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Developing A Framework for Life Cycle Management of Combinational Products

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Abstract
Combination products—comprising drug-device, drug-biologic, or device-biologic elements—present unique regulatory and management challenges throughout their life cycle. As global regulatory bodies such as the US FDA, EMA, and CDSCO continue to refine policies governing such products, there is a critical need for a structured framework to guide their development, approval, post-market surveillance, and regulatory compliance. This project aims to develop a comprehensive, regulatory-focused life cycle management framework for combination products, aligning with international standards and focusing on non-laboratory processes. The study will involve in-depth literature analysis, regulatory guideline comparison, expert interviews, and workflow mapping to ensure effective regulatory strategy and compliance management.

Keywords: Combination products, life cycle management, regulatory framework, drug-device, FDA, EMA, CDSCO, post-market surveillance, regulatory compliance

Introduction
Combination products, which integrate two or more regulated components—such as a drug and device, a drug and biologic, or a device and biologic—represent a rapidly evolving class of medical interventions. These products are designed to offer enhanced therapeutic efficacy, improved patient compliance, and novel modes of administration. Examples include drug-eluting stents, pre-filled auto-injectors, and antibody-coated diagnostic tools. While these innovations hold significant promise for personalized and efficient healthcare delivery, their hybrid nature also presents considerable regulatory and management complexities across their life cycle^[1,2].

The global market for combination products is witnessing robust growth, driven by technological advancements, the rise in chronic disease prevalence, and increasing demand for integrated therapeutic solutions. Market reports suggest that this sector is projected to grow at a CAGR of over 8% in the coming years, with substantial investments from both pharmaceutical and medtech industries. This surge is prompting regulatory agencies across jurisdictions to revisit and refine their oversight mechanisms to ensure safety, efficacy, and quality compliance without hindering innovation^[3,4].

However, the regulation of combination products is fraught with challenges that differ significantly from single-entity products. These include difficulties in product classification, divergent regulatory pathways, dual jurisdiction between centers (e.g., drugs vs. devices), and

inconsistencies in data requirements. Additionally, product developers often struggle with the absence of harmonized guidelines, especially when seeking global approvals. Post-market surveillance, change management, and device recalls further complicate the regulatory landscape due to the interplay between the different components of the product^[5–7].

A key limitation in the current scenario is the lack of a structured regulatory strategy that spans the full product life cycle—from early development through market entry and beyond. Existing frameworks tend to focus on laboratory validation, clinical trials, or component-level evaluation, often overlooking integrated life cycle planning. As a result, manufacturers face delays, regulatory uncertainties, and compliance risks that could be mitigated with better upfront planning^[8,9].

This study aims to address this gap by developing a comprehensive, regulatory-focused life cycle management framework tailored specifically for combination products. The proposed framework emphasizes non-laboratory processes—such as regulatory submission strategy, stakeholder alignment, post-market surveillance, and compliance tracking—and seeks to align with international best practices. Through regulatory literature review, comparative analysis, expert consultations, and process mapping, the framework intends to serve as a practical guide for industry stakeholders navigating the complex and evolving regulatory ecosystem of combination products.

Methodology

To develop a robust and practical life cycle management framework for combination products, a multi-step methodological approach was adopted, integrating qualitative research techniques with regulatory and process analysis. The focus remained on non-laboratory elements such as regulatory submission planning, compliance, and post-market oversight.

Literature Review

A comprehensive literature review was conducted to capture the regulatory landscape governing combination products across key global agencies—namely the **U.S. Food and Drug Administration (FDA)**, **European Medicines Agency (EMA)**, **Central Drugs Standard Control Organization (CDSCO, India)**, and **Pharmaceuticals and Medical Devices Agency (PMDA, Japan)**. This review included official guidance documents, legislative frameworks, and position papers released between 2005 and 2024.

Scientific articles from journals such as *Regulatory Affairs Journal Pharma*, *Nature Reviews Drug Discovery*, and *The Journal of Medical Devices* were screened. In addition, white papers from industry groups and international harmonization bodies like ICH, IMDRF, and WHO were considered to provide context on global best practices.

