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POSTMARKETING SAFETY REPORTING: A COMPREHENSIVE REVIEW OF USFDA PERSPECTIVES ON COMBINATION PRODUCTS

ASHOKKUMAR G AND RAJU KAMARAJ*

Department of Pharmaceutical Regulatory Affairs, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur-603203 Chengalpattu, Tamil Nadu, India

***Corresponding Author: Dr. Raju Kamaraj: E Mail: kamarajr@srmist.edu.in**

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ABSTRACT

The post marketing safety reporting for combination products is a crucial aspect of ensuring the continued safety and effectiveness of these complex medical innovations. Combination products, which merge drugs, medical devices, and biologics, present unique challenges in pharmacovigilance due to their diverse components and potential interactions. This abstract provides an overview of the key considerations and requirements for post marketing safety reporting of combination products. Regulatory agencies, such as the FDA in the United States, play a central role in overseeing post marketing surveillance. Manufacturers, healthcare professionals, and consumers are encouraged to report adverse events and safety concerns related to combination products to these agencies. Timely and accurate reporting facilitates the detection of new or rare adverse events, enabling swift risk assessment and management. The complexity of combination products necessitates coordinated efforts among different regulatory divisions responsible for drugs, medical devices, and biologics. Manufacturers must follow distinct reporting guidelines for each constituent part of the combination product. Additionally, combination products subject to Risk Evaluation and Mitigation Strategies (REMS) require compliance with specific safety reporting requirements. Post marketing safety reporting provides valuable insights into the ongoing benefits and risks associated with combination products in real-world settings. Continuous advancements in surveillance methodologies and data analytics enhance the identification of safety signals and the understanding of long-term safety profiles.

Keywords: Surveillance, Biologics, Medical devices, FDA, NDA

INTRODUCTION

Combination products, which merge drugs, medical devices, and biological products, represent a growing category of innovative healthcare solutions that offer unique therapeutic benefits and improved patient outcomes **[1]**. As these products come to market, ensuring their safety and effectiveness becomes paramount. The post marketing phase is a critical period where potential adverse events and safety issues may emerge after the product is available to a broader patient population **[2]**. To safeguard public health, regulatory agencies, particularly the Food and Drug Administration (FDA) in the United States, have established robust post marketing safety reporting requirements for combination products **[3]**. When dealing with combination product makers, it can be difficult to navigate a complex regulatory environment while complying to different reporting requirements for each component part of their product. The practice of post-marketing safety surveillance may be made more complicated by the reporting requirements for adverse events involving pharmaceuticals, medical devices, and biological products. The essential criteria for combination product-specific post marketing safety reporting are examined in this paper **[4]**. We'll go into the important rules that the FDA has detailed, which are used as a primary guide by manufacturers and medical practitioners to guarantee prompt and correct reporting of adverse occurrences. We will also go over the importance of individual case safety reports, regular safety reporting, and Risk Evaluation and Mitigation Strategies (REMS) as key elements of a successful post marketing safety surveillance system **[5]**.

Combination Products

The Food and Drug Administration (FDA) of the United States defines combination. “A product made up of two or more regulated components, such as drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; two or more separate products packaged together in a single package or as a unit and made up of drug and device products, device and biological products, or biological and drug products."**[6]** A drug, device, or biological product packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, both are required to achieve the intended use, indication, or effect. the labelling of the approved product would need to be changed,

e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose **[7]**.

Post marketing surveillance (PMS)

Post marketing surveillance is a critical aspect of ensuring the safety and efficacy of drugs, medical devices, and biologics after they have been approved and are available for use in the general population. It involves the systematic monitoring and evaluation of these products in real-world settings to identify and assess any adverse effects, safety concerns, or unexpected issues that may not have been evident during pre-market clinical trials or studies **[8]**.

a. Post marketing Surveillance for Drugs:

