'Post market surveillance, Vigilance and Handling communication with competent authorities' Refer to / taken from Ensuring Compliance: Navigating the EU MDR for Drug-Device Combination Products

**This item addresses Vigilance and Handling communication with competent authorities (ISO 13485:2016 §8.2.3) and Post market surveillance (ISO 13485:2016 §8.2.1)**

## A. QMS Requirements

### 1. EU Requirements

- **The regulatory pathway determines the reporting procedure**.

  Since Single Integral DDCs are registered as medicinal products, Pharma Company should **report to EMA or Competent Authority (CA) only**. There is therefore no requirement to comply with EU MDR 2017/745 Article 10 General obligations of a manufacturer, section 9:
  - (*i*) *setting-up, implementation and maintenance of a post-market surveillance system, in accordance with Article 83;*
  - *(j) handling communication with competent authorities, notified bodies, other economic operators, customers and/or other stakeholders;*
  - *(k) processes for reporting of serious incidents and field safety corrective actions in the context of vigilance;*
  - *(m) processes for monitoring and measurement of output, data analysis and product improvement.*

- **Vigilance reporting**

  EU MDR Articles 87 & 88 do not apply to Pharma Company manufacturing and marketing single integral DDCs.

- **Medicinal Products reporting rules in EU are as per following;**

  The reporting concerns either:
  **Adverse reactions/adverse events**, where Pharmacovigilance rules apply. in line with Directive 2010/84/EU, Regulation (EU) No 1235/2010, Commission Implementing Regulation (EU) No 520/2012, Regulation (EU) No 1027/2012 and Directive 2012/26/EU.
  **Quality defect**: EMA has a dedicated system for reporting quality defects (including suspected quality defect) for centrally approved products
  https://www.ema.europa.eu/en/human-regulatory/post-authorisation/compliance/quality-defects-recalls/reporting-quality-defect-ema

- **Post-marketing surveillance**

  From a QMS perspective, **an annual market surveillance** for the device component, **as per MDR Annex II which refers to article 83-86, is not required.**

Directives 2010/84/EU amending as regards with pharmacovigilance 2001/83/EC, should therefore be considered.
The authors recommend industry to adapt its PQS system so that post production activities are monitored and feed-in the CAPA system for continuous improvement.

## 2. US Requirements

- **21 CFR 4 subpart B PMS reporting for Combination Products**
- **Under 21 CFR 820.10 Requirements for a quality management system incorporated from the ISO 13485:2016: §8.5.2 (corrective action and (Preventive action)**
- **21 CFR Part 803**

Under **21 CFR §4B** regulation and guidelines, there is an intent to ensure comprehensive reporting consistent with the underlying requirements called out in the rule associated with each of the constituent parts. Reporting is driven by Combination Product Application Type (*i.e.,* NDA/ANDA, BLA or Device application) and Applicant Type (Combination Product Applicant or individual constituent-part applicant).

Combination products submitted under NDA/ANDA report through CDER. Combination products submitted under BLA report through CBER. Device Applications are reported through CDRH. (Field Alert Reports (FARs) and Biologic Product Deviation Reports (BPDRs) do not follow this application-based approach.)

Combination products submitted under NDAs/ANDAs are subject to the safety reporting requirements described in **21 CFR Part 314**. Combination products submitted under BLAs are subject to the safety reporting requirements described in **21 CFR Parts 600 and 606**. Device Applications are subject to the safety reporting requirements described in **21 CFR Parts 803 and 806**. This foundational reporting is supplemented with specific reporting elements for each of the other constituent part(s) of the combination product

Same-similar reporting requirements also apply (see **21 CFR 803.50**).

## B. Background on Vigilance and Communicating with Regulatory Authorities

Vigilance and effective communication with regulatory authorities are crucial for the pharmaceutical and medical devices industries where safety and compliance are paramount. It's a critical component of a robust quality management system.

(Text from European Federation of Pharmaceutical Industries and Associations (EU-US Quality Management System (QMS) Requirements Comparison for Drug-Device Combination Products and Medicinal Products Co-packaged with Medical Devices)).

- Both the EU and the US mandate an adequate pharmacovigilance system for medicinal products. This system must comply with obligations for recording

and reporting suspected adverse reactions, as well as meeting post-marketing surveillance requirements related to the medicinal product.