Table 1: Regulatory Documents Reviewed by Region

Agency	Document Type	Key Focus Area	Year

FDA	Guidance for Industry: Current Good Manufacturing Practice for Combination Products	Post-approval compliance	2013
EMA	Guideline on the quality requirements for drug-device combinations	Device integration in drug products	2019
CDSCO	Medical Device Rules, Schedule Y	Combination product categorization	2017
PMDA	Regulatory Review Process for Drug-Device Products	Market authorization pathways	2020

2. Comparative Regulatory Analysis

To better understand the divergence in regulatory approaches, a comparative analysis was conducted across the major agencies. Parameters such as **product classification**, **primary mode of action (PMOA) evaluation**, **submission pathway**, **timeline**, and **post-market surveillance requirements** were mapped and compared.

Table 2: Comparative Overview of Regulatory Requirements

Criteria	FDA	EMA	CDSCO	PMDA
Classification Mechanism	PMOA via OCP	Risk-based + primary function	Device-first or drug-first	Product-type-specific review
Approval Pathway	IND/NDA or 510(k)/PMA	MAA (with notified body)	DCGI + Medical Device Division	NDA or Device Dossier
Review Time (avg.)	9–12 months	12–14 months	9–18 months	12–18 months
Post-Market Requirements	Annual reports + MDR	Vigilance + periodic reviews	Pharmacovigilance + audits	Reevaluation every 5 years

3. Expert Interviews

To enrich the framework with real-world insight, **semi-structured interviews** were conducted with regulatory affairs professionals from pharmaceutical and medtech industries. Participants had 5–20 years of experience working with combination products in global regulatory functions.

Key questions addressed included:

- Major bottlenecks in combination product submissions
- Experience with dual-agency review processes
- Common causes of regulatory delays or rejections
- Strategies for regulatory harmonization and proactive compliance

Themes emerging from the interviews were categorized using **qualitative content analysis** and incorporated into the design of the framework.

4. Workflow Mapping

To visualize and optimize the regulatory management of combination products, **workflow mapping** techniques were applied to the life cycle phases:

- **Development and Pre-market Planning**
- **Regulatory Submission and Approval**
- **Post-market Surveillance and Compliance**

Using tools like **RACI matrices**, **regulatory decision trees**, and **process flowcharts**, the responsibilities, timelines, and regulatory touchpoints were clearly defined for each phase. These visual tools aimed to streamline interdepartmental coordination and clarify regulatory expectations throughout the product life cycle.

Table 3: RACI Matrix for Regulatory Life Cycle Management

Phase	Activity	Responsible	Accountable	Consulted	Informed
Development	Classification Assessment	Reg Affairs	QA Head	R&D	Clinical
Submission Planning	Pathway Determination	Reg Affairs	Regulatory Lead	Legal	Quality
Post-Market Surveillance	Adverse Event Reporting	Pharmacovigilance	Safety Officer	Regulatory	CEO
Change Management	Dossier Update for Device Change	QA	Reg Affairs	R&D	Sales

This comprehensive methodology enabled the creation of a practical, harmonized, and globally relevant framework for managing the regulatory life cycle of combination products beyond laboratory processes.

Results

1. Proposed Framework Structure

The developed framework divides the life cycle of combination products into three primary regulatory phases, each with defined objectives and processes to ensure regulatory compliance and traceability across global markets.

Table 1: Regulatory Life Cycle Phases and Key Focus Areas

Phase	Key Activities
Pre-market	- Product classification (e.g., primary mode of action) - Jurisdictional assignment - Regulatory pathway selection (IND, IDE, NDA, PMA, 505(b)(2), etc.) - Submission strategy planning (global harmonization)
Market Authorization	- Preparation of CTD / eCTD format - Inter-center collaboration (drug/device/biologic divisions) - Responding to regulatory queries and deficiency letters - Coordinated review tracking (lead agency management)
Post-market	- Pharmacovigilance and device vigilance integration - Post-approval change management (supplements, variations) - Complaint handling and field safety actions - Periodic safety updates and renewal filings

This structured approach ensures the seamless transition of regulatory data, documentation, and decisions across the life cycle and between stakeholders.

2. Roles and Responsibilities

The framework outlines clear roles and responsibilities for different functions, aiming to reduce overlaps and ensure accountability in regulatory decision-making and compliance activities.