Post marketing surveillance for drugs, also known as pharmacovigilance, involves the ongoing collection, analysis, and evaluation of data related to adverse drug reactions (ADRs) and any other safety concerns that arise following a drug's approval and widespread use. Pharmaceutical companies, healthcare professionals, and consumers all play crucial roles in reporting adverse events to regulatory authorities. The primary purpose of drug surveillance is to detect previously unknown or rare side effects, assess their severity and frequency, and take appropriate measures to protect patient safety. Data collected during post marketing surveillance may lead to label updates, safety communications, or, in extreme cases, the withdrawal of a drug from the market **[9]**.

b. Post marketing Surveillance for Medical Devices:

Post marketing surveillance for medical devices involves monitoring and assessing the performance, safety, and reliability of devices that are already in use by patients and healthcare providers. The surveillance process includes collecting data on adverse events, malfunctions, or device-related complications. Manufacturers, healthcare facilities, and users are encouraged to report adverse events associated with medical devices to regulatory agencies, such as the Food and Drug Administration (FDA) in the United States. Post marketing surveillance enables the identification of potential design flaws, usability issues, or rare adverse events that may not have been detected during pre-market testing **[10]**.

c. Post marketing Surveillance for Biologics:

Biologics are complex products derived from living organisms and can include vaccines, blood and blood products, gene therapies, and cell-based therapies. Post marketing surveillance for biologics is crucial to monitor their safety, efficacy, and long-term effects in real-world settings. The evaluation of data from post marketing surveillance helps identify any unexpected adverse reactions or issues that may not have been evident during clinical trials. As with

drugs and medical devices, regulatory authorities, healthcare professionals, and manufacturers collaborate to collect and analyse post marketing safety data for biologics to ensure ongoing patient safety **[11]**.

Process Considerations for Combination Product Applicants

How to Submit Combination Product PMSR Information to FDA

1. Timelines followed for submitting the reports

With the exception of combination products that receive marketing authorization under a Device Application, fifteen-day reports required by 21 CFR 314.80 or 600.80 can be submitted within 30 calendar days rather than within 15 calendar days. Combination Product Applicants follow the deadlines associated with the report type **[12]**.

Table 1: Timelines for Various Combination Product PMSR Requirements

Report Type	Timeline for Reporting
Fifteen-day Reports	**ANDA, NDA, and BLA combination products: No later than 15 calendar days from initial receipt of the information by the applicant Device Application combination products: No later than 30 calendar days from initial receipt of information by the applicant [13]**
Follow-ups to Fifteen-day Reports	**ANDA, NDA, and BLA combination products: Within 15 calendar days of receipt of new information Device Application combination products: No later than 30 calendar days from initial receipt of new information by the applicant [14]**
Five-day Reports	• **No later than 5 work days after the day that the applicant "becomes aware" that a reportable event(s) necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health [15]**
Death/Serious Injury/Malfunction Reports	**No later than 30 calendar days after the day that the applicant receives information or otherwise becomes aware of the event**
Supplemental/ Follow-up reports to Five-day/ Death/ Serious Injury/ Malfunction Report	**Within 30 calendar days of the day that the applicant receives information**
Field Alert Reports	**Within 3 working days of receipt of the information by the applicant**
Biological Product Deviation Reports	**As soon as possible but not to exceed 45 calendar days from the date of acquiring information reasonably suggesting that a reportable event has occurred**
Correction and Removal Reports	• **Within 10 working days of initiating correction or removal**

2. Submission process

• A Device Application combination product, submit all ICSRs (including Fifteen-day reports) in accordance with 21 CFR 803.12(a) and associated guidance;

• An NDA or ANDA combination product, submit all ICSRs (including Five-day reports and Malfunction reports, if the combination product includes a device constituent part) in accordance with 21 CFR 314.80(g) and associated guidance;

• A BLA combination product, submit all ICSRs (including Five-day reports and Malfunction reports, if the combination product includes a device constituent part) in

accordance with 21 CFR 600.80(h) and associated guidance **[16]**.