This highlights the critical role of pharmacovigilance in monitoring the safety and effectiveness of medicinal products even after they have been released to the market. It helps ensure ongoing patient safety and compliance with regulatory standards
In the EU medicines vigilance applies for drug-device combination products. Application-based reporting is supplemented with specific reporting elements for each of the other constituent part(s) of the combination product. Same-similar reporting requirements also apply, whereby if a reportable event occurs on a same-or-similar constituent part of a combination product, there is an expectation that such event be reported in the US against the US-marketed product.

- **Vigilance reporting in the EU**

In the EU, reporting to the competent authority for the medicinal product is generally sufficient (i.e., the Competent Authority or the European Medicines Agency). However, there is no clear recommendation regarding the reporting of device complaints that might impact drug delivery between the National Competent Authority where the Notified Body is located and the Reference Authority for the medicinal product. It is advisable to also communicate any device problems with the Notified Body that issued the Notified Body Opinion Report, particularly in the case of a non-CE marked device.

Timescales EU-vigilance reports (where necessary to meet reporting timelines, an (incomplete) initial report is submitted that is followed up by a complete report.

| Incident type | Time line |
|---|---|
| Serious incident | **IMMEDIATELY** after having established the causal relationship between incident and device or that such causal relationship is reasonably possible **and no later than 15 calendar days after becoming aware of incident**. |
| Serious public health threat | **IMMEDIATELY** and **no later than 2 calendar days after becoming aware of threat**. |
| Death or unanticipated serious deterioration in a person's state of health | **IMMEDIATELY** after having established or suspected a causal relationship between device and serious incident **but no later than 10 calendar days after becoming aware of serious incident.** |

- **Postmarket Safety Reporting in the US**

In the US post marketing safety reporting is driven by application type and applicant type.

- **Application Type**: The requirements for post-marketing safety reporting can vary depending on the type of application submitted for regulatory approval (e.g., New Drug Application (NDA), Biologics License Application (BLA), etc.).
- **Applicant Type**: The entity responsible for submitting the application (e.g., manufacturer, distributor) also influences the reporting requirements.

- Supplemental Reporting Elements are:
  For combination products (products that combine different types of medical products, such as drugs and devices), postmarket safety reporting is supplemented with specific elements for each constituent part. This means that if a combination product includes a drug and a device, safety reporting must address both the drug component and the device component.

- Same-Similar Reporting Requirements:
  These requirements ensure that if a reportable event occurs in a constituent part of a combination product, the event must be reported for the US-marketed product. This applies even if the event occurs with a similar or identical part that is not part of the combination product but is marketed separately.

**EU Reporting to National Competent Authority for Device part**

In the EU, reporting to the competent authority for medicinal product is sufficient (Competent Authority / European Medicines Agency only). There is however no clear recommendation of reporting of device complaints with potential impact of drug delivery between National Competent Authority where the Notified Body is located and the Reference Authority of the medicinal product.

(Text from Integrated Quality Management System Framework: Incorporation of 21 CFR Part 820, ISO 13485:2016, ISO 9000:2015, and QMSR Requirements - § 820.10 Requirements for a quality management system)

**US Reporting / ISO 13485 requirement**

If applicable regulatory requirements require notification of complaints that meet specified reporting criteria of adverse events or issuance of advisory notices, the organization shall document procedures for providing notification to the appropriate regulatory authorities. Records of reporting to regulatory authorities shall be maintained.
Under Clause 8.2.3 of ISO 13485, which deals with complaint handling, manufacturers must notify the FDA of complaints that meet the reporting criteria outlined in 21 CFR Part 803.

(Text from Integrated Quality Management System Framework: Incorporation of 21 CFR Part 820, ISO 13485:2016, ISO 9000:2015, and QMSR Requirements - Part 4—

Regulation of Combination Products - Subpart B Postmarketing Safety Reporting for Combination Products)

If a combination product or its device constituent part has received marketing authorization under a device application, the manufacturer must comply with the postmarketing safety reporting requirements specified in **parts 803 and 806 of Title 21 of the Code of Federal Regulations (CFR)**.

- **§ 4.102 Reporting Requirements**

What reports must you submit to FDA for your combination product or constituent part?

(a) In general. If you are a constituent part applicant, the reporting requirements applicable to you that are identified in this section apply to your constituent part, and if you are a combination product applicant, the reporting requirements applicable to you that are identified in this section apply to your combination product as a whole.

(b) Reporting requirements applicable to both combination product applicants and constituent part applicants. If you are a combination product applicant or constituent part applicant, you must comply with the reporting requirements identified in paragraphs (b)(1), (b)(2), or (b)(3) of this section for your product based on its application type. If you are a combination product applicant, you are required to submit a report as specified in this paragraph unless you have already submitted a report in accordance with paragraph (c) of this section for the same event that: Includes the information required under the applicable regulations identified in this paragraph, is required to be submitted in the same manner under § 4.104, and meets the deadlines under the applicable regulations identified in this paragraph.