Table 2: Stakeholder Roles Across the Combination Product Life Cycle

Stakeholder	Pre-market	Market Authorization	Post-market
Manufacturer (Sponsor)	Initiate classification, regulatory strategy	Compile dossier, coordinate agency meetings	Monitor safety, implement corrective actions
Regulatory Affairs	Jurisdictional mapping, submission planning	Lead submission process, respond to agency queries	Track compliance updates, manage change submissions
Quality Assurance	Design control and QMS compliance	Support inspections and audits	Oversee vigilance, handle complaints

Clinical Affairs	Study design alignment	Clinical data submission	PMS and registry management
Legal / Compliance	IP considerations, risk analysis	Labeling, jurisdictional defense	Legal support during recalls or litigation

This RACI-style matrix ensures all life cycle phases have function-specific contributions clearly mapped.

3. Tools Developed

To operationalize the framework, the following tools were designed for internal regulatory use:

- **Regulatory Checklist:**
  A phase-wise checklist covering classification criteria, global submission document requirements (e.g., labeling, device master file, CMC, non-clinical, and clinical modules), post-approval surveillance protocols, and adverse event reporting formats.

- **Harmonized Documentation Templates:**
  Common templates for combination product summaries, integrated risk-benefit assessments, bridging studies, and declaration of conformity for multi-regulatory submissions (FDA, EMA, CDSCO).

- **Life Cycle Traceability Matrix:**
  A traceability matrix that connects product design, regulatory documentation, approval conditions, and post-market surveillance outcomes to ensure audit readiness and product history transparency.

4. Comparative Insights

A comparative review of regulatory pathways and review timelines revealed significant differences in approach across agencies:

Table 3: Comparison of Regulatory Requirements Across Major Agencies

Parameter	FDA (USA)	EMA (EU)	CDSCO (India)
Primary Mode of Action (PMOA)	Determines lead center (CDER, CBER, CDRH)	Drug primary → EMA; Device primary → NB	CDSCO decision with inputs from relevant panels
Submission Pathway	NDA/ANDA, PMA, De Novo, BLA, IND, IDE	Centralized Procedure, CE mark + dossier	CTD with Form MD-29 for device-drug products
Review Timelines (Standard)	10–12 months (NDA), 180 days (PMA)	210 days (excluding clock-stops)	90–120 working days depending on classification

Post-approval Changes	Supplements (CBE-0, PAS, annual reports)	Variations (Type IA/B, Type II)	Amendments or fresh applications depending on scope
Vigilance System	FAERS + MedWatch + MDR reporting	EudraVigilance + Manufacturer reporting	Materiovigilance + PvPI for drug components

These differences highlight the need for a harmonized internal framework to ensure consistency in submissions and post-market compliance across regions.

Discussion

The development of a regulatory-focused life cycle management framework for combination products presents a significant advancement in managing the complexities associated with these hybrid entities. Given the intersection of drug, device, and biologic regulatory pathways, the proposed framework enables manufacturers and regulatory professionals to reduce compliance risks, streamline submission timelines, and enhance interdepartmental coordination. By establishing structured roles, harmonized documentation, and decision-making checkpoints across the product life cycle, the framework aligns with the expectations of major global regulatory bodies such as the FDA, EMA, and CDSCO. This not only minimizes the chances of regulatory delays or rejections but also ensures traceability and preparedness for audits or inspections.

During the course of the framework development, several critical challenges were identified. A primary concern is the issue of **overlapping jurisdiction**, where combination products may fall under multiple regulatory centers (e.g., CDRH and CDER in the U.S.), often leading to ambiguity in submission strategy and review responsibility. Additionally, the **lack of unified global guidance** means that manufacturers must customize their approach for each target market, which can be resource-intensive and error-prone. The **post-market phase**, in particular, remains fragmented due to disparate vigilance systems for drugs and devices, creating inconsistencies in safety reporting, recall mechanisms, and corrective actions.

To address these challenges, the study recommends **early regulatory engagement**—especially during the pre-market phase—to gain clarity on classification and jurisdictional authority. Proactive interaction with regulators (e.g., pre-submission meetings or scientific advice sessions) can significantly improve the alignment of development strategy with regulatory expectations. Moreover, the study advocates for **greater alignment with international standards**, such as ICH guidelines for drugs and IMDRF principles for medical devices, to streamline cross-border submissions. A major recommendation is the development of a **Global Combination Product Master File** or a **centralized regulatory dossier model** that integrates drug, device, and biologic components into a single, modular format that can be adapted per region. Such a system could drastically reduce redundancy, ensure data consistency, and support digital transformation in regulatory operations.

