AN OVERVIEW OF THE EVOLVING REGULATORY PARADIGM FOR DRUG - DEVICE COMBINATION PRODUCTS

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ABSTRACT

Breakthrough innovations in drug and biologic based therapies as well as technological developments in design and development of medical devices have led to the rapid rise in the use of combination products in the last few decades. The product research and development, clinical translation as well as regulatory evaluation of combination products are complex and challenging. This review firstly introduced the general consideration and designation of combination products. Key areas of systematic regulatory review on regulatory perspectives of combination products. Global trends, regulatory science, preclinical and clinical evaluation of combination products was discussed. Lastly, the safety consideration, regulatory challenges and framework for combination products was described. New tools of computational modeling and simulation, novel technologies such as artificial intelligence, needs of developing new standards, evidence-based research methods, new approaches including the designation of innovative or breakthrough medical products have been reviewed and could be used to assess the safety, efficacy, quality and performance of combination products. Taken together, the fast development of combination products with great potentials in healthcare provides new opportunities for the advancement of regulatory review as well as regulatory science.

Keywords: combination products, regulatory challenges.

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INTRODUCTION

Combination products with any two or three products of medical devices, pharmaceuticals and biological products combined emerged in 1970s. These products have their own unique effectiveness. For example, antibiotic-loaded bone cements, made originally by Buchholz and Engelbrech in 1970, could reduce postoperative infection rate from 6% to 1.6% in artificial total hip replacement. Drug-elution stents, i.e. drug-coated scaffolds, could prevent neointima hyperplasia in blood vessels. Herein, combination products were growing rapidly in many product areas, including antibiotic-loaded bone cements, drug-eluting stents, prefilled syringes, nicotine patches, and balloon catheters filled with radioactive liquid suspensions. (1-2)

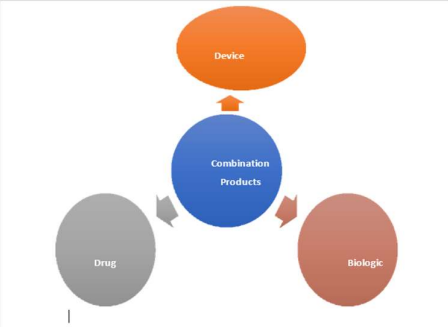

Figure 1. Development of Combination product

Figure 1 visually represents the intricate process of developing combination products, which integrate drugs, devices, and biologics to create innovative healthcare solutions. Figure likely outlines the various stages of development, from conceptualization to market launch, illustrating key steps such as research, design, regulatory approval, and manufacturing. It serves as a visual guide, highlighting the collaborative efforts required among interdisciplinary teams to navigate the complexities of combination product development effectively. (3) The
U.S. Food and Drug Administration (FDA) has regulated com bination products since 1970.
(4) For addressing regulatory issues with these products, the U.S. Food, Drug, and Cosmetic Act

was revised in 1990. These products were defined as "constituting a combination of a drug,
device, or biological product". (5-6) Combination products range from physical or chemical combinations, to products packaged together and products that are separately packaged but need to be used together. With the development of manufacturing technology, the universe and complexity of combination products are becoming increasingly prevalent. In 1991, combination products were firstly defined in Code of Federal Regulations Title 21 3.2(e) (21 CFR 3.2(e). (7) Combination products were reported to account for about 30% of medical products. Although the composition of combination products has been approved separately, the use of combination products may also pose additional risks. The addition of drugs or biological components may result in new intended uses and/or constitute different technical characteristics from the same variety of instruments, causing different safety and efficacy issues. Therefore, the development and complexity of combination products call for efficient regulation to ensure their safety and efficacy. For the best regulation of combination products, the definition and designation of combination products should be firstly understood and examined. (8)

The Food and Drug Administration Modernization Act (FDAMA) of 1997 passed the regulation of combination products. (9) On December 24, 2002, FDA established Office of Combination Products (OCP) to ensure the prompt assignment and the timely and effective premarket review of combination products, according to modified section 503(g) in the Medical Device User Fee and Modernization Act of 2002 (MDUFMA). (10) On July 22, 2013, FDA issued "Current Good Manufacturing Practice Requirements for Combination Products" (21 CFR Part 4). FDA's regulation of combination products was updated and modernized in the 21st Century Cures Act. (11)

Combination products are a unique regulatory category. FDA published a proposed rule for the definition of "mode of action" (MOA) and "primary mode of action" (PMOA). Combination products include more than one type of regulated article. Each constituent part has one MOA. The most important MOA is PMOA. The rule also sets forth an algorithm to assign combination products to an agency when the agency cannot determine the most important therapeutic action. If the classification of combination products is unclear or in dispute, a sponsor can submit pre-request for designation (RFD) or RFD to OCP according to 21 CFR part 3 to obtain a formal classification determination. FDA's determination is mainly based on statutory definition, PMOA/MOA and the degree of innovation or the future use risks. OCP assigns audit responsibility for combination products to the Lead Center- Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER) or Center for Devices and Radiological Health (CDRH). (12) For the designation of drug/device combination products, drug-led combination products should be registered as drugs, and medical device-led combination products should be registered as medical devices. In 2019, NMPA issued the "announcement on adjusting the relevant matters concerning the definition of the attributes of drug/device combination products" (No. 28 of 2019). This announcement has been consolidated into No. 52 of 2021. The Center for Medical Device Standards Administration of NMPA (CMDSA) is responsible for the attributes-definition of drug/device combination products. The CMDSA has established a coordination system for the definition of at tributes with the Center for Medical Device Evaluation of NMPA (CMDE) as well as the Center for Drug Evaluation (CDE). The CMDE is the lead center for medical device-led combination products, and the CDE is the lead center for drug-led combination products. If the designation of combination products is unclear or in dispute, the CMDSA would consult with experts in the field and/or hold expert committee meetings for proper designations. (13-14) Continuing innovation in drug and biologic based therapies coupled with technological developments in design and development of delivery systems have resulted in a proliferation of drug-device combination products. The past 30 years have seen breakthrough innovation in drug and biologic based therapies which have created opportunities for novel delivery techniques. This, coupled with techno logical developments in design and development of delivery systems, especially due to advances in material sciences and additive manufacturing, have resulted in a proliferation of drug-device combination products. Drug-Device Combination products are a result of con vergence of two traditionally independent constituents— drug and medical device. A drug-led combination product is essentially a drug delivery mechanism (device) combined with a drug source that transfers the drug onto or into the patient's body for diagnostic or therapeutic purposes. Drug delivery devices bring to the table numerous advantages including improving adherence to the drug regimen, provide localized delivery, drive patient centricity and satisfaction, create intellectual property, a way to differentiate the drug product in a competitive market and ultimately leading to innovation that benefits public health. One such example is SPRAVATO® (Esketamine), an antagonist of the N-methyl D-aspartate (NMDA) glutamate receptor, which is delivered via a nasal spray device. (15-16)