(1) If your combination product or device constituent part received marketing authorization under a device application, you must comply with the requirements for postmarketing safety reporting described in parts 803 and 806 of this chapter with respect to your product.

(2) If your combination product or drug constituent part received marketing authorization under an NDA or ANDA, you must comply with the requirements for postmarketing safety reporting described in part 314 of this chapter with respect to your product.

(3) If your combination product or biological product constituent part received marketing authorization under a BLA, you must comply with the requirements for postmarketing safety reporting described in parts 600 and 606 of this chapter with respect to your product.

(c) Reporting requirements applicable only to combination product applicants. If you are a combination product applicant, in addition to compliance with paragraph (a) of this section, you must also comply with the reporting requirements identified under this paragraph as applicable to your product based on its constituent parts. If you are a combination product applicant, you are required to submit a report as specified in this paragraph unless you have already submitted a report in accordance with paragraph (b) of this section for the same event that: Includes the information required under the applicable regulations for the report identified in this paragraph; is required to be submitted in the same manner under § 4.104 of this chapter; and, unless otherwise specified in this paragraph, meets the deadlines under the applicable regulations for the report identified in this paragraph.

(1) If your combination product contains a device constituent part, you must submit:

(i) Five-day reports;

(ii) (ii) Malfunction reports; and

(iii) Correction or removal reports, and maintain records as described in § 806.20 of this chapter for corrections and removals not required to be reported.

(2) If your combination product contains a drug constituent part, you must submit:

(i) Field alert reports; and

(ii) Fifteen-day reports as described in § 314.80 of this chapter, which must be submitted within 30 calendar days instead of 15 calendar days if your combination product received marketing authorization under a device application.

(3) If your combination product contains a biological product constituent part, you must submit:

(i) Biological product deviation reports; and

(ii) Fifteen-day reports as described in § 600.80 of this chapter, which must be submitted within 30 calendar days instead of 15 calendar days if your combination product received marketing authorization under a device application.

(d) Other reporting requirements for combination product applicants.

(1) If you are the combination product applicant for a combination product that contains a device constituent part and that received marketing authorization under an NDA, ANDA, or BLA, in addition to the information otherwise required in the periodic safety reports you submit under § 314.80 or § 600.80 of this chapter, your periodic safety reports must also include a summary and analysis of the reports identified in paragraphs (c)(1)(i) and (ii) of this section that were submitted during the report interval.

(2) If you are the combination product applicant for a combination product that received marketing authorization under a device application, in addition to the reports required under paragraphs (b) and (c) of this section, you must submit reports regarding postmarketing safety events if notified by the Agency in writing that the Agency requires additional information. We will specify what safety information is needed and will require such information if we determine that protection of the public health requires additional or clarifying safety information for the combination product. In any request under this section, we will state the reason or purpose for the safety information request, specify the due date for submitting the information, and clearly identify the reported event(s) related to our request.

- **§ 4.103 Information to share with other constituent part applicants**

§ 4.103 What information must you share with other constituent part applicants for the combination product?

(a) When you receive information regarding an event that involves a death or serious injury as described in § 803.3 of this chapter, or an adverse experience as described in § 314.80(a) of this chapter or § 600.80(a) of this chapter, associated with the use of the combination product, you must provide the information to the other constituent part applicant(s) for the combination product no later than 5 calendar days of your receipt of the information.

(b) With regard to information you must provide to the other constituent part applicant(s) for the combination product, you must maintain records that include:

(1) A copy of the information you provided,

(2) The date the information was received by you,

(3) The date the information was provided to the other constituent part applicant(s), and

(4) The name and address of the other constituent part applicant(s) to whom

you provided the information.

- **§ 4.104 How and where to submit postmarketing safety reports**

§ 4.104 How and where must you submit postmarketing safety reports for your combination product or constituent part?

(a) If you are a constituent part applicant, you must submit postmarketing safety reports in accordance with the regulations identified in § 4.102(b) that are applicable to your product based on its application type.

(b) If you are a combination product applicant, you must submit postmarketing safety reports required under § 4.102 in the manner specified in the regulation applicable to the type of report, with the following exceptions:

(1) You must submit the postmarketing safety reports identified in § 4.102(c)(1)(i) and (ii) in accordance with § 314.80(g) of this chapter if your combination product received marketing authorization under an NDA or ANDA or in accordance with § 600.80(h) of this chapter if your combination product received marketing authorization under a BLA.