The utility of this framework is particularly evident in multinational product development and regulatory audits. With increasing globalization, manufacturers often seek simultaneous approvals in the U.S., Europe, and emerging markets like India. The framework serves as a strategic tool to coordinate submissions, manage document harmonization, track changes post-approval, and respond to region-specific requirements with agility. It also supports internal

teams by providing standardized templates, checklists, and stakeholder matrices—thereby fostering better cross-functional collaboration.

Conclusion

This study presents a comprehensive, structured framework for the life cycle management of combination products, with a strong emphasis on regulatory strategy and operational efficiency. The framework successfully bridges a critical gap in current industry practice by offering a unified approach to managing classification, regulatory submissions, and post-market responsibilities for drug-device-biologic products. It not only reduces the risk of regulatory non-compliance but also promotes better planning, accountability, and alignment with evolving global standards.

The proposed model has strong potential for adoption across regulatory, quality, and product development functions within pharmaceutical and medtech companies. Its modular design allows for flexibility in application, whether for new product submissions or existing product updates. Importantly, it empowers teams to take a proactive stance in managing regulatory complexity, which is vital in the rapidly evolving landscape of combination products.

Looking ahead, the framework can be further validated through **real-world case studies**, pilot implementations, and expert feedback. Future work could also explore **integration with AI-based regulatory intelligence platforms**, which can automate compliance tracking, identify global regulatory changes, and assist in preparing adaptive submissions. As the regulatory ecosystem embraces digitization and convergence, frameworks like the one proposed in this study will play a crucial role in shaping the next generation of combination product oversight.

References

1. Gupta DK, Yadav Y, Joshi M, et al. Ensuring safety and efficacy in combination products: regulatory challenges and best practices. *Front Med Technol*. 2024;1:1377443.
2. Pallathadka LK, Kumar A, Keshamma E, Jyothsna BS, Pallathadka H. A review research in drug-device using combination product from invention. *Int J Pharm Sci Res*. 2021;6(4):6-11.
3. Regulatory Knowledge Guide for Combination Products. NIH SEED Innovator Support Team. 2023.
4. West Pharma. Post-market strategies/lifecycle management of co-packaged drug/device combinations – a device manufacturer's perspective. *West Pharma Blog*. 2024 Aug.
5. AAPS Open. Stability considerations for drug-device combination products. 2023;5:00078-5.
6. FDA. Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products. 2015.
7. RAPS. Drug-device combination products: device regulatory submission considerations. *Regulatory Focus*. 2023 Dec.
8. Freyr Solutions. Regulatory strategies for combination products: navigating complex pathways. 2025.
9. Premier Research. Regulatory strategy for combination devices: working with the FDA for program success. 2021.
10. Complex Generics. Session 7: Drug-Device Combination Products. 2022.
11. Sciencedirect. The combination of medical devices and medicinal products: regulatory interface review. 2021.

12. ScienceDirect. Drug–device combinations in rare diseases: regulatory approaches and case studies. 2025.
13. AAPS Open. Stability considerations for drug-device combination products. 2023.
14. NIH SEED. Regulatory Knowledge Guide for Combination Products. 2023.
15. FDA. 21 CFR Part 4 final rule. 2013.
16. FDA. Part 4.4(b) streamlined approach for combination products. 2013.
17. FDA. CGMP requirements for combination products. 2015.
18. FDA. Definitions of single-entity, co-packaged, cross-labeled. 2015.
19. FDA. Office of Combination Products: role and responsibilities. 2015.
20. Medical Device Courses. Review of Combination Products: FDA center assignment. 2018.
21. Freyr Solutions. Regulatory strategies for combination products. 2025.
22. Redica. Navigating FDA guidelines for combination products. 2024.
23. Complex Generics. Drug-Device Combination Products session. 2022.
24. American Pharm Review. Product development and manufacturing challenges for combination products. 2018.
25. RAPS. Regulatory submission of device constituent in combination products. 2023.
26. West Pharma. Lifecycle management responsibilities: co-packaged combination products. 2024.
27. ScienceDirect. Rare disease drug-device combinations: regulatory case studies. 2025.
28. Frontiers in MedTech. Best practices in combination product efficacy evaluation. 2024.
29. NIH. Regulatory Knowledge Guide: defining combination products. 2023.
30. FDA. CGMP companion guidance: definitions and compliance. 2015.