International Journal of Engineering Research and Development
e- ISSN: 2278-067X, p-ISSN: 2278-800X, www.ijerd.com
Volume 21, Issue 9 (September 2025), PP 174-182

Global Perspectives on Combination Products: Regulation, Safety–Efficacy, and Rare Disease Challenges

Jagannadham Naga Jaya Surya*[1], Mangalagiri Krishna Rekha*[2], Gorle SnehaLatha*[3]
A.U. College of Pharmaceutical Sciences Andhra University, Visakhapatnam 530003, Andhra Pradesh, India.

Abstract
Combination products (CPs), particularly drug–device combinations (DDCs), are increasingly important in healthcare, as they integrate diverse technologies into a single product. These innovations show strong potential to improve treatment outcomes and address unmet needs, especially in rare diseases. However, development and approval remain complicated due to classification uncertainties, inconsistent regulatory oversight, and complex operational requirements. Global trends highlight three key directions: the move toward harmonized frameworks, greater use of real-world evidence, and collaborative evaluations among agencies. Risk management plays a crucial role, focusing on safety monitoring, post-market surveillance, and robust evaluation of clinical effectiveness. In rare diseases, targeted delivery systems and implantable devices illustrate the promise of DDCs, though regulatory barriers still delay patient access. Looking forward, flexible pathways, digital tools, and international cooperation are expected to drive innovation while safeguarding patient safety. CPs thus represent a rapidly evolving field requiring balanced regulation and patient-centered strategies.
Keywords: *Combination products, Drug–device combinations, Rare diseases, Regulatory challenges, Risk management, Global harmonization*

Date of Submission: 02-09-2025 Date of acceptance: 12-09-2025

I. INTRODUCTION:

A combination product (CP) is a therapeutic product that combines more than two different categories of regulated drug, biologic, medical, or in vitro diagnostic product categories while still being governed as a single unit. Examples include prefilled syringes, inhalers, drug-coated contact lenses, and devices seeded with living cells. The conventional lines separating medications, devices, and biologics are becoming less distinct as a result of these advancements [1].Combination solutions may offer greater therapeutic benefits than single-entity devices such as drugs and biologics (2). Combination products are medical and diagnostic devices that include a mix of drugs, instruments, and/or biological elements (3).These innovative and multifaceted healthcare solutions, which offer state-of-the-art treatment techniques with tremendous promise, have transformed the patient care industry (4). Combination products, like drug-eluting stents and combination vaccinations, have demonstrated promise in enhancing therapeutic outcomes, increasing patient adherence, and solving some of the most challenging medical issues. (5) The complex process of creating combination products, which combine medications, equipment, and biologics to produce novel medical solutions, is depicted in figure 1.The figure most likely shows the various stages of development, including crucial procedures like production, research, design, and regulatory approval, from conception to market launch. It acts as a visual aid, emphasizing how interdisciplinary teams must work together to successfully negotiate the challenges of combination product development.In addition to offering integrated and synergistic treatments, combination products can address unmet medical needs, which makes them significant in the healthcare industry (6). By combining multiple therapy modalities, they offer unique advantages that can lead to improved clinical outcomes and a higher quality of life for patients (7). The field's ever-increasing rate of invention underscores their importance as a catalyst for the ongoing advancement of medical science (8).

Figure 1: Development of combination product. [9]

Regulatory challenges for combination products

Figure 2 gives readers a graphic depiction of the complex regulatory issues that arise throughout the creation and approval of combination products, highlighting the significance of all-encompassing regulatory approaches and cooperation in successfully resolving these issues.https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.frontiersin.org%2Fjournals%2Fmedical-technology%2Farticles%2F10.3389%2Ffmedt.2024.1377443%2Ffull&psig=AOvVaw3e9qcGm9hcnPtbatD585Kb&ust=1756272761344000&source=images&cd=vfe&opi=89978449&ved=0CBUQjRxqFwoTCKic747gp48DFQAAAAAdAAAAABAE[10]

Key Challenges in Regulatory Operations.