(2) You must submit the postmarketing safety reports identified in § 4.102(c)(2)(ii) and (c)(3)(ii) in accordance with § 803.12(a) of this chapter if your combination product received marketing authorization under a device application.

**§ 4.105 Postmarketing safety reporting recordkeeping requirements**

§ 4.105 What are the postmarketing safety reporting recordkeeping requirements for your combination product or constituent part?

(a) If you are a constituent part applicant:

(1) You must maintain records in accordance with the recordkeeping requirements in the applicable regulation(s) described in § 4.102(b).

(2) You must maintain records required under § 4.103(b) for the longest time period required for records under the postmarketing safety reporting regulations applicable to your product under § 4.102(b).

(b) If you are a combination product applicant, you must maintain records in accordance with the longest time period required for records under the regulations applicable to your product under § 4.102.

## A. Background on Post-Market Surveillance (PMS)

PMS is systematic process to collect and analyze experience gained from medical devices that have been placed on the market.
Post-marketing surveillance is essential for ensuring ongoing product safety, regulatory compliance, risk mitigation, product improvement, stakeholder trust and legal protection. It's a critical component of a robust quality management system.

(Text from Section 4 Post Marketing Surveillance)

Post-Market 'Safety' Reporting (PMS) and demonstrating compliance with post-approval modifications are critical components of the **EU Medical Device Regulation (MDR), ISO 13485:2016, and Quality Management System Regulation (QMSR)**.

In contrast to the USA, in the EU, there is no requirement to comply with the EU MDR 2017/745 Articles 83-86 requirements for post-market surveillance (PMS) of the device component of a Single Integral Drug-Device Combination (DDC) product *that is not CE marked*.

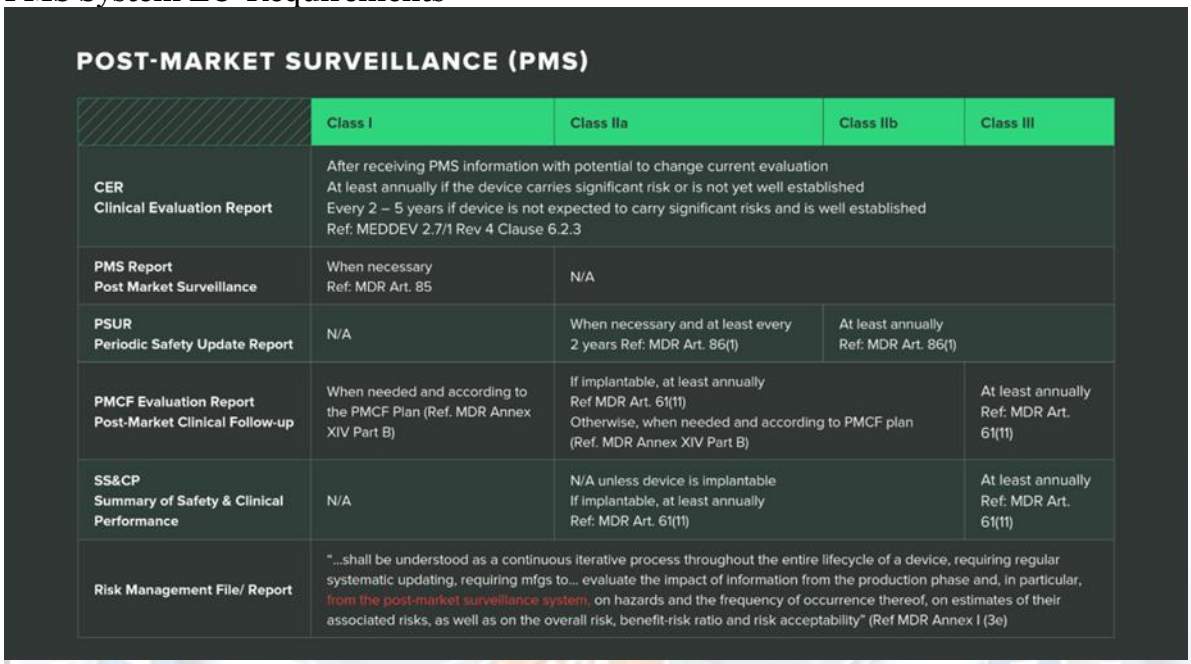
However, if the device component bears the CE mark of conformity, PMS is a Quality Management System (QMS) requirement per MDR, and it is subject to audits by notified bodies. Conversely, if the device is not CE marked but a notified body has confirmed that the device meets the General Safety and Performance Requirements (GSPRs), the PMS processes and indeed none of the QMS processes are subject to notified body assessments.