Challenges with Regulating Combination Products:

- Combination items can be difficult to market because they comprise at least two components that are governed by distinct sections of the FDA when examined as independent devices.
- Policy, regulatory, scientific, and review management challenges occur. The regulatory compliance pathway that allows for market entry affects all aspects of product development, including preclinical testing, clinical research, market application, manufacturing controls, quality controls, adverse event reporting, and post-market adjustments **[17]**.
- When applications for combination product market clearance and individual case regulations are taken into account, regulation becomes more complicated.
- Due to a competitive advantage or benefit, such as drug exclusivity or advantages associated with orphan medications, a producer may decide to submit more than one application for a specific combination product.
- In other circumstances, when more than one company is engaged, two submissions may be preferred for the protection of private information.
- Due to the additional layer of difficulty in obtaining market clearance, post-market adjustments in such instances may be challenging to handle. Determining which (cGMP) for the drug or biologic constituent part and which (QSR) for the device constituent part needs to be followed presents extra difficulties due to quality system management.
- You can follow the component part. FDA will permit a simplified process where the manufacture may be fully compliant with either the cGMP or the QSR requirements for single-entity and kit combination goods. If the manufacturer is fully complying with QSR rules, then the manufacturer must also be compliant with a subset of cGMP standards to account for gaps between cGMP and QSR laws. A subset of QSR standards must also be followed in order to comply with the requirements of the streamlined method, even if the manufacturer is completely compliant with cGMP regulations. The numerous methods are offered **[18]**.

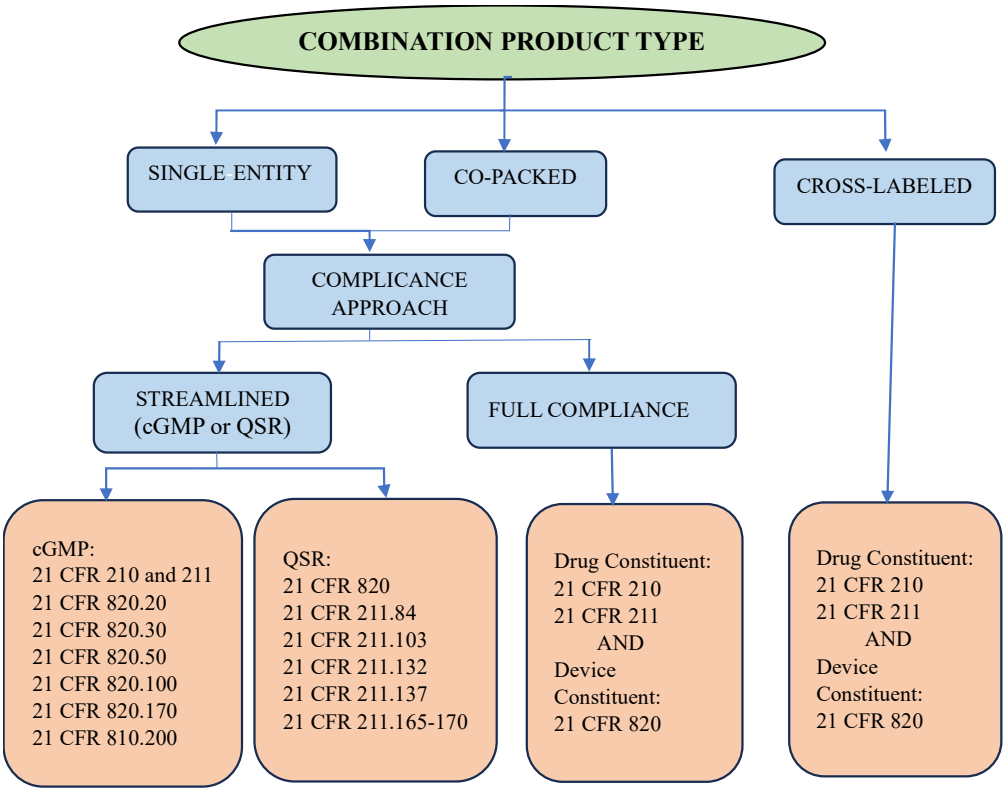

Figure 1: Approaches to quality systems for combination products

Regulation and reviewing of combination products:

- The CBER, the CDER, or the CDRH review and regulate combination products. According to Section 503(g) of the Federal Food, Drug, and Cosmetic Act, the FDA must designate a centre as having main jurisdiction for the regulation of a combination product based on the product's primary mode of action (PMOA).
- According to the FDA, the "therapeutic" action or effect includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease or affect the structure or any function of the body (21 CFR 3.2(k)). The FDA defines mode of action as "the means by which a product achieves its intended therapeutic effect or action."
- The PMOA is described by the FDA as "the single mode of action of a combination product that provides the key therapeutic effect of the combination product."**[19]**

Process that FDA use to determine the PMOA and the lead centre:

A product's regulatory classification as a medicine, device, biological product, or

combination product is frequently obvious. Similar to that, a combination product's PMOA is frequently evident. The location of a product's jurisdiction, however, could occasionally be ambiguous or in question. In these circumstances, sponsors may submit a Request for Designation to have the classification and assignment of a product determined **[20]**.

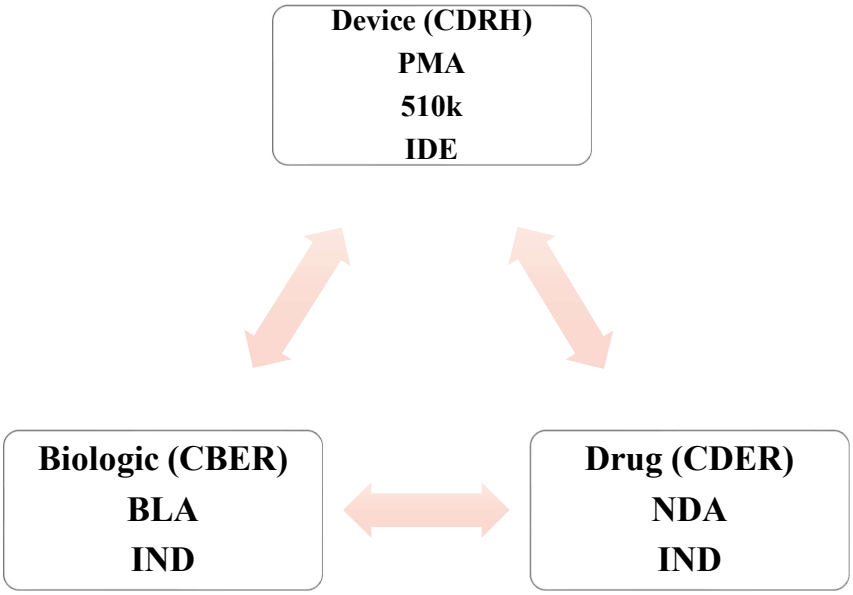

Figure 2: Regulatory approaches. Combination products combine drugs, devices, and biologics

CONCLUSION

Post marketing safety reporting for combination products is a critical component of ensuring the continued safety and efficacy of these complex medical innovations in real-world settings. As combination products bring together drugs, medical devices, and biologics, their diverse nature demands a comprehensive and collaborative approach to surveillance and reporting. Manufacturers, healthcare professionals, and regulatory agencies must work in tandem to collect and analyse adverse event data, identify potential risks, and implement appropriate safety measures promptly. By fostering a culture of vigilant reporting, the healthcare community can swiftly address emerging safety concerns, leading to improved patient outcomes and public health protection. The FDA in the United States and similar regulatory agencies worldwide play pivotal roles in overseeing the post marketing safety reporting process for combination products. Adherence to their guidelines ensures that any new safety information is promptly communicated to healthcare providers and patients, enabling informed decisions regarding treatment options. Continuous advancements in pharmacovigilance

technologies and surveillance methodologies further enhance our ability to detect and understand potential safety issues associated with combination products. By leveraging real-world data and analytics, regulatory bodies can gain deeper insights into long-term product safety profiles, enabling evidence-based decision-making and timely risk mitigation strategies. post marketing safety reporting remains an essential pillar in upholding patient safety and public confidence in combination products. Embracing a proactive and collaborative approach to monitoring, reporting, and addressing safety concerns ensures that these innovative medical solutions continue to deliver the intended therapeutic benefits while minimizing potential risks to patients worldwide.

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CONFLICT OF INTEREST

The author declared no conflict of interest.

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