The following are some considerations to make when navigating the regulatory procedures for drug-device combinations:Keeping up with the most recent rules and modifications, recognizing products Figure 1: Development of combination products. categorization and regulatory procedures, covering post-market concerns, patient care, usability testing, and technical and scientific requirements. Combination products pose unique regulatory challenges that require manufacturers and regulatory agencies to manage a variety of complex issues because they combine drugs, devices, and biologics. The complex process of classifying these compounds, identifying their primary mode of action (PMOA), and selecting the proper regulatory pathway are some of these difficulties. Because certain combination items are subject to multiple regulatory bodies, regulations that overlap make matters considerably more challenging. Devices and biologics together, for instance, may be subject to both device and biologics regulations. The difficulty is increased by the quick development of healthcare technology since incorporating digital technologies into combination products necessitates lax regulatory standards. The need to harmonize foreign regulations for international market entry and post-market surveillance for ongoing safety and efficacy adds even more complications. Take the case of

drug-eluting stents, where the identification of these combination products requires a thorough assessment of the pharmacological effect of the drug component and the mechanical action of the stent. Additionally, wearable combination products like insulin pumps are challenging traditional regulatory constraints, necessitating new regulations that take technological advancements into account. Because it is difficult to manage the side effects and interactions of several components, combination vaccines need close post-market surveillance. In order to overcome these regulatory barriers and ensure the safety and efficacy of combination goods, producers and regulatory bodies need to collaborate, possess interdisciplinary expertise, and remain informed about evolving regulations [10].

Global Trends in Combination Products:

As drug-device combo products have become more mature globally, three significant trends have emerged:

1. Drug Administration's Increasing Use of Medical Devices Medical devices present an alluring alternative for the delivery of pharmaceutical drugs for a number of reasons, including convenience, privacy, and safety for both patients and healthcare providers. The number of combination product applications submitted to the US Food and Drug Administration (US FDA) [11]increased by approximately 10% over the course of the five years, from 317 in 2014 to 518 in 2019 [12]. This suggests that the use of medical devices for drug delivery is expanding. By 2025, it is anticipated that the global combination product market will be valued at $139 billion, growing at a compound annual growth rate of 7% [13].
2. Growing Complexity of Drug Delivery Systems The expansion of new treatments and delivery modalities has also resulted in novel product/system configurations and the ensuing increase in complexity in four areas: supply chain, technical development, product quality, and regulation.

A. Technological Development When integrating the drug and device, which are the combination product's component parts, in complex configurations, special considerations in the characterization of the product constituents, their interactions, and the combination product system-level performance are required. For example, a patch pump that is electromechanical and has software built into it to deliver highly viscous biologics.

B. Product Quality To establish performance standards for medications and devices during the clinical and commercial stages and ensure that these performance standards are upheld throughout the product's life, appropriate quality systems for the component parts and the combined product must be chosen and put into place.

The creation of a single-entity combination product, such as an autoinjector for the delivery of a biologic, necessitates the implementation of design and purchasing controls in addition to the adoption of quality standards for the biologic constituent. It is also necessary to construct other components of the quality system, such as CAPA and management responsibility under 21 CFR 820.

c. Regulatory Which regulatory process is the most efficient and streamlined for complex product configurations depends on a number of factors, including the primary mode of action, regulatory precedents, and market experience with current goods.

d. Line of Supply Complex global supply chains and logistics are required because of the intricacy of product configurations. In a global supply chain for combination products, common steps include manufacturing the drug ingredient, excipients, drug product, and device constituents; assembling the constituents; and finally packaging and labeling the finished product. Furthermore, additional shipping, warehousing, distribution, and other issues are required due to different product configurations, regulatory status, and labeling variations by country.

3. Expanding Understanding of Product Experience and Risk Over the years, health authorities all over the world have required and put into place transparency measures that have improved the public'savailability and accessibility of market performance information for medical devices . The US FDA's web-based Adverse Event Reporting System (FAERS) database offers a thorough dashboard-style listing of adverse events. The public now has greater access to global health authority databases thanks to open-source pharmacovigilance data analysis tools like Open Vigil. Due to the exponential growth in public engagement on social media, especially social networking sites, microblogs, wikis, and media sharing sites, the experience and risks of healthcare products are often discussed on platforms with a global reach.

Controlling the Risk of Combination Products:

Throughout a product's lifecycle, risk management is an ongoing process that includes proactive hazard and harm identification, risk assessment, risk mitigation and control, risk-benefit analysis, and routine evaluation of the efficacy and adequacy of risk control measures as well as any new risks. According to Quality Risk Management (ICH Q9) and Medical Device Risk Management (ISO 14971), respectively, drug and device risk management components are part of the integrated risk management process for drug-device combination

products. References on the integrated approach for drug-device combination products include Medical Devices—Guidance on the implementation of ISO 14971 (ISO TR 24971:2020) [14] and Combination Products Risk Management (AAMI TIR105:2020) [15]. The integrated risk management framework is incorporated into design controls, manufacturing process controls, purchasing controls, and management control processes.

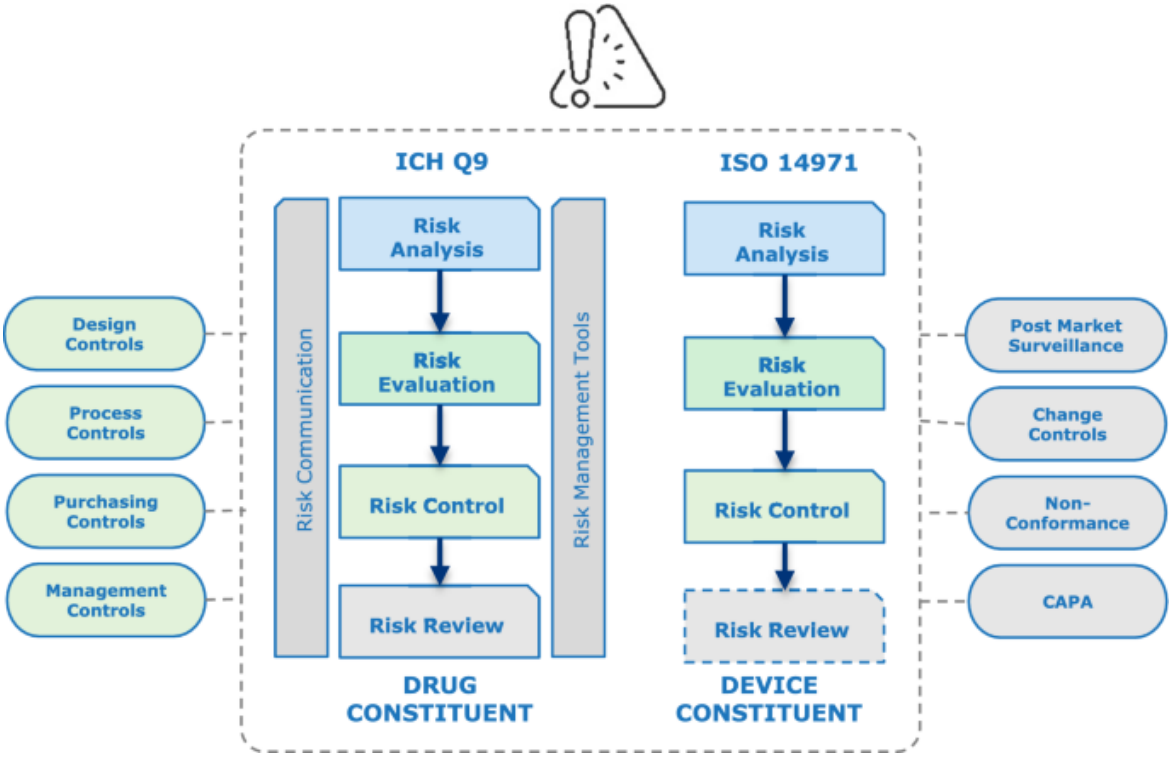

Fig : 3 -Simplified view of integrated risk management process during combination product lifecycle https://link.springer.com/article/10.1007/s43441-022-00425-w/figures/1**[16]**

Throughout the lifecycle, the risk management files are updated in response to new information obtained from post-market surveillance, change control, and corrective and preventative action (CAPA) procedures. The main characteristic that sets risk management for drug-device combination products apart is the evaluation and reduction of risks that arise from the interaction of the drug and device hazards from the individual components as well as the combined product. Product hazards that manifest in their commercial use typically originate in the product's design or manufacturing process. System-level failure is usually caused by a series of events involving use error and/or latent circumstances that can be connected to design or manufacturing [17]. When there is the greatest opportunity for change implementation, integrated risk management in upstream design and manufacturing guarantees the identification, evaluation, and control of risks .Risk management in design and development can be used to identify and control critical safety and efficacy needs. For example, in support of harms/hazard analysis, design and process hazards can be identified using Failure Modes and Effects Analysis (FMEA). Research on product characterization, experiment design, and ultimately control measures are all influenced by the information gathered from these assessments. Similarly, the design of formative and summative human factor studies is based on a use-related risk analysis. [18]

Regulation of combination products

The U.S. Food and Drug Administration (FDA) and other pertinent regulatory bodies around the world oversee the strict regulatory framework for combination goods (19). Since the Office of Combination Products chooses the primary course of action to assign the proper regulatory pathway, the FDA plays a critical role in the United States (20). Whether a product conforms with biologic, device, or medication regulations depends on its classification. The FDA prioritizes an integrated approach to address safety and efficacy across diverse product components in partnership with multiple centers, such as the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH) (21,22).Device-dominated products follow the New Drug Application (NDA) or Biologics License Application (BLA) pathways, drug-dominated products follow the Premarket Approval (PMA) or 510(k) procedures, and balanced products follow a customized pathway based on their primary mode of action (23). Among medical devices, the FDA 510(k) program serves

as the dominant pathway to market, whereas only about 2% of devices requiring premarket review reach the market via the more stringent Premarket Approval (PMA) process (24). This complex regulatory framework emphasizes the value of cooperation, openness, and adherence to changing regulations in order to guarantee that combination products fulfill strict safety and efficacy standards (25).

Safety Considerations	**Effectiveness Considerations**
Complex interactions between drugs, devices, and biologics may cause unexpected risks [26].	Effectiveness depends on integrated performance of drug, device, and biologic components [31].
Compatibility issues and potential device malfunctions [26].	Clinical trials are the gold standard with endpoints based on PMoA [31,32].
Adverse Events (AEs) and product-related complaints must be monitored [30].	Post-market surveillance tracks long-term performance and outcomes [33,34].
Comprehensive risk assessment required throughout the life cycle [27].	Real-world evidence (RWE) and digital tools (e.g., wearables) provide dynamic insights [33].
Regulatory oversight ensures compliance with global safety standards [29].	Biological safety evaluations apply to container closure systems and device parts [35].
Manufacturers must adopt mitigation strategies to reduce hazards [27].	In vitro, in vivo, toxicological, and chemical testing are all included in bioassessment [36].
Patient and healthcare professional education supports safe use [28].	Lack of standardized guidelines complicates global effectiveness evaluation [37].

Table : 1 - Safety and Effectiveness Considerations of combinational products

Drug–device combinations in rare diseases:-

Therapeutic or diagnostic products that combine a drug or biologic component with a device are known as drug–device combinations (DDCs), or combination products. For example, it include drug-eluting stents [38] , drug-coated wound dressings, drug-delivery pumps, and antimicrobial catheters. These products provide synergistic benefits that cannot be achieved by drugs or devices alone, such as improved drug delivery, localized release, enhanced diagnostic capability, and better overall patient outcomes. DDCs are especially valuable in the treatment of rare diseases, where traditional therapies often face limitations. Rare diseases affect about 350 million people worldwide, with children representing up to 80% of cases, and many lack effective treatment options. Targeted drug delivery systems and implantable devices can overcome barriers like the blood–brain barrier, reduce systemic side effects, and maximize efficacy. Additionally, DDCs support personalized therapy by tailoring treatments to specific disease mechanisms, improving adherence through wearable or implantable devices, and enabling diagnosis or monitoring. Drug-eluting devices can maintain effective drug concentrations without frequent dosing, which makes therapy more convenient and effective for rare diseases with poor oral bioavailability. [39]

Table 2 : Comparative Overview of Drug–Device Combination (DDC) Regulations Across Key Jurisdictions [10,1]

Country / Region	**Governing Legislation**	**Regulatory Authority**	**Product Classification Approach**	**Collaboration Between Authorities**	**Post-Market Surveillance**	**Unique Regulatory Challenges**	**ISO 13485 Requirement**	**Notified Body Involvement**
United States (USA)	FDA Regulations	U.S. Food and Drug Administration (FDA) – Office of Combination Products	Classification based on Primary Mode of Action (PMoA) and integration level.	Collaboration between FDA, CDER (drugs), and CDRH (devices).	Stringent requirements, continuous monitoring.	Nuanced PMoA assessment; complex product classification.	Applies to medical devices, not specifically to DDCs.	Not applicable.
European Union (EU)	Medical Device Regulation (MDR), Pharmaceuticals Legislation	European Medicines Agency (EMA) & European Commission	PMoA-based: Integral, Co-packaged, or Separate supply.	Uniform laws and cooperation between EMA and EU member states.	Enhanced pharmacovigilance; centralized database.	Evolving definitions and guidance for DDCs.	Applies to medical devices, including DDCs.	Required for CE mark approval and conformity assessment.
United Kingdom (UK)	UK MDR (aligned with EU MDR principles)	Medicines and Healthcare products Regulatory Agency (MHRA)	Defines DDCs as single integral products intended for exclusive combined	Close alignment with EU systems.	Similar post-market vigilance as EU.	Transitioning from EU regulatory alignment post-Brexit.	Applies to medical devices, including DDCs.	Required for CE mark during EU conformity period; evolving UK-

			use.					specific process.
Australia	Therapeutic Goods Act	Therapeutic Goods Administration (TGA)	Classified by type of therapeutic good (drug–device, biological–device, etc.) based on claims and intended use.	Collaboration within TGA divisions.	Ongoing monitoring per therapeutic good category.	Balancing classification with intended therapeutic claims.	Applies to medical devices, including DDCs.	Not applicable.
China	2021 Circular on Combination Products	National Medical Products Administration (NMPA)	Must meet drug registration requirements.	Coordination between drug and device divisions.	Post-market safety monitoring per drug regulations.	No rare-disease-specific DDC rules; classification challenges remain.	Applies to medical devices, including DDCs.	Not applicable.
India	Drugs and Cosmetics Act (1940), Drugs and Cosmetics Rules (1945)	Drug Controller General of India (DCGI) & Central Drugs Standard Control Organization (CDSCO)	Combination products classified as Fixed Dose Combinations (FDCs).	CDSCO under Ministry of Health & Family Welfare.	Manufacturers must prove safety, effectiveness; multifactorial research often required.	Stricter proof requirements for active ingredient functionality duration.	Required for validating production facility quality systems.	Not applicable in the same context.

Table : 3 - Examples of Drug–Device Combinations (DDCs) in Rare Diseases [39]

Rare Disease	Drug Component	Device/Delivery System	Outcome/Benefit	Challenges	Regulatory Status
CLN2 disease (Batten disease)	**Cerliponasealfa** (enzyme replacement therapy)	Intraventricular infusion via **Ommaya/Rickham reservoir + catheter**	Direct CNS delivery; slows neurodegeneration (seizures, dementia, motor decline)	Surgical implantation required; device originally approved for other uses (off-label use)	FDA (2016), EMA (2017)
Spinal Muscular Atrophy (SMA)	**Nusinersen (Spinraza®)** – antisense oligonucleotide	**Subcutaneous intrathecal catheter system** (infusion port + intrathecal catheter)	Reliable long-term delivery; improved upper limb function	Invasive; device-related risks (meningitis, hemorrhage); spinal deformities complicate delivery	FDA & EMA approved
Cystic Fibrosis (CF)	**Cayston® (aztreonam inhalation)**	**Altera® nebulizer system**	Direct lung delivery; improved lung function, weight, QoL; reduced bacterial burden	Requires specialized nebulizer; limited to Pseudomonas infections	FDA & EMA approved; orphan drug
Cystinosis (ocular form)	**Cysteamine (Cystaran® eye drops)**	Developing **cysteamine-loaded contact lenses**	Potential for sustained release, fewer doses, better adherence	**Manufacturing & drug stability issues**; not yet available	Eye drops approved (FDA, EMA); lens under development

Table : 4 -The regulatory landscape for drug–device combinations (DDCs) with a focus on rare disease considerations [39].

Country / Region	Orphan Drug Legislation	Orphan Device Legislation	DDC Regulatory Authority	DDC Classification Basis	Specific Orphan Incentives for DDCs	Key Guidance / Support Mechanisms
United States (USA)	Yes – Orphan Drug Act	Yes – Orphan Device Legislation	FDA – Office of Combination Products	Primary Mode of Action (PMoA) & integration level	None (DDCs benefit indirectly if drug or device is orphan-designated)	FDA guidance on classification, scientific advice, post-market surveillance
European Union (EU)	Yes – EU Orphan Regulation	Recently introduced guidance for orphan	EMA & European Commission	PMoA – classified as integral, co-packaged, or	None	EMA scientific advice, centralized pharmacovigilance database

		devices		separate supply		
Japan	Yes – Orphan Drug Legislation	Yes – Orphan Device Legislation	Pharmaceuticals and Medical Devices Agency (PMDA)	PMoA& intended use	None	PMDA guidance on classification, pre-market consultations
China	No specific orphan drug law	No orphan device legislation	National Medical Products Administration (NMPA)	Must meet drug registration requirements (2021 Circular)	None	Basic classification guidance; no rare disease-specific DDC pathways
India	No comprehensive orphan drug law	No orphan device legislation	Drug Controller General of India (DCGI) & CDSCO	Classified as Fixed Dose Combinations (FDCs)	None	Limited classification guidance; general FDC framework applies
Australia	Yes – Orphan Drug Program	No dedicated orphan device framework	Therapeutic Goods Administration (TGA)	Category-based (drug–device, biological–device, etc.)	None	TGA advice services, category-based classification rules

Future Perspectives on DDCs in Rare Diseases .

1. **Targeted Drug Delivery** – DDCs can enhance precision in delivering therapies to specific sites, including hard-to-reach areas like across the blood–brain barrier.
2. **Improved Therapeutic Outcomes** – Potential to improve efficacy and patient outcomes through controlled and sustained drug release mechanisms.
3. **Dedicated Regulatory Frameworks** – Need for specialized regulatory pathways tailored to the unique challenges of DDCs in rare diseases.
4. **Industry Collaboration** – Stronger partnerships between pharmaceutical developers and device manufacturers to optimize integration and design.
5. **Policy Support & Incentives** – Introduction of financial support, grants, or extended market exclusivity to encourage innovation.
6. **Innovation Stimulation** – Reducing barriers to entry in this high-cost, complex field to drive technological advancements.
7. **Enhanced Patient Access** – Broader availability of novel therapies that address unmet needs in rare disease management.
8. **Better Patient Adherence** – Improved delivery systems may enhance compliance and long-term treatment outcomes.
9. **Quality of Life Improvements** – Ultimately, DDCs can provide more effective, safer, and patient-friendly therapeutic options.[39]

Future Directions of Combination Products

1. **Closer Industry–Regulatory Collaboration**
   - Stronger partnerships between stakeholders and regulatory agencies to streamline approval processes and establish standardized international standards [40].
2. **Digital Technology Integration**
   - Use of smart devices and real-world evidence (RWE) to enhance post-market surveillance and efficacy assessment [41].
3. **Regulatory Evolution**
   - Development of specialized pathways and improved classification systems for combination products.
   - More flexible, adaptive regulations to accommodate cross-disciplinary innovations and emerging technologies [40].
4. **Patient-Centered Healthcare**
   - Greater patient involvement in product development and monitoring.
   - Increased use of patient-reported outcomes (PROs) and experiences in evaluating efficacy [41].
5. **Innovation in Technology Integration**
   - Exploration of advanced biomaterials and artificial intelligence (AI) to design next-generation combination products.
   - Potential emergence of intelligent and adaptive healthcare solutions [42].

II. CONCLUSION:

The development of drug–device combinations reflects the growing shift toward patient-centered and technology-driven healthcare. Although promising, the regulatory environment for combination products remains complex, with persistent challenges in classification, oversight, and operational compliance. Emerging global trends indicate progress through harmonized regulatory frameworks, increased reliance on real-world

evidence, and collaborative evaluations. In rare diseases, where treatment options are scarce, DDCs provide opportunities to close therapeutic gaps. While examples of innovative products demonstrate improved outcomes, approval delays due to regulatory uncertainties often restrict timely access. Effective risk management through transparent evaluation, continuous monitoring, and structured benefit–risk assessment is essential to strengthen confidence in these therapies. Looking forward, the success of CPs will depend on adaptable regulatory systems that encourage innovation while safeguarding safety. International harmonization, advanced digital technologies, and patient-focused evaluations will play central roles. Particularly in rare diseases, flexible approval pathways and global collaboration may accelerate access to life-saving treatments.

REFERANCE :

[1]. Kim, Joo & Kwon, Sera & Seol, Ju & Kim, Mi & Kim, Su. (2024). Regulatory Framework for Drug-Device Combination Products in the United States, Europe, and Korea. Therapeutic innovation & regulatory science. 58. 10.1007/s43441-024-00661-2.

[2]. Tsourounis M, Stuart J, Smith M, Toscani M, Barone J. Challenges in the development of drug/device and biologic/device combination products in the United States and European union: a summary from the 2013 DIA meeting on combination products. TherInnovRegul Sci. (2015) 49(2):239–48. doi: 10.1177/ 2168479014553900

[3]. Sun G, Zhou Y-H. AI In healthcare: navigating opportunities and challenges in digital communication. Front Digit Health. (2023) 5:1–5. doi: 1291132.10.3389/ fdgth.2023.1291132

[4]. Sachdeva P, Kaur K, Fatima S, Mahak FNU, Noman M, Siddenthi SM, et al. Advancements in myocardial infarction management: exploring novel approaches and strategies. Cureus. (2023) 15:9. doi: 10.7759/cureus.18617

[5]. Avula MN, Grainger DW. Addressing medical device challenges with drug–device combinations. Drug-Device Combinations Chronic Dis. (2015) 11(1):1–38. doi: 10. 1002/9781119002956.ch01

[6]. Sen S, Chakraborty R. Toward the integration and advancement of herbal medicine: a focus on traditional Indian medicine. Bot Targets Ther. (2015) 2 (1):33–44. doi: 10.2147/BTAT.S66308

[7]. Kazdin AE. Evidence-based treatment and practice: new opportunities to bridge clinical research and practice, enhance the knowledge base, and improve patient care. Am Psychol. (2008) 63(3):146. doi: 10.1037/0003-066X.63.3.146

[8]. Gelijns A, Rosenberg N. The dynamics of technological change in medicine. Health Aff. (1994) 13(3):28–46. doi: 10.1377/hlthaff.13.3.28

[9]. https://medtechintelligence.com/wp-content/uploads/2015/11/CombinationProduct.jpg

[10]. Gupta DK, Tiwari A, Yadav Y, Soni P, Joshi M. Ensuring safety and efficacy in combination products: regulatory challenges and best practices. Front Med Technol. 2024 Jul 10;6:1377443. doi: 10.3389/fmedt.2024.1377443. PMID: 39050909; PMCID: PMC11266060.

[11]. Shailaja Pashikanti, Krishna SV, Comparative Regulatory framework for clinical Development of Covid-19 vaccines and their filing procedures in India, USA, Europe, International journal of Biology, Pharmacy, and Allied Sciences. ISSN NO: 2277-4998, December 2021.

[12]. FY2019 Office of Combination Products Performance Report to Congress as required by the Medical Device User Fee and Modernization Act of 2002. Available at: https://www.fda.gov/media/144887/download. Accessed Dec. 2021.

[13]. Srivastava M, Jaiswal P. Drug-Device Combination Products Market. Allied Market Research, Sept 2018 at: https://www.alliedmarketresearch.com/drug-device-combination-products-market (Last Accessed December 2021)

[14]. Association for the Advancement of Medical Instrumentation. Risk management guidance for combination products. AAMI TIR105:2020. Arlington, VA: AAMI, 2020.

[15]. International Organization for Standardization. Medical devices-Guidance on the application of ISO 14971. ISO TR 24971:2020. Geneva: ISO, 2020

[16]. https://link.springer.com/article/10.1007/s43441-022-00425-w/figures/1

[17]. Reason J. Human error: models and management. BMJ. 2000;320(7237):768–70.Article CAS Google Scholar

[18]. U.S. Food and Drug Administration, Learn About Drug and Device Approvals. Available at: https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review. Accessed Dec 2021.

[19]. Darrow JJ, Avorn J, Kesselheim AS. FDA approval and regulation of pharmaceuticals, 1983–2018. Jama. (2020) 323(2):164–76. doi: 10.1001/jama.2019.16980

[20]. Corbin J, Walker AJ. FDA Overview. In: Translational Radiation Oncology. Boston: Academic Press (2023). p. 453–7. doi: 10.1016/B978-0-323-88423-5.00019-4

[21]. U.S. Food and Drug Administration. Classify Your Medical Device. Available online at: https://www.fda.gov/medical-devices/overview-de regulation/classify-your medical-device (February 7, 2020).

[22]. Shailaja P, Divya SS, Sravani KL, Snehalatha G. Overview on the regulatory pathway for prosthesis in U.S.A and current ethical aspects of prosthetic care. *[IJCSPUB]*. [2023];Volume: 13.

[23]. Valencia G, Oscar A, Suppadungsuk S, Thongprayoon C, Miao J, Tangpanithandee S, et al. Ethical implications of chatbot utilization in nephrology. J Pers Med. (2023) 13(9):1363. doi: 10.3390/jpm13091150

[24]. Swathilakshmi U*, Revathi K, Sowjanya K, Shailaja P, Sravani S and Indira P, Review on Substantial Equivalence of Medical Devices-USFDA,Modern Applications of Bioequivalence & Bioavailability. 2. DOI : 10.19080/MABB.2017.02.555600.

[25]. Reis ME, Bettencourt A, Ribeiro HM. The regulatory challenges of innovative customized combination products. Front Med (Lausanne). (2022) 9:2148. doi: 10. 3389/fmed.2022.854225

[26]. Sharma A, Luthra G. A comprehensive review of risk management in the medical device industry. J Pharm Res Int. (2023) 35(6):14–23. doi: 10.9734/jpri/ 2023/v35i630325

[27]. Berry D. EBOOK: Risk, Communication and Health Psychology. Berkshire: Open University Press (2004).

[28]. Kohn LT, Corrigan JM, Donaldson MS. Setting performance standards and expectations for patient safety. In: In to Err is Human: Building a Safer Health System. Washington, DC: National Academies Press (US) (2000).

[29]. CFR-Code of Federal Regulations Title 21. (n.d.). Available online at: https:// www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=820.3#:~:text=(b)%20 Complaint%20means%20any%20written,it%20is%20released%20for%20distribution

[30]. Koban MU. Impact of health technology assessment (reimbursement) on considerations for international regulatory strategies wissenschaftlicheprüfungsarbeit.

[31]. Wiklund I. Assessment of patient-reported outcomes in clinical trials: the example of health-related quality of life. FundamClinPharmacol. (2004) 18 (3):351–63. doi: 10.1111/j.1472-8206.2004.00265.x
[32]. Zou KH, Salem LA, Ray A. Real-World Evidence in a Patient-Centric Digital Era. Oxon: CRC Press, Taylor and Francis Group (2022).
[33]. World Health Organization. Guidance for Post-Market Surveillance and Market Surveillance of Medical Devices, Including in Vitro Diagnostics. Geneva: World Health Organization (2020).
[34]. Latoz C, Larkin L, Huynh-Ba K. Stability considerations for drug-device combination products-21 CFR part 4 update. AAPS Open. (2023) 9(1):10. doi: 10. 1208/s12248-022-00703-8
[35]. Gelijns AC. Comparing the development of drugs, devices, and clinical procedures. In: Gelijns AC, editor. Modern Methods of Clinical Investigation: Medical Innovation at the Crossroads: Volume I. Washington, DC: National Academies Press (US) (1990).
[36]. Faulkner A. Medical Technology into Healthcare and Society: A Sociology of Devices, Innovation and Governance. London: Palgrave Macmillan (2008).
[37]. Jayasheel BG. Regulatory requirements for marketing fixed dose combinations. PerspectClin Res. (2010) 1(4):120. doi: 10.4103/2229-3485.71768
[38]. Swathilakshmi U, Shailaja P, Ratna V, Prasanth S and Daniel BA, "Post Marketing Surveillance Requirements of Drug Eluting Stents in India and European union", ISSN- 2167-7689 Pharmaceutical Regulatory Affairs 6th Sep 2017.
[39]. E.A. Tataru, M. Dooms, C. Gonzaga-Jauregui, A.M.G. Pasmooij, D.J. O'Connor, A.H. Jonker, Drug–device combinations in rare diseases: Challenges and opportunities. Drug Discov Today. 2025;30(4):104343. doi:10.1016/j.drudis.2025.104343.
[40]. Reis ME, Bettencourt A, Ribeiro HM. The regulatory challenges of innovative customized combination products. Front Med (Lausanne). (2022) 9:821094. doi: 10. 3389/fmed.2022.821094
[41]. Algorri M, Abernathy MJ, Cauchon NS, Christian TR, Lamm CF, Moore CM. Re-envisioning pharmaceutical manufacturing: increasing agility for global patient access. J Pharm Sci. (2022) 111(3):593–607. doi: 10.1016/j.xphs.2021.08.032
[42]. Tian J, Song X, Wang Y, Cheng M, Lu S, Xu W, et al. Regulatory perspectives of combination products. Bioact Mater. (2022) 10:492–503. doi: 10.1016/j.bioactmat. 2021.12.005