Although it may seem ambiguous, it is advisable to document and implement the required Post-Market Surveillance (PMS) system. Implementing a PMS system for a non-CE marked device component in a Drug-Device Combination (DDC) product not only enhances patient safety and product quality but also prepares the manufacturer for future regulatory changes, builds trust, and provides a competitive market advantage.

**Importance of PMS:**

- Continuous Monitoring: PMS involves the continuous monitoring of medical devices once they are on the market. This helps identify any unforeseen risks or issues that may arise during the device's lifecycle.
- Timely Identification of Risks: PMS allows manufacturers to detect and address risks promptly, ensuring the safety and effectiveness of the device.
- Regulatory Compliance: PMS is a regulatory requirement under the MDR (Articles 83-86) and ISO 13485:2016 / QMSR (Clause 8). Compliance with these requirements is essential for maintaining market authorization.
- Improvement Opportunities: PMS provides insights into potential improvements for the device, enhancing its performance and user satisfaction.

PMS System EU-Requirements




For the EU, the following formats may apply to your device:

| | |
|---|---|
| **PMS Plan** | Annual plan addressing 'PMS' for class I devices, 'PSUR' for class IIa, IIb and III devices and, if decided to perform, 'PMCF' for all risk classes.<br>*Note: if motivated, the PMS Plan of the previous year may be continued for the next year.*<br><br>The plan covers at least:<br>-a proactive and systematic process to collect any information referred to in Section 6.2.1. The process shall allow a correct characterization of the performance of the devices and shall also allow a comparison to be made between the device and similar products available on the market;<br>-effective and appropriate methods and processes to assess the collected data;<br>-suitable indicators and threshold values that shall be used in the continuous reassessment of the benefit-risk analysis and of the risk management as referred to in Section 3 of Annex I;<br>-effective and appropriate methods and tools to investigate complaints and analyze market-related experience collected in the field;<br>-methods and protocols to manage the incidents subject to the trend |

| | |
|---|---|
| | report as provided for in Article 88, including the methods and protocols to be<br><br>used to establish any statistically significant increase in the frequency or severity of incidents as well as the observation period;<br>-methods and protocols to communicate effectively with competent authorities, notified bodies, economic operators and users;<br>-reference to procedures to fulfil the manufacturers obligations laid down in Articles 83, 84 and 86;<br>-systematic procedures to identify and initiate appropriate measures including corrective actions;<br>-effective tools to trace and identify devices for which corrective actions might be necessary; and<br>-a PMCF plan as referred to in Part B of Annex XIV, or a justification as to why a PMCF is not applicable |
| **PMS Report** | Post market surveillance report concerning class I devices (MDR Article 85). Output of the PMS Plan for class I devices. |
| **Post Market Clinical Follow-up (PMCF) study** | A study carried out following the market release of a device and intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of a device when used in accordance with its approved labeling including post-production monitoring activities which identify and investigate potential risks associated with the use of the product placed on the market |
| **Periodic Safety Update Report (PSUR)** | Periodic Safety Update (PSU) Report summarizing the results and conclusions of the analyses of the:<br>(a) benefit-risk determination, (b) main findings of the PMCF and (c) the volume of sales of the device and an estimate evaluation of the size and other characteristics of the population using the device and, where practicable, the usage frequency of the device, together with a rationale and description of any preventive and corrective actions taken concerning each device and where relevant for each category or group of risk class IIa, class IIb and class III devices.<br>Output of the PMS Plan for class IIa, IIb and III devices. |

**Demonstrating Compliance with Post-Approval Modifications is important because of:**

- Ensuring Safety and Performance: Post-approval modifications must be managed to ensure that any changes do not compromise the safety and performance of the device.
- Regulatory Approval: Substantial changes require approval from the Notified Body before implementation. This ensures that the device continues to meet

regulatory requirements.

- Documentation and Traceability: All modifications and their impacts must be documented and traceable, as required by ISO 13485:2016 / QMSR and the MDR.
- Lifecycle Management: Effective management of post-approval modifications is part of a comprehensive lifecycle management strategy, ensuring the device remains compliant throughout its lifecycle.

By prioritizing post-market safety reporting and compliance with post-approval modifications, manufacturers can maintain the highest standards of safety, performance, and regulatory compliance for their medical devices.