GENERAL CONSIDERATION

The key issues for the technical review of

combination products are the risk identification and the overall risk-benefit evaluation of final products. If drugs or medical devices in combination products have been individually approved by the regulatory authorities, the risks of these individual parts have been evaluated. The previous evaluation could be used as supporting information to further support the safety and efficacy of the combination products. If combination products have new MOA, new indications, new target populations and new methods of use, for individually approved components, they need to be assessed through scientific evidence. For example, adding steroids to pacing conductors can reduce the inflammatory reaction at the wire tissue interface, and reduce polarization potential, pacing threshold, and pacing energy consumption. (17)

The methods and intended use of steroids on electrode conductors are different from what they were approved separately as drugs. Scientific evidence is needed to support their claimed efficacy. In addition, while analyzing and discussing the clinical benefits of combination products after adding pharmaceutical ingredients, it is also necessary to analyze the potential new risks that may be associated with them. For example, medical implants added or coated with antibiotics could achieve antibacterial efficacy. However, low-level antibiotic exposure could induce resistance, which should not be ignored in the evaluation of such combination products. Therefore, risks for adding drugs, especially new risks, should be the focus during evaluation. (18)

DESIGN RATIONALE AND PRIMARY MODE OF ACTION (PMOA)

For combination products, the design rationale of adding a specific drug should be fully analyzed and demonstrated. For example, coronary stents are usually added with drugs including paclitaxel, rapamycin and its derivatives to reduce the restenosis rate caused by neointima hy perplasia. (19) However, which drug should be included in the drug-eluting stents should be demonstrated by the design rationale of the products. Similar examples also include hyaluronic acid gel with lidocaine, which could be more effective for pain relief than hyaluronic acid alone, and antibiotic loaded bone cement, which could reduce hip and knee prosthetic joint infections. For combination products, it is necessary to study whether their PMOA is led by the drug or the device component. The PMOA is the means by which the product achieves the desired therapeutic efficacy. The PMOA of a combination product is the means by which the product is expected to make the greatest contribution to the overall intended therapeutic efficacy. Combination product based on the PMOA of medical device is a medical device-led product. For these products, drugs play a supporting role on the PMOA of medical devices. It is necessary to study the principle of roles of drugs in the products, the mechanisms to achieve the intended use and the duration of action. (20)

COMBINATION PRODUCT GLOBAL TRENDS

The maturity of drug-device combination products globally has resulted in three key trends

A) Expanding Adoption of Medical Devices for Drug Delivery

Medical devices present an attractive option for the delivery of drug products on multiple fronts, whether it is for convenience, privacy, or safety of the patient as well as health care provider. The increasing adoption of medical devices in drug delivery is evident from the number of combination product submissions to the United States Food and Drug Administration (US FDA) which increased from 317 in 2014 to 518 in 2019, which represents a ~ 10% growth year over year in those 5 years. Similarly, the global combination product market value continues to grow at a compound annual growth rate of 7% and estimated to be valued at $139 billion by 2025.

B) Increasing Complexity of Drug Delivery Systems

The growth of new therapeutics and delivery technologies have also led to novel product/system configurations and the resultant increase in complexity in four areas, namely Technical Development, Product Quality, Regulatory, and Supply Chain.

a) Technical Development Integrating the constituent parts of the combination product, namely the drug and the device in complex configurations, for example an electro-mechanical patch pump with embedded software for the delivery of highly vis cous biologics, requires unique considerations in characterization of the product constituents, their interactions, and the combination product system level performance.

b) Product Quality Establishing drug and device performance requirements during clinical and commercial stages and ensuring that the drug and device performance is maintained throughout the life of the product requires defining and adopting appropriate quality systems for the constituent parts and the combination product. For example, the development of an autoinjector for the delivery of a bio logic, a single entity combination product, requires the adoption of quality systems for the biologic constituent as well as application of design controls and purchasing controls for the development of the auto injector.

c) Regulatory Identifying the most efficient and streamlined regulatory pathway for complex product configuration depends on several factors including its primary mode of action, regulatory precedents, and market experience with current products.

d) supply Chain Complexity in product configurations requires employing complex global supply chain and logistics. Combination product supply chain typically involves manufacturing of the drug substance, the excipients, the drug product, the device constituents, the assembly of the constituents and subsequent packaging and labeling at various sites in a global supply chain.

C) Growing Awareness of Product Experience and Risk

Over the years, health authorities around the world have required and adopted transparency measures leading to increasing availability and access to market performance data of healthcare products in the public domain. The US FDA's Adverse Event Reporting System (FAERS) database is a web-based tool containing detailed listing of Adverse Events in a dashboard format. Open-source pharmacovigilance data analysis platforms like Open Vigil have enhanced public access to global health authority databases. (21-22)

PRECLINICAL EVALUATION

A) Interactions of different components in combination products

The interactions of different components in combination products should be considered firstly. Addition of drugs to a device product may change the original product's production process, storage conditions, indications, contraindications and precautions. For example, heparin-containing oxygenators, triclosan-containing sutures, coronary stents with paclitaxel could achieve anticoagulant, antibacterial, and inhibition of local cell hyperproliferation, respectively. However, their drug loading processes may affect the mechanical properties and surface properties of the final devices. When a device is used as a drug carrier, its production additives, processes or storage conditions may have an impact on drug activity, drug release, and overall product quality. For example, the production process and critical control points of antibiotic-loaded bone cements may include the effect of mixing process, the distribution of the drugs, and the effects of terminal sterilization on the drugs' performance. Considering the local use of drugs with medical devices, drug safety evaluation should be conducted on the carrier polymers (if any) and processing aids. The composition of drugs and their polymer carriers play very important roles in the final combination products. The following focuses on drug-eluting stents as an example. The drugs in the drug eluting coronary stents are designed to be released and absorbed at the target site of blood vessels. (23)

Although drug concentration in the blood plasma after the implantation of drug eluting coronary stent is low, the concentration in the local tissue of the target vascular wall (especially when the stent is overlapped) may be much higher than that in the blood after the product is systemically used. (24) Polymer carriers should be able to coat enough drugs on the stent, and also affect the release profile of drugs from the stents. (25) Therefore, it is necessary to carry out research on drug dose density selection, total dose concentration selection in a single stent, drug and carrier polymer formation selection, coating stability, and in vitro/in vivo release characteristics of drugs to evaluate the overall toxicology risks of final products. (26)

B) Qualitative, quantitative and in vitro release of drugs in combination products

The rationale for determining drug content/dose in combination products should be investigated. In wound dressing products with antibacterial ingredients, the dosage of antibacterial ingredients is determined by the minimum inhibitory concentration and safety thresholds for the whole body. (27) For antibiotic-loaded bone cements, antibiotic content, antibiotic delivery volume and rate, topical antibiotic concentration change, the minimum inhibitory concentration (MIC), resistant variants value concentration (MPC value), resistance caused by low-dose local antibiotics, and the effective release time should be evaluated. (28) If the content of a drug refers to a current combination product, the research should be conducted on the impact of design differences between the current and predicted products. Structural design and carrier material formulations could change the release rate of drugs. For combination products that achieve functions by releasing drugs to the intended site (such as sustained release, controlled release or other release methods), such as drug-eluting stents, drug-containing balloon catheters, and silver-containing dressings, drug release studies are needed. In vitro release study can be used to evaluate the stability of final products and coatings. For combination products containing bioactive substances, such as orthopaedic devices containing osteoinductive agents and growth factors and surgical instruments containing heparin coating, studies on MOA are needed. For example,

qualitative and quantitative investigation could be conducted through the research of content, activity, and efficacy of bioactive

substances. (29-30)

C) Biological evaluation

For combination products, biological evaluation of final products could reference to the series of ISO 10993 standards. Drugs may affect the results of biological evaluation tests. Drug coatings of drug-elution stents may also have an impact on biocompatibility after stents are placed. (31-32) As a result, researchers need to combine the MOA of the drugs and clinical benefits to demonstrate whether the biological risks introduced by the drugs are acceptable. Drugs in combination products typically have a local effect. If drugs in combination products were approved previously for indications different from that of the combi nation products, the safety of the final combination product should be evaluated in conjunction with drug safety data. However, it is necessary to consider whether the new combination will cause any change of the established or understood safety and efficacy of drugs. If the exposed local or systemic drug concentration of combination products is greater than the approved drug dose, additional safety studies may be needed, such as the neurotoxicity of intracranial devices. (33) For some com bination products, such as drug-containing balloon catheters, since body contact time and frequency of the drug may be different from that of the device, it may be not accurate to use single contact method to assess the biological risk. (34)

D) Animal studies

According to technical features of combination products, animal studies need to be designed to include in vivo drug release dynamics and in vivo pharmacodynamics. For example, the animal studies of a drug eluting stent should include the performance of drug delivery, systemic toxicity, local toxicity, screening of drug doses, formulation and coating thickness of carrier polymer, and drug release as well as pharmacokinetics. (35-36) For animal studies on silver-containing wound dressing products, animal models and wound or disease models must be identified. The wound or disease models should cover the intended use of the product. The application method and frequency and the outcome measures and their rationale and standards should be evaluated by animal studies. Whether the addition of silver affects the local healing of the tissue also need to be investigated. The absorption, distribution, metabolism and excretion of silver in the animal body need to be studied to evaluate the accumulation and existence of silver in the body. (37)

CLINICAL EVALUATION

Before carrying out clinical evaluation of combination products, it is necessary to clarify and understand their MOA and PMOA, intended efficacy, potential risks, and adverse events. Standards for quality control of medical device clinical trials" should be followed to conduct clinical evaluation of combined products. (38) Combining the risks and benefits of combination products, a reasonable clinical evaluation path can be selected to demonstrate the safety and efficacy, and to provide a basis for the Products' Instructions for use. The key components of clinical trial protocols for combination products include sample size, statistical methods, clinical endpoints, intended uses, efficacy claims, and the number of clinical studies if multiple trials are included. The purpose of adding pharmaceutical ingredients to devices is often to improve product functions or reduce adverse events related to the product uses. It is necessary to demonstrate the products' clinical risks and benefits. It is also necessary to combine the performance characteristics and intended efficacy of combination products to demonstrate their science and adequacy of the clinical design. For example, due to the differences in the goals of clinical treatments, different drug-eluting stents may have different safety and efficacy evaluation outcome measures. (39)

If the combination products contain new active drug ingredients, special attention should also be paid to the safety of drugs in clinical trials. Preliminary studies might be necessary to characterize the pharmacokinetics and metabolism of the drug as well as to determine the safety of the drug for human use, prior to the clinical study of the combination product. These studies might not be necessary for drugs with previous approval for use in human or with available human safety information. Taken together, the goal of regulation and supervision of combination products is to scientifically and comprehensively evaluate and ensure their safety and efficacy. Their regulatory review and technical evaluation are complex, scientifically demanding, and systematic with multi-step and multi-level assessments. (40)

REGULATORY SCIENCE FOR COMBINATION PRODUCTS

As aforementioned, the safety and efficacy evaluation of combination products is difficult and complex. In the 21st century, the concept of regulatory science has gradually been accepted by FDA and later developed to an important field to ensure the safety and efficacy of medical products. In August 2011, the FDA developed its Strategic Plan for Regulatory Science. To promote research in regulatory science, FDA not only established a dedicated office, but also
worked with the universities. In China, NMPA launched its Regulatory Science Action Plan (RSAP) in April 2019. "Combination Products" was among the first batch of nine key regulatory science projects initiated by NMPA. Based on the concept initiated by FDA, regulatory science of

medical product is the science of developing new tools, new technologies, new methods, new standards, and new approaches to assess the safety, efficacy, quality and performance of medical products throughout their life cycles. This section looks into the current and future prospects of regulatory science for combination products from new tools and technologies, new standards, new methods, and new approaches. (41-42)

A) New tools and technologies

a) Computational Models and Simulation

Computational Models and Simulation (CM&S) used in medical de vices is to apply computational modeling science and simulation technology to evaluate medical products. In FDA, the research on CM&S associated with medical devices conducted by Office of Science and Engineering Laboratories (OSEL) is "Credibility of Computational Models Program", which is used to minimize the risk of erroneous decisions based on computational predictions. CM&S could also be used to simulate the clinic settings for virtual patients and to reduce clinical trials. CM&S could reveal the interaction between products and patients, and reduce adverse reactions by adequate quantification of risks and security testing. CM&S could also reduce the cost and duration of clinical research. For example, computational simulation of clinically- relevant bioprosthetic valve performance metrics could rovide scientific evidence for accurate and long-term deformation performance of transcatheter heart valves. CM&S could assess the performance of bioprosthetic heart valves (BHV) because of excellent agreement between the computational and experimental results for the outcome measures commonly used to assess BHV performance. A multi modal imaging-based anatomical model of the human head and neck could be used to analyze the safety and efficacy of medical products. CM&S instead of clinical trials was applied in the regulatory approval of Advisa SR to demonstrate safety. CM&S is successfully used to study drug deposition in coronary arteries with overlapping drug-eluting stents, solving the problems of complex three-dimensional geometry of deployed stents together with the drug transport. CM&S is also applied to study mechanics and drug release properties and model flow-mediated drug transport of combination products, such as drug-eluting stents. The results of CM&S could provide scientific evidence and recommendations for the clinical practice of combination products. (43-45)

b) Artificial intelligence

Artificial intelligence (AI) is a powerful tool to gain insights from a large amount of data from the real-world use and daily healthcare experience with computational models, expert systems and machine learning (ML). Consequently, healthcare could be importantly transformed by AI. According to FDA, AI is defined as "the science and engineering of making intelligent machines, especially intelligent computer programs". As an AI technique, ML can be used to create new software algorithms based on real world data. AI and ML technologies could create medical products to better improve patient care and assist healthcare providers. AI/ML could be involved in the research and development of pharmaceuticals throughout the lifespan, such as design, drug screening, prediction of the physicochemical properties, bioactivity and toxicity, quality regulation, and clinical evaluation. In medical devices, AI/ML-based medical devices are developed to contribute in image acquisition and processing, earlier disease detection and diagnosis, prognosis, risk assessment, new patterns identification on human physiology, and personalized diagnostics and therapeutics. GI Genious is the first device that help detect potential signs of colon cancer using AI. Abilify My Cite (aripiprazole tablets with sensor) is an FDA-approved pill using AI and has the ability to digitally track patient medications. (46-47)

c) Organs-on-chips

Human organs-on-chips are microfluidic devices created with microchip manufacturing methods, which linked with living human cells. Human organs-on-chips could accurately mimic the physiology and mechanical environment in human body by reproduce blood and air flow in their tiny fluidic channels. Organ-on-chips could recapitulate the multicellular architectures, vascular perfusion, tissue-tissue interfaces and physicochemical micro environments of human organs. The human airway chip could recreate the lung environment, such as airways and blood vessels, which could be used to study the effect of different drug and pathogens on lung function. Recently, organ-on-chips could model organ-level physiology and disease and develop cancer-on-a-chip models. Organ-on-chips could make progress in tissue development, disease etiology and organ physiology, which is valuable for the research in toxicity testing, molecular MOA, and drug/medical device shielding. Organ-on-chips could be used in adsorption, distribution, metabolism, elimination and toxicity (ADMET) testing, PK/PD modeling, efficacy testing and drug discovery. (48-49)

B) New standards

According to the document produced by International Medical De vice Regulators Forum (IMDRF), standards are defined as "part of regulatory compliance, their development can benefit from these Essential Principles of Safety and Performance". International standards reflect the best experience of industry, researchers,

consumers and regulators around the world and serve as an important basis for regulatory compliance assessments, providing an effective way to simplify and coordinate regulatory processes worldwide. The fast development of combination products calls for new standards and their own standard system to provide guides, test methods and specifications for common and repeated use. New standards and their standard system also provide consistent and accurate results, which is extremely helpful to the safe and effective supervision and technical review of combination products. ISO 12417-1 sets a good example of standard of a combination product by specifying minimum requirements for vascular device-drug combination products. Existing standards face challenge for combination products in product testing, developing performance characteristics, testing methods, scientific protocols, product standards and specifications. A standard can be "a physical object/material (e.g., reference materials/ reference standard), a document (e.g., documentary standard that defines terms and describes the use of rules, conditions, guidelines or characteristics for products or related processes and production methods, as well as related quality management systems, a test method or a specification) or a set of reference data". Therefore, the development of standards could be divided to several levels. Standards development could further accelerate product development by providing a platform for the convergence of diverse scientific approaches to promote evaluation and regulation of combination products. (50-51)

C) New methods

Evidence-based research is the research using approaches such as systematic review and meta-analysis that were developed by evidence- based medicine. Evidence-based research is an important method for preclinical and clinical research of medical products. This method provides scientific evidence for the evaluation of the safety, efficacy, quality and performance of medical devices. Evidence-based research can be used to prove safety and effectiveness to the greatest extent and eliminate the unnecessary burden of repeated research. Evidence-based
research can provide fully cumulative evidence about the safety and efficacy of medical products. The evidence can assess feasibility, benefits and risks of clinical translation of novel medical products, and can help to identify the main risks of medical products for the regulatory review and technical evaluation. (52) Evidence-based research can evaluate the quality of evidence for combination products and provide scientific basis for determining the drug selection and dose in the final products, which is one of the critical points whether drugs can play the expected roles in the clinical use. In addition, novel polymeric materials as drug carriers are one of the evaluation focuses for combination products. Because the drugs may also be used in the novel polymeric materials, how to evaluate their safety has become the focus of research of combination products. Evidence-based research methods such as systematic reviews and meta- analyses could provide useful methods to perform such safety evaluations. Real world evidence (RWE) is defined as "the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD)". Real-world research could provide supplementary evidence besides evidence from traditional clinical trials. Compared with traditional clinical trials, real-world research has the advantages of large amount of data, rich data dimension, wide coverage of patient population, long follow-up time, good external authenticity of treatment process and result evaluation, and good extrapolation of research results. As the recognized value continues to increase, RWE will certainly facilitate the regulatory approval processes for combination products. For example, it could be used to evaluate the long-term safety and effectiveness of high-risk combination products, and to support the potential modification of indications of the combination products. (53-54)

D) New approaches

Countries around the world all pay close attentions to innovative medical products, and have issued a number of policies and regulations to encourage innovative products research and development. Break through Therapy/Device Designation is an FDA program intended to accelerate the development and review of new drugs and medical de vices for serious or life-threatening diseases. (55) Such designation was provided by Food and Drug Administration Safety and Innovation Act (FDASIA), signed on July 9, 2012. This new designation is a novel review path of FDA, following fast track, accelerate approval and priority review. In Japan, the amended Pharmaceutical Affairs Law established regulations and controls of regenerative medicine products. Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has
established a Regulatory Science Center in 2018 to further strengthen the review and safety of regenerative medicine products. China also encourages the development of innovative medical products. From 2014 to 2018, the State Council of the People's Republic of China and NMPA issued several documents about innovative medical devices. (56)

COMBINATION PRODUCT REGULATORY LIFECYCLE

The regulatory designation of a combination product, as a drug, device, or both, has a significant

impact on the quality systems adopted as well as the product development and commercial go-to-market strategies. If the combination product is regulated as a device, then its risk classification defines its regulatory and quality strategy. The increasing complexity of drug delivery systems, dis cussed above, results in increasing regulatory ambiguities. Navigating this ambiguity is possible by adopting a robust regulatory strategy based on risk-informed scientific practices, especially in the application of performance standards to the combination product. Collective industry experience indicates proactive alignment, transparency, and open engagement with regulators on risk-based approaches to product development, pre-market submissions and lifecycle management results in predictability of outcomes. The US FDA, for example, has established several path ways for expedited regulatory review and approval of com bination products based on both the drug and device primary modes of action (PMOA). For combination products with drug PMOA, these regulatory pathways include the Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval, and Priority Review Designation. (57) Similarly for combination products with device PMOA, the regulatory pathways include the Breakthrough Device Program (58) and the Safer Technologies Program. (59)

REGULATORY FRAMEWORK FOR COMBINATION PRODUCT

The regulatory framework for combination products involves a meticulous process governed by the U.S. Food and Drug Administration (FDA) and other relevant regulatory authorities globally. (60) In the United States, the FDA plays a central role, with the Office of Combination Products determining the primary mode of action to assign the appropriate regulatory pathway.

(61) This classification influences whether the product follows drug, device, or biologic regulations. The FDA collaborates with multiple centers, including the Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH), emphasizing an integrated approach to address safety and efficacy across diverse

product components. (62) The classification further guides the approval processes, with drug-dominated products following New Drug Application (NDA) or Biologics License Application (BLA) pathways, device-dominated products undergoing Premarket Approval (PMA) or 510(k) processes, and balanced products navigating a customized pathway based on primary mode of action. (63) This intricate regulatory framework underscores the importance of collaboration, transparency, and adherence to evolving guidelines to ensure the effective development, evaluation, and approval of combination products that meet rigorous safety and efficacy standard. (64) Table 1 A comprehensive comparison of combination product regulations, aiding in navigating the regulatory landscape in different jurisdictions

Table 1. Comparative regulatory framework for combination products

Regulatory aspect	India	European union	United states
Governing Legislation	Drugs and Cosmetics Act of 1940, Drugs and Cosmetics Rules of 1945	Medical Device Regulation (MDR), Pharmaceuticals Legislation	FDA Regulations
Regulatory Authority	Drug Controller General of India (DCGI), Central Drugs Standard Control Organization (CDSCO)	European Medicines Agency (EMA), European Commission	U.S. Food and Drug Administration (FDA)
Product Classification	Combination products categorized as Fixed Dose Combinations (FDCs)	Explicit definitions in MDR for drug-device combinations	Office of Combination Products

Collaboration Between Authorities	Regulatory oversight by CDSCO under the Ministry of Health and Family Welfare	Harmonized regulations, collaboration between EU Member States and EMA	Collaboration between FDA, CDER, and CDRH
Post-Market Surveillance	Manufacturers prove effectiveness and safety, multi factorial research often required	Enhanced pharmacovigilance guidelines, centralized database	Stringent requirements, continuous monitoring
Unique Regulatory Challenges	Stricter requirements for proving	Evolving guidelines and definitions for drug-device	Nuanced assessment of primary mode of
	functionality duration of active ingredients	combinations	action (PMOA)
ISO 13485 Certification Requirement	Necessary for validating quality systems of production facilities	Applies to medical devices, including drug-device combinations	Applies to medical devices, not specifically combination products
Notified Body Involvement (EU)	Not applicable in the same context	Involvement for CE mark approval, conformity assessments	Not applicable

COMBINATION PRODUCT REGULATION IN INDIA

Regulators, authorities, and outside parties should be consulted by manufacturers of combination items in India. The effectiveness or safety of the product should be proven by the manufacturer for each component. Multi-factorial research is often required for this, in which each factor is evaluated individually and in conjunction with a placebo control. Manufacturers must clearly justify every proposed active ingredient combination with a sound clinical explanation. (65) Goods like auto injectors, inhalers, pre-filled syringes, pre-filled pens for nebulizers, and transdermal patches are examples of drug-device combination goods. The following are some recommendations for creating combo items in India:

- Define the primary mode of action (PMOA)
- Research global regulatory guidelines
- Develop an appropriate CGMP quality compliance strategy
- Implement a design freeze during the combination product development process
- Seek advice from regulators, authorities, and competent third parties regarding the documentation required to support CE mark approval applications
- Obtain the services of a Notified Body
- Demonstrate compliance with either the drug CGMPs (21 CFR parts 210 and 211) or the device Quality System (QS) regulation (21 CFR part 820). (66)

The Drugs and Cosmetics Act of 1940 and the Drugs and Cosmetics Rules of 1945 govern combination goods in India. Additionally, called Fixed Dose Combinations (FDCs), they are. Medical device regulation is handled by the Drug Controller General of India (DCGI) under the Central Drugs Standard Control Organization (CDSCO). No person or business may enter into a combination that has or is likely to have a negative impact on competition in the relevant Indian market, according to Section 6 of the Act. A combination's active ingredients ought to all function for about the same amount of time. If not, the applicant must provide an explanation and justification for the combination. As part of the Plant Master File (PMF) application procedure, the ISO 13485 certification is necessary to validate the quality system(s) of the legitimate and/or real production facilities. (67)

Table 2 facilitates comprehension of the regulatory framework in India, aiding stakeholders in navigating the regulatory landscape and ensuring compliance with applicable regulations for combination products

Table 2. Combination products regulations in India

Regulation aspect	Description
Governing Legislation	Drugs and Cosmetics Act of 1940 and Drugs and Cosmetics Rules of 1945.
Regulatory Authority	Drug Controller General of India (DCGI) under the Central Drugs Standard Control Organization (CDSCO).
Product Categorization	Combination products, also known as Fixed Dose Combinations (FDCs), which integrate drugs and medical devices.
Competition Regulation	Section 6 of the Drugs and Cosmetics Act prohibits combinations likely to have a negative impact on competition in the relevant Indian market.
Active Ingredients' Functionality	Active ingredients in combinations should function for about the same duration; any variations require justification.
ISO 13485 Certification	ISO 13485 certification is necessary for the validation of quality systems of production facilities.

Plant Master File (PMF) Application	Part of the application procedure, providing information on the quality system(s) of legitimate production facilities.
Regulatory Approval Process	Manufacturers must prove the effectiveness and safety of each component, often requiring multi
	factorial research.
Regulatory Recommendations	– Define the primary mode of action (PMOA). Research global regulatory guidelines. Develop a CGMP quality compliance strategy. Implement a design freeze during development. Seek advice from regulators and competent third-parties for CE mark approval applications. Obtain services of a Notified Body. Demonstrate compliance with either drug CGMPs or device Quality System regulation.

COMBINATION PRODUCT RISK MANAGEMENT

Risk management is an ongoing process throughout the product lifecycle which includes proactive identification of hazards and harms, evaluation of those risks, mitigating and controlling the risks, conducting the risk benefit analysis, and continually reviewing the adequacy and effective ness of the risk control measures as well as any new risks. For drug-device combination products, the integrated risk management process involves elements of drug and device risk management following Quality Risk Management (ICH Q9) and Medical Device Risk Management (ISO 14971), respectively. Combination Products Risk Management (AAMI TIR105:2020) and medical devices-Guidance on the application of ISO 14971 (ISO TR 24971:2020) are helpful references on the integrated approach for drug device combination products. The relationship between risk management and other development and lifecycle management processes are shown in Figure 2 (68)

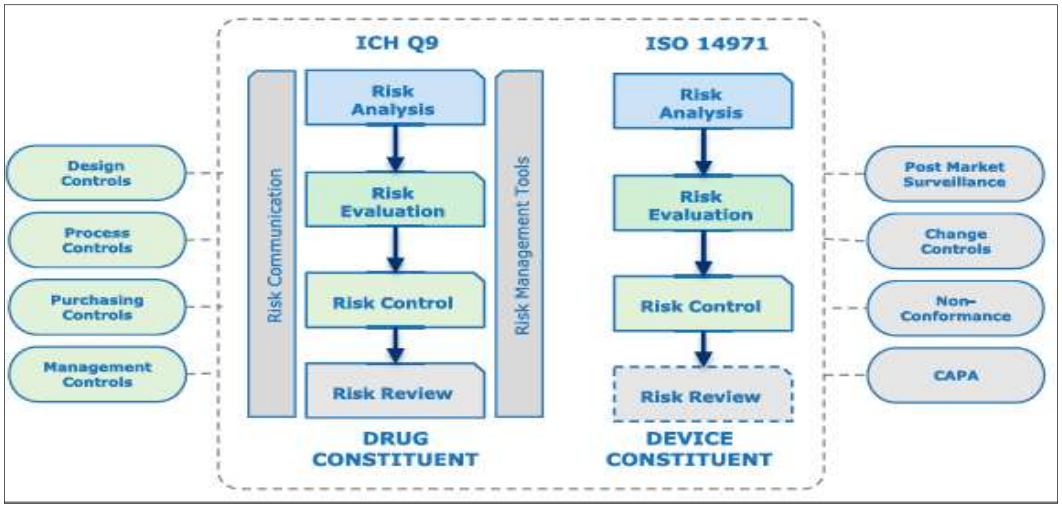

Figure 2. Simplified view of integrated risk management process during combination product lifecycle

The integrated risk management framework is embedded within design controls, manufacturing process controls, purchasing controls, and management control processes. The risk management files are updated in the lifecycle as new information becomes available from post-market surveillance, change control and corrective and preventive action (CAPA) processes. The key differentiating aspect of drug-device combination product risk management is the evaluation and mitigation of risks arising from the interaction of the drug and device constituents and the combination product, in addition to risks from the constituent parts. Product risks that manifest in their commercial use typically originate upstream in product design or manufacturing. System level failure usually occurs through a series of events involving use error and/or latent conditions which can be traced to design or manufacturing. The use of integrated risk management in upstream design and manufacturing ensures the identification, assessment, and control of risks when flexibility for change implementation is maximum. The application of risk management in design and development enables the identification and control of critical requirements for safety and efficacy. For example, design and process hazards can be identified using Failure Modes and Effects Analysis (FMEA), in support of Harms/Hazard Analysis. The insights from such assessments serve as inputs into the development of design of experiments and product characterization studies, and ultimately control strategies. Similarly, formative, and summative human factor studies are designed based on a Use-Related Risk Analysis. (69)

SAFETY CONSIDERATIONS FOR COMBINATION PRODUCTS

Safety considerations for combination products are of paramount importance, given their intricate fusion of drugs, devices, and biologics. These products introduce unique challenges as they may present unforeseen interactions and synergies. Potential risks and adverse events must be thoroughly explored, encompassing issues related to compatibility, potential device malfunctions, and the specific pharmacological effects of the incorporated drugs or biologics.

(70) Comprehensive risk assessment is crucial throughout the product life cycle, from development to post-market surveillance. Manufacturers must employ rigorous strategies to mitigate identified risks, ensuring user safety and product effectiveness. The importance of clear communication and education for healthcare professionals and patients cannot be overstated, contributing to informed use and proper risk management. Regulatory agencies play a vital role in overseeing these considerations, emphasizing a proactive and collaborative approach among manufacturers, healthcare providers, and regulatory bodies to ensure the highest standards of safety for combination products. The Adverse Event (AE): Key Definitions (Source: ICH E2A)-Any adverse medical event that occurs in a patient or clinical research participant who is given a pharmaceutical product; the event need not be directly related to the treatment and same time (21 CFR 820.3) complaint-Any written, electronic, or spoken communication that makes assertions regarding the identity, composition, reliability, robustness, safety, effectiveness, or usage of a device after it is released for public use. (71)

REGULATORY CHALLENGES FOR COMBINATION PRODUCTS

Regulatory challenges in the realm of combination products arise from their unique nature, blending drugs, devices, and biologics, and require manufacturers and regulatory agencies to address several key complexities. (72) These challenges include the intricate process of classifying these products, determining their primary mode of action (PMOA), and choosing the appropriate regulatory pathway. (73) Overlapping regulations further complicate matters, with some combination products falling under the purview of multiple regulatory authorities.

(74) For instance, devices combined with biologics may be subject to both device and biologics regulations. The rapid evolution of healthcare technology adds to the challenge, with the integration of digital technologies in combination products demanding adaptive regulatory guidelines. (75) post-market surveillance for ongoing safety and efficacy, along with the need to harmonize international regulations for global market entry, introduce additional complexities. Figure 3 provides readers with a visual representation of the multifaceted regulatory challenges inherent in the development and approval of combination products, emphasizing the importance of comprehensive regulatory strategies and collaboration in addressing these challenges effectively. Table 3 a clear and organized overview of various combination products and their regulatory classifications, aiding in the understanding of the regulatory landscape for these innovative healthcare interventions.

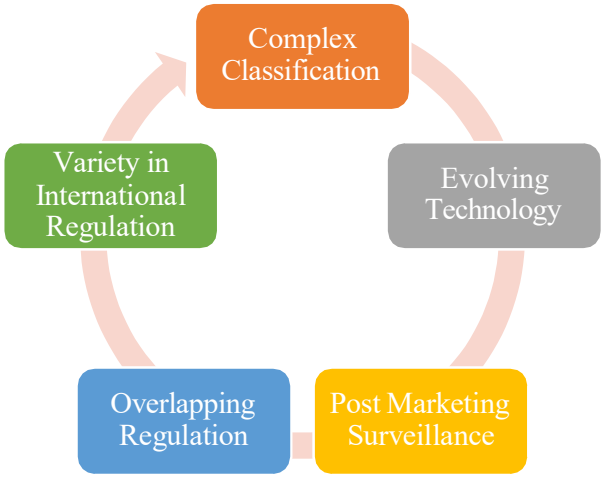

Figure 3. Regulatory challenges

Table 3. Different types of combination products, their components, regulatory pathways, and examples

Combination products	Components	Regulatory pathway	Examples
Combination vaccines	Multiple vaccines	biologics	MMRV (Measles, Mumps, Varicella, Rubella)
Drug eluting stents	Drug, medical device	Device or biologics	Xience V. Promus Premier, Resolute Integrity
Drug device inhalers	Drug, medical device	Device or biologics	Advair Diskus, symbicort

A) Case studies

Drug-eluting stents' classification is complex due to the need to consider both the mechanical action of the stent and the pharmacological action of the drug component. (76) Wearable combination products (integrated with pharmaceuticals) like insulin pumps, challenge traditional regulatory boundaries, requiring adaptive guidelines. (77) Combination vaccines demand long-term post-market surveillance to address varying components' adverse events and interactions. (78)

B) Challenges facing by regulatory agencies

Regulatory agencies are confronted with a multitude of challenges as they endeavour to oversee and regulate healthcare interventions and products, including the increasingly rapid pace of technological advancements that continually introduce novel and intricate medical solutions. The interdisciplinary nature of combination products, which combine drugs, devices, and biologics, poses complexities that demand extensive expertise and coordination. Resource constraints, encompassing both financial and human resources, often limit the capacity of these agencies. Moreover, the imperative of global harmonization necessitates the alignment of regulations and standards across countries. The changing risk profiles of emerging technologies and treatments demand that regulatory authorities develop the ability to effectively access and manage these risks, while post-market surveillance systems must be established to monitor safety and efficacy continually. Collaboration with other agencies, adaptation to evolving regulations, and maintaining transparency and open communication are pivotal. Furthermore, as public expectations and demands for transparency and responsiveness rise, regulatory agencies must navigate increased scrutiny. (79) Additionally, bioethical challenges, such as those related to genetic editing or stem cell therapies, further complicate their tasks. In response to these multifaceted challenges, regulatory agencies are compelled to refine their approaches, update guidelines, and engage with various stakeholders to adapt to the changing landscape and to ensure the safety and efficacy of healthcare interventions. (80)

FUTURE DIRECTION OF COMBINATION PRODUCTS

Future directions in the field of combination products hold promise and challenges, shaped by emerging trends and technological advancements. Collaboration between regulatory bodies and industry stakeholders is likely to intensify, fostering the development of harmonized global standards to streamline the regulatory process. The integration of digital technologies, such as real-world evidence and smart devices, is poised to revolutionize efficacy assessments and post-market surveillance, providing richer and more dynamic data sets. (81) Regulatory changes may focus on refining classification processes and creating more tailored pathways for combination products. The need for increased flexibility to accommodate evolving technologies and interdisciplinary innovations may drive regulatory frameworks to become more adaptive and responsive. Additionally, the emphasis on patient-centric healthcare may lead to enhanced patient involvement in the development and monitoring of combination products. Patient-reported outcomes and experiences could become integral components of efficacy assessments, reflecting a broader shift toward personalized and patient-centered care.

As technological advancements continue, manufacturers may explore novel combinations, such as integrating advanced biomaterials or incorporating artificial intelligence into combination products. This could usher in a new era of smart and responsive healthcare solutions. (82-84)

CONCLUSION

The advancement of innovative biomaterials and technologies has promoted the research and development of combination products, which was originated in 1970s. The designation of combination products depends on the regulations specified by regulatory authorities. The goal of the regulatory review of combination products is to evaluate and ensure their safety and efficacy. A systematic approach of regulatory review of combination products should focus on their design rationale, PMOA, preclinical evaluation and clinical evaluation. However, there are difficulties in the designation of combination products with controversial MOA. The future combination products may be more complex and innovative with novel compositions, technologies and intended uses. Novel combination products may bring new benefits as well as risks. Advanced regulatory evaluation system and post-market surveillance system are required for the regulation of innovative combination products. The difficulty and complexity of regulatory evaluation of combination products present both challenges and opportunities to the regulatory authorities, calling for the development of regulatory science. Promising research areas in regulatory science of combination products include new tools and technologies (CM&S, AI and organ-on-chips), new standards, new methods such as evidence-based research and new approaches including the designation of innovative or breakthrough products programs. Regulatory inputs especially contributions of regulatory science will greatly benefit the future development of combination products.

The exponential rise in the development, approval, and use of combination products has been fueled by breakthrough innovations in drug and biologic based therapies as well as technological developments in design and development of delivery systems. The maturity of combination products as a market category has led to key global trends including expanding adoption of medical devices for drug delivery, increasing complexity and growing awareness of product experience and risk. Integrated product risk management enables robust product development and manufacturing strategies as well as efficient regulatory pathways.

The dynamic landscape of combination products presents a complex interplay of regulatory challenges, safety considerations, and efficacy assessments. Manufacturers must navigate the intricate classification processes and collaborate seamlessly with regulatory bodies, particularly the FDA, to ensure a streamlined and comprehensive approach. Safety considerations demand meticulous risk assessment and mitigation strategies to address potential complications arising from the amalgamation of drugs, devices, and biologics. the development and regulation of combination products stand at the forefront of innovation in healthcare, offering immense potential to improve patient outcomes and address complex medical challenges. However, realizing this potential requires a concerted effort from manufacturers, regulators, healthcare professionals.

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