occurs in a similar constituent part of a combination product. There is an expectation that such an event would be reported in the U.S. against the U.S.-marketed product. Hence, the manufacturer has the obligation to monitor similar products.

In the EU, reporting to the competent authority for the medicine product is sufficient. There is, however, no clear recommendation for reporting device complaints with potential impact on drug delivery between the National Competent Authority, where the NB is located, and the Reference Authority of the medicinal product. There is an assumption that the NB and the National Competent Authority will communicate issues with each other.

To operate in this complex environment, vigilance procedures must cover complaints, escalation and reporting for all constituent parts and products as a whole. We need to update Corrective and Preventative Action (CAPA) systems and reporting procedures and improve processes for complaint handling to ensure vigilance obligations.

Final Thoughts

Integrating medical devices into pharmacovigilance portfolios is an evolving and multifaceted challenge. As DDCs continue to proliferate, pharmacovigilance teams must leverage professional support and stay abreast of diverse regulatory landscapes and industry innovations to ensure the safety and efficacy of their products and keep pace with the dynamic field of medical device integration.

Ensuring compliance requires robust interfacing between quality, surveillance, and regulatory departments, along with well-defined procedures for complaint handling, vigilance, and post-marketing surveillance.

Continuous education and strategic adaptation are crucial for success in this evolving landscape. Expert services and innovative solutions are crucial for navigating these complexities and meeting regulatory requirements effectively.

REFERENCES

1. https://www.fda.gov/media/144887/download
2. https://www.globenewswire.com/news-release/2022/4/19/2424699/0/en/Drug-device-Combination-Products-Market-to-Expand-at-CAGR-of-7-3-During-Forecast-Period-Notes-TMR-Study.html
3. https://www.alliedmarketresearch.com/drug-device-combination-products-market

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