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Review Article

Regulatory Strategies for Global Approval of Biologic–Medical Device Combination Products: FDA, EMA, and International Perspectives

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Abstract:

Biologic–medical device combination products represent one of the fastest-growing and most scientifically complex categories of healthcare products. These products integrate biologics, including monoclonal antibodies, vaccines, recombinant proteins, cell therapies, and gene therapies, with medical devices that facilitate delivery, administration, monitoring, or therapeutic performance. Examples include prefilled syringes, autoinjectors, wearable injectors, infusion pumps, inhalation systems, and advanced therapy delivery platforms. The increasing prevalence of chronic diseases, the transition toward patient-centric healthcare, and advances in biotechnology have accelerated the development and commercialization of combination products worldwide [1,3–5].

Despite their clinical and commercial advantages, biologic–medical device combination products present significant regulatory challenges because they must satisfy requirements applicable to both biologics and medical devices. Regulatory authorities are required to evaluate not only the safety, efficacy, and quality of individual constituent parts but also the performance, reliability, usability, and risk profile of the integrated product throughout its lifecycle [11–20]. Differences in product classification, primary mode of action (PMOA) determination, quality management systems, clinical evidence requirements, and post-market surveillance obligations further complicate global development and regulatory approval strategies [3,11,12,32–38].

The United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada, the National Medical Products Administration (NMPA), and other international regulatory authorities have established increasingly sophisticated regulatory frameworks to address the unique challenges associated with combination products [11–30]. In particular, implementation of Regulation (EU) 2017/745 and Article 117 requirements for integral drug–device combinations have introduced additional expectations regarding conformity assessment, technical documentation, and lifecycle management of device constituents incorporated within medicinal products [21–24]. Concurrently, harmonization initiatives led by the International Council for Harmonisation (ICH), the International Organization for Standardization (ISO), and the International Medical Device Regulators Forum (IMDRF) have promoted greater convergence in quality, risk management, usability engineering, and product lifecycle management principles [32–42].

This review examines regulatory strategies for achieving global approval of biologic–medical device combination products. Key topics include regulatory classification, Chemistry, Manufacturing and Controls (CMC), Quality by Design (QbD), risk management, human factors engineering, clinical development, quality system integration, post-market surveillance, and emerging challenges associated with advanced therapies and digital health technologies. Practical recommendations are provided to support efficient product development, facilitate global regulatory submissions, and promote successful commercialization across major international markets.

Keywords: biologic–medical device combination products; combination products; biologics; medical devices; FDA; EMA; Medical Device Regulation (MDR); Article 117; regulatory affairs; Quality by Design.

Introduction

The convergence of biotechnology and medical device innovation has transformed the treatment landscape over the past two decades. Biologic therapies—including monoclonal antibodies, recombinant proteins, vaccines, cell-based therapies, and gene therapies—have demonstrated substantial clinical benefits across a wide range of therapeutic areas, including oncology, immunology, endocrinology, and rare diseases [4,5]. However, many of these therapies require specialized delivery systems to ensure accurate administration, product stability, patient convenience, and optimal therapeutic outcomes. Consequently, biologic–medical device combination products have emerged as a critical component of modern healthcare delivery.

Combination products are generally defined as therapeutic or diagnostic products composed of two or more regulated constituents, including drugs, biologics, and medical devices, that are physically, chemically, or otherwise combined into a single product or intended for use together to achieve a therapeutic effect [11,12]. Common examples include monoclonal antibody autoinjectors, insulin pens, wearable infusion devices, prefilled syringes, drug-eluting implants, and cell therapy administration systems. The integration of biologics and devices offers numerous advantages, including improved dosing accuracy, enhanced patient adherence, reduced administration errors, and increased access to home-based treatment [1,2,43].

The commercial significance of biologic–medical device combination products has increased substantially as healthcare systems seek to improve treatment efficiency while reducing healthcare resource utilization. Patient-centric healthcare models increasingly emphasize self-administration and decentralized care, creating growing demand for delivery systems that are safe, reliable, and easy to use. Consequently, pharmaceutical and biotechnology companies now frequently incorporate device development into biologic product development strategies from the earliest stages of research and development [7–9].

From a regulatory perspective, combination products create unique challenges because they exist at the intersection of pharmaceutical, biologic, and medical device regulations. Historically, these product categories were regulated independently, with separate requirements governing manufacturing, quality systems, clinical evaluation, and post-market surveillance. The integration of multiple regulated constituents into a single product has therefore required regulatory authorities to establish specialized frameworks capable of evaluating not only individual components but also the safety, effectiveness, and performance of the integrated product system [3,13,14].

In the United States, the Food and Drug Administration (FDA) established the Office of Combination Products (OCP) to coordinate review activities and determine regulatory jurisdiction based on a product's Primary Mode of Action (PMOA) [11,16]. The PMOA determines whether primary review responsibility resides with the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH). Accurate classification is critical because it influences regulatory pathways, submission requirements, manufacturing controls, quality system obligations, and post-market surveillance activities [15,16].

Within the European Union, the regulatory environment has evolved significantly following implementation of Regulation (EU) 2017/745 on Medical Devices (MDR). Article 117 of the MDR introduced a fundamental regulatory change by requiring manufacturers of integral drug–device combination products to provide evidence that the device constituent complies with applicable General Safety and Performance Requirements (GSPRs) [21,22]. This requirement frequently necessitates involvement of a Notified Body and has increased the complexity of marketing authorization applications for medicinal products incorporating medical devices [21–24]. EMA guidance further emphasizes the importance of demonstrating compatibility between medicinal products and associated device constituents, particularly where device performance may influence product quality, safety, or efficacy [22].

Globally, regulatory authorities increasingly recognize the importance of harmonized approaches to product development and lifecycle management. The International Council for Harmonisation (ICH) has established foundational quality guidelines, including ICH Q8(R2) (Pharmaceutical Development), Q9(R1) (Quality Risk Management), Q10 (Pharmaceutical Quality System), and Q12 (Product Lifecycle Management), which support risk-based approaches to development and regulatory decision-making [32–35]. Similarly, ISO 13485, ISO 14971, IEC 62366-1, and IMDRF guidance documents have become important references for quality management, risk management, usability engineering, and software-enabled medical technologies [36–42].

The regulatory landscape continues to evolve as biologic therapies become increasingly sophisticated and digital health technologies are incorporated into therapeutic delivery systems. Advanced therapies, including cell and gene therapies, frequently require specialized administration devices and integrated delivery platforms, creating additional regulatory considerations related to manufacturing, product quality, clinical evaluation, and lifecycle management [4,5,43]. At the same time, advances in connected medical devices and software-enabled healthcare technologies have expanded regulatory expectations regarding usability, cybersecurity, and real-world performance monitoring [41,42].

This review examines regulatory strategies for achieving global approval of biologic–medical device combination products. Particular emphasis is placed on regulatory classification, Chemistry, Manufacturing and Controls (CMC), Quality by Design (QbD), risk management, human factors engineering, clinical development, quality system integration, post-market surveillance, and emerging regulatory challenges associated with advanced therapies and digital health technologies. By comparing major international regulatory frameworks and identifying common regulatory principles, this review aims to provide

practical guidance for organizations seeking efficient development, global market access, and successful lifecycle management of biologic–medical device combination products.

Global Regulatory Frameworks for Biologic–Medical Device Combination Products

The regulatory oversight of biologic–medical device combination products has evolved significantly over the past two decades in response to advances in biotechnology, drug delivery systems, and patient-centered healthcare. Regulatory agencies worldwide recognize that combination products present unique challenges because they incorporate multiple regulated constituents that have historically been reviewed under separate legal and regulatory frameworks. Consequently, regulators have established specialized mechanisms to determine product classification, assign review responsibility, and evaluate the safety, efficacy, quality, and performance of integrated products throughout their lifecycle [11,12,43].

Although regulatory authorities generally apply risk-based principles, significant differences exist among jurisdictions regarding classification methodologies, review pathways, quality requirements, and post-market obligations. Understanding these differences is essential for organizations pursuing global development and commercialization strategies.

Figure 1. Evolution of Combination Product Regulation

United States Food and Drug Administration (FDA):

The United States has developed one of the most comprehensive regulatory frameworks for combination products. The FDA defines a combination product as a product composed of two or more regulated constituents, including drugs, biologics, and medical devices, that are physically combined, co-packaged, or intended for use together [12]. Examples include biologic-filled prefilled syringes, autoinjectors, infusion systems, and drug-eluting medical devices.

To facilitate consistent regulation, the FDA established the Office of Combination Products (OCP), which is responsible for product classification, jurisdictional determinations, and coordination among FDA review centers [20]. The primary regulatory principle used by FDA is the Primary Mode of Action (PMOA), defined as the mode of action expected to make the greatest contribution to the overall intended therapeutic effect of the product [16].

Depending on the PMOA, review responsibility is assigned to one of three FDA centers:

- Center for Biologics Evaluation and Research (CBER)
- Center for Drug Evaluation and Research (CDER)
- Center for Devices and Radiological Health (CDRH)

For example, a monoclonal antibody delivered through an autoinjector is generally regulated by CBER because the biologic constituent provides the principal therapeutic effect. Conversely, certain device-led products incorporating medicinal substances may fall under CDRH oversight [16,43].

FDA regulations governing combination products are primarily established under 21 CFR Part 3 (Product Jurisdiction) and 21 CFR Part 4 (Current Good Manufacturing Practice Requirements for Combination Products) [11,12]. Sponsors may seek regulatory clarification through the Request for Designation (RFD) and Pre-RFD programs, which provide formal classification determinations and facilitate early regulatory engagement [16,19]. FDA guidance further emphasizes early interaction with regulatory authorities during the development of innovative combination products to ensure alignment regarding scientific, technical, and clinical evidence requirements [14].

In addition to premarket review, FDA has issued guidance addressing human factors engineering, bridging studies, quality system integration, and post-market safety reporting for combination products [13,18]. This integrated framework is widely regarded as one of the most mature regulatory models for combination product oversight globally.

European Union: EMA and Medical Device Regulation (MDR):

The European Union employs a distinct regulatory framework that combines medicinal product legislation with the Medical Device Regulation (EU MDR 2017/745). Unlike the FDA's PMOA-based jurisdictional model, the EU framework focuses on determining whether the medicinal product or device component constitutes the principal intended action of the product [21].

One of the most significant developments in European regulation has been the implementation of Article 117 of the MDR. This provision requires applicants seeking marketing authorization for medicinal products that incorporate integral medical devices to demonstrate compliance of the device constituent with applicable General

Safety and Performance Requirements (GSPRs) under the MDR [21,22].

In many cases, manufacturers must obtain a Notified Body Opinion (NBOp) confirming conformity of the device constituent with applicable General Safety and Performance Requirements (GSPRs) before marketing authorization can be granted. This requirement commonly applies to biologic–medical device combination products such as prefilled syringes, injection pens, autoinjectors, inhalation systems, and infusion devices. As a result, manufacturers are expected to generate comprehensive device documentation, risk management records, and conformity assessment evidence to support the overall marketing authorization application and demonstrate compliance with Article 117 requirements [21–24].

To support implementation of Article 117, the European Medicines Agency (EMA) published the "Guideline on Quality Documentation for Medicinal Products When Used with a Medical Device." This guideline specifies quality documentation requirements for medicinal products incorporating integral, co-packaged, or separately obtained medical devices and emphasizes evaluation of product-specific device characteristics that may affect medicinal product quality, safety, or efficacy [22].

The MDR has substantially increased regulatory expectations regarding risk management, technical documentation, post-market surveillance, and lifecycle management. Manufacturers must now demonstrate a greater degree of integration between pharmaceutical and device development programs than was required under previous European legislation [21].

China: National Medical Products Administration (NMPA):

China's National Medical Products Administration (NMPA) has significantly expanded its regulatory framework for combination products over the past decade. The NMPA applies a risk-based classification approach and has issued dedicated guidance documents addressing registration requirements for drug-device combination products [29,30].

Similar to FDA approach, Chinese regulators consider the product's principal mechanism of action when determining regulatory jurisdiction. Products may be regulated as pharmaceuticals, biologics, medical devices, or combination products depending on the dominant therapeutic contribution of each constituent [29].

Recent reforms have strengthened China's alignment with international regulatory practices, including greater adoption of ICH guidelines and enhanced requirements for quality management systems, risk management, and lifecycle oversight [30].

Health Canada:

Health Canada regulates combination products through a policy framework that considers the product's primary mechanism of action and intended use [25,26]. Similar to FDA approaches, products are generally assigned to the regulatory framework most closely aligned with the constituent responsible for the primary therapeutic effect.

Health Canada's guidance emphasizes coordinated review processes, integrated quality assessments, and risk-based regulatory decision-making. The Canadian framework is generally considered flexible and has demonstrated substantial alignment with international regulatory principles [25].

Global Harmonization Efforts:

The increasing globalization of healthcare innovation has highlighted the need for

greater regulatory convergence. Several international organizations play critical roles in promoting harmonization of regulatory expectations for combination products.

The International Council for Harmonisation (ICH) has developed foundational quality guidelines including ICH Q8(R2) Pharmaceutical Development, ICH Q9(R1) Quality Risk Management, ICH Q10 Pharmaceutical Quality System, and ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management [32–35].

These guidelines support science-based and risk-based approaches to product development and lifecycle management [32–35].

Similarly, international standards such as ISO 13485, ISO 14971, IEC 62366, and IMDRF guidance documents provide common frameworks for quality management, risk management, usability engineering, and software-enabled medical technologies [36–42].

Although significant differences remain among regulatory jurisdictions, increasing convergence in quality management, risk management, lifecycle management, and usability engineering principles has reduced many historical barriers to multinational development programs. Adoption of internationally recognized frameworks, including ICH Q8(R2), Q9(R1), Q10, and Q12, together with ISO 13485, ISO 14971, IEC 62366-1, and IMDRF guidance documents, has provided manufacturers with a more consistent foundation for global product development and regulatory submissions [32–42]. Organizations that incorporate these internationally accepted principles into development strategies are better positioned to achieve efficient approvals and effective lifecycle management across multiple regulatory jurisdictions.

Table 1. Comparison of Global Regulatory Frameworks for Biologic–Medical Device Combination Products

Regulatory Authority	Classification Approach	Lead Review Determination	Key Regulatory Requirement	Unique Consideration
FDA (United States)	Primary Mode of Action (PMOA)	CBER, CDER, or CDRH	21 CFR Parts 3 and 4	Office of Combination Products (OCP) coordinates review
EMA / EU MDR	Principal intended action	EMA + Notified Body	MDR Article 117	Notified Body Opinion may be required
NMPA (China)	Risk-based classification	NMPA determination	Drug–Device Combination Product Guidance	Local registration requirements
Health Canada	Principal mechanism of action	Health Canada review bureau	Drug-Medical Device Combination Policy	Flexible case-by-case approach

References: [11–31]

Regulatory Classification Strategies and Primary Mode of Action Determination

Regulatory classification is one of the most important strategic decisions in the global development of biologic–medical device combination products. Classification determines the applicable legal framework, lead review authority, submission pathway, evidence requirements, quality system expectations, labeling obligations, and post-market surveillance responsibilities. Because biologic–device products integrate constituents that may independently fall under different regulatory categories, classification should be addressed early in development rather than deferred until submission preparation [1,3,11,12].

Importance of Early Classification:

Early classification provides the foundation for the entire regulatory strategy. A biologic delivered through an autoinjector, for example, may require evaluation of the biologic's safety, purity, potency, and efficacy while also requiring evidence that the device can reliably deliver the intended dose under expected use conditions. If the product is misclassified, the sponsor may prepare an inappropriate submission package, omit necessary device or biologic data, or fail to engage the correct regulatory review center [11,16].

From a development perspective, classification affects several critical decisions, including whether the product will be submitted as a biologics license application, new drug application, device premarket application, marketing authorization application, or a region-specific hybrid submission. It also affects the timing and content of human factors studies, design verification and validation, stability studies, compatibility assessments, and post-market reporting systems [13–18].

Primary Mode of Action in the United States:

In the United States, the FDA classifies combination products primarily according to the product's Primary Mode of Action (PMOA). PMOA refers to the mode of action expected to make the greatest contribution to the overall intended therapeutic effect of the combination product [11,16]. This determination is particularly important because it identifies the FDA center with primary jurisdiction over the product.

For biologic–device combination products, the lead center is commonly the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER), when the biologic or drug constituent provides the principal therapeutic effect. The Center for Devices and Radiological Health (CDRH) may lead review when the device constituent provides the primary therapeutic effect and the biologic plays a secondary or supporting role [11,12,16].

Sponsors can request formal classification assistance through the Request for Designation (RFD) process. The RFD provides a binding FDA determination regarding product classification and assignment to a lead review center. Sponsors may also use the Pre-RFD process to obtain nonbinding feedback before submitting a formal RFD. These mechanisms are especially useful for innovative products where the principal therapeutic effect is not immediately obvious [16,17].

EU Classification Approach:

The European Union applies a different but conceptually related approach. Rather than using the FDA's PMOA terminology, the EU evaluates whether the principal intended action is achieved by pharmacological, immunological, or metabolic means, or by physical or mechanical action associated with

a medical device [21,22]. This distinction determines whether the product is primarily regulated as a medicinal product or as a medical device.

Table 2. Comparison of FDA and EU Regulatory Requirements for Biologic–Medical Device Combination Products

Regulatory Element	FDA	European Union
Classification Basis	Primary Mode of Action (PMOA)	Principal Intended Action
Regulatory Authority	FDA OCP, CBER, CDER, CDRH	EMA, National Authorities, Notified Bodies
Device Conformity Assessment	Integrated within FDA review	MDR Article 117 and Notified Body Opinion
Quality Requirements	21 CFR Parts 210, 211, 820, Part 4	EU GMP + MDR + ISO 13485
Human Factors Requirements	FDA Human Factors Guidance	IEC 62366 + MDR GSPR Requirements
Post-Market Surveillance	Pharmacovigilance + Medical Device Reporting	PMS, PSUR, Vigilance Reporting
Software Oversight	FDA Digital Health Guidance	MDR + MDCG Guidance
Lifecycle Management	ICH Q12-aligned approach	Lifecycle oversight through EMA and MDR

References: [12–24]

For integral drug-device and biologic-medical device combinations, such as prefilled syringes or autoinjectors containing biologics, the medicinal product generally provides the principal therapeutic action. However, the device constituent must still comply with applicable General Safety and Performance Requirements under the EU Medical Device Regulation. Article 117 of MDR 2017/745 requires applicants to provide evidence of conformity for the device constituent, including a Notified Body Opinion where applicable [21–23].

This EU model requires sponsors to plan both medicinal product and device documentation from the beginning of development. Even when the medicinal product is the primary regulated component, failure to adequately document device conformity may delay marketing authorization [22–24].

Classification in Other International Jurisdictions:

In addition to the United States and European Union, several international regulatory authorities have established frameworks for the classification and regulation of biologic–medical device combination products. China's National Medical Products Administration (NMPA) applies a risk-based classification approach and has issued dedicated guidance documents addressing registration requirements for drug–device combination products [29,30]. Similar to FDA practice, Chinese regulators consider the principal mechanism of action and the dominant therapeutic contribution of each constituent when determining regulatory jurisdiction.

Health Canada regulates combination products through a policy framework that considers the product's principal mechanism of action and intended use [25,26]. Products are generally assigned to the regulatory pathway most closely aligned with the constituent responsible for the primary therapeutic effect. Health Canada's guidance emphasizes coordinated review processes,

integrated quality assessments, and risk-based regulatory decision-making.

Because terminology, documentation requirements, and review procedures differ among jurisdictions, sponsors should not assume that a classification assigned in one region will automatically apply elsewhere. A biologic-led product in the United States may still require extensive device conformity documentation in the European Union or additional local registration requirements in China. Consequently, classification strategies should be developed on a jurisdiction-specific basis while maintaining a globally harmonized development program.

Strategic Classification Workflow:

An effective classification strategy should begin during early feasibility and concept development. Sponsors should first define the product's intended use, target population, route of administration, mode of action, device function, and therapeutic claims. The sponsor should then map these characteristics against jurisdiction-specific definitions of biologics, drugs, devices, and combination products [1,3,11,21].

A practical workflow includes:

1. Define the intended use and clinical claims.
2. Identify each constituent part and its regulatory category.
3. Determine the principal therapeutic effect.
4. Assess whether the device contributes directly to therapy or only enables delivery.
5. Review jurisdiction-specific classification rules.
6. Seek early regulatory advice when classification is uncertain.
7. Document the classification rationale in the regulatory strategy.
8. Update classification assessments as the product design or claims evolve.

This workflow should be documented in the regulatory strategy plan and revisited whenever product design, labeling claims, formulation, delivery route, or intended users change.

Common Classification Challenges:

Several factors frequently complicate classification of biologic–device combination products. First, the therapeutic effect may depend on close interaction between the biologic and the device. For example, a biologic may only achieve the intended clinical benefit if delivered at a specific rate, volume, depth, or anatomical location. In such cases, the device may not provide the principal therapeutic mechanism, but its performance is essential to overall safety and effectiveness [14,15,43].

Second, advanced biologic therapies may involve delivery systems that are technologically sophisticated and clinically important. Cell-based therapies, gene therapies, and regenerative medicine products often require specialized administration systems, catheters, infusion devices, or customized delivery platforms. In these situations, regulatory authorities may request additional justification regarding whether the biologic constituent, the device constituent, or the integrated system provides the principal therapeutic effect. These products frequently require enhanced coordination between biologic development, device engineering, and regulatory strategy teams [4,5,43].

Third, digital and connected products may introduce software functions that support dosing, adherence, monitoring, or clinical decision-making. These features may trigger additional device or software regulatory expectations, including IMDRF and IEC usability or software-related considerations [40–42].

Classification and Development Planning:

Classification should directly inform the development plan. For biologic-led products, sponsors must prioritize biologic quality, pharmacology, toxicology, immunogenicity, and clinical efficacy while integrating device performance data. For device-led products incorporating biologic constituents, sponsors may need to emphasize device design controls, biocompatibility, risk management, and performance testing while also addressing biologic safety and stability [13,15,36–39].

The classification decision also influences manufacturing strategy. Biologic-led combination products may be manufactured under pharmaceutical GMP systems with additional device quality system elements, whereas device-led products may be subject to medical device quality management systems with pharmaceutical GMP controls for the biologic constituent [12,13,36].

Global Classification Risk Mitigation:

Sponsors pursuing global approval should develop a classification matrix comparing regulatory treatment across target markets. The matrix should include the United States, European Union, Japan, China, United Kingdom, Canada, and other target regions. For each jurisdiction, the matrix should identify the likely classification, lead authority, submission pathway, applicable guidance, device documentation requirements, and planned regulatory interactions.

Risk mitigation measures should include:

- Early FDA Pre-RFD or RFD submission when appropriate.
- FDA combination product meetings and early development interactions.
- EMA scientific advice or consultation with national competent authorities.
- Early Notified Body engagement to support Article 117 compliance.
- NMPA classification and registration planning for China.
- Health Canada classification review where Canadian market entry is planned.
- Continuous monitoring of evolving regulatory guidance and international standards.

These activities reduce uncertainty, improve development efficiency, and help prevent late-stage regulatory deficiencies [16,21–30].

Table 3. Recommended Regulatory Strategy by Development Stage

Stage	Recommended Activity
Discovery	Initial classification assessment
Preclinical	Regulatory intelligence gathering
Phase I	FDA Pre-RFD / Scientific Advice
Phase II	Human factors strategy
Phase III	Global submission planning
Registration	Parallel submission preparation
Commercial	PMS and lifecycle management

References: [3, 11, 14, 16, 21–35]

Conclusion:

Classification is not merely an administrative exercise; it is a strategic determinant of development, submission, approval, and lifecycle management. For biologic–medical device combination products, the sponsor must understand how each constituent contributes to the product's intended therapeutic effect and how each jurisdiction interprets that contribution. Early

classification planning, documented rationale, and proactive regulatory engagement are essential for successful global approval.

Quality by Design (QBD) and Risk-Based Development Strategies

Introduction to Quality by Design:

Quality by Design (QbD) has become a foundational principle in the development of biologic–medical device combination products because it promotes a systematic, science-based, and risk-based approach to product development and lifecycle management. Unlike traditional quality approaches that rely primarily on end-product testing, QbD emphasizes designing quality into the product from the earliest stages of development through a thorough understanding of product characteristics, manufacturing processes, and sources of variability [32,33].

The concept was formally established through International Council for Harmonisation (ICH) guidelines, particularly ICH Q8(R2) Pharmaceutical Development, ICH Q9(R1) Quality Risk Management, and ICH Q10 Pharmaceutical Quality System [32–34]. Although originally developed for pharmaceutical products, QbD principles have become increasingly relevant to biologic-medical device combination products because product performance depends not only on the biologic constituent but also on device design, usability, and manufacturing consistency [1,3].

For biologic–medical device combination products, QbD facilitates integration of pharmaceutical development, device engineering, human factors engineering, risk management, and quality systems into a unified development strategy. This integrated approach aligns with regulatory expectations from the FDA, EMA, Health Canada, NMPA, and other international authorities that increasingly emphasize lifecycle management, product understanding, and risk-based decision-making [13,14,22,25,29].

4.2 Critical Quality Attributes and Device Performance Characteristics:

A central element of QbD is identification of Critical Quality Attributes (CQAs), defined as physical, chemical, biological, or microbiological properties that must be maintained within appropriate limits to ensure product quality [32].

For biologic constituents, critical quality attributes (CQAs) typically include potency, purity, immunogenicity profile, aggregation levels, stability, protein structural integrity, and sterility. These attributes directly influence product safety, efficacy, and consistency and therefore require careful characterization throughout development and lifecycle management. For combination products, evaluation of these biologic CQAs must be integrated with assessment of device performance characteristics to ensure consistent therapeutic delivery and product functionality [32–34].

However, combination products require consideration of additional device-related performance attributes that may directly affect product quality and clinical performance. Critical device attributes commonly include dose delivery accuracy, injection force, activation reliability, needle deployment performance, flow rate control, device integrity, and container closure integrity. These parameters should be incorporated into product design, risk assessments, and control strategies because variability in device performance may affect biologic delivery, patient usability, and overall therapeutic effectiveness. Therefore, identification and control of these attributes are essential elements of a Quality by Design

(QbD) approach for biologic–medical device combination products [32–37].

Because device performance directly affects therapeutic delivery, regulators increasingly expect sponsors to evaluate biologic and device attributes together rather than independently [4,13].

Risk Management Integration:

Risk management is a fundamental component of QbD and is strongly supported by ICH Q9(R1) and ISO 14971 [33,37].

Combination product development requires evaluation of a broad range of potential risks, including incorrect dose delivery, device malfunction, protein degradation, user-related errors, microbial contamination, material incompatibilities, and software failures in connected devices. Because these risks may originate from either the biologic constituent, the device constituent, or their interaction, regulators increasingly expect manufacturers to adopt integrated risk management strategies throughout the product lifecycle [33,37].

Commonly used risk assessment methodologies include Failure Mode and Effects Analysis (FMEA), Design Failure Mode and Effects Analysis (dFMEA), Process Failure Mode and Effects Analysis (pFMEA), Fault Tree Analysis (FTA), and Hazard Analysis and Critical Control Point (HACCP) approaches [33,37].

Regulators increasingly expect risk management activities to be continuously updated as new information becomes available during development and post-market surveillance [33,37,38].

Design Space and Lifecycle Management:

QbD encourages development of a design space, defined as the multidimensional combination of material attributes and process parameters that consistently produce acceptable product quality [32].

For biologic–medical device combination products, the design space may encompass formulation characteristics, device material selection, filling parameters, assembly conditions, storage requirements, transportation conditions, and user-interface characteristics. Understanding the interactions among these variables enables manufacturers to establish scientifically justified operating ranges that support consistent product quality and device performance [32,35].

Implementation of QbD supports more effective lifecycle management by establishing a robust scientific foundation for post-approval changes, manufacturing improvements, and process optimization. ICH Q12 further promotes structured lifecycle management approaches that facilitate regulatory flexibility while maintaining product quality, safety, and efficacy. For combination products, this framework is particularly valuable because modifications to either the biologic or device constituent may influence overall product performance and therefore require scientifically justified change management strategies [35].

Regulatory Implications:

QbD provides a scientifically justified framework for managing complexity in biologic–medical device combination products. Regulatory agencies increasingly view QbD not merely as a development tool but as a strategic approach for ensuring consistent product quality throughout the product lifecycle. Sponsors that incorporate QbD principles early in development are often better positioned to manage regulatory expectations, manufacturing changes, and post-market quality challenges [32–35].

Chemistry, Manufacturing, And Controls (CMC) Considerations for Biologic–Medical Device Combination Products

CMC Complexity in Combination Products:

Chemistry, Manufacturing, and Controls (CMC) requirements represent one of the most challenging aspects of biologic-medical device combination product development. Unlike conventional biologics, combination products require simultaneous evaluation of both pharmaceutical quality and device performance. Regulatory authorities expect manufacturers to demonstrate that the biologic and device constituents function together safely and effectively throughout the product's intended shelf life [4,5,13].

The complexity of CMC programs increases because changes affecting either constituent may influence the overall performance of the combination product. Consequently, manufacturers must establish integrated development strategies capable of evaluating interactions between biologics, packaging systems, delivery devices, and manufacturing processes [1,2].

Biologic–Device Compatibility:

One of the most critical CMC considerations is compatibility between biologic formulations and device materials. Biologic products are highly sensitive molecules whose stability may be affected by contact with device components.

Compatibility assessments should evaluate potential interactions between biologic formulations and device materials, including protein adsorption to contact surfaces, silicone oil interactions, extractables and leachables, protein aggregation, chemical degradation, lubricant interactions, and elastomer compatibility. These interactions may affect critical quality attributes and ultimately influence product safety, efficacy, and stability [4,10,43].

For example, silicone oil used as a lubricant in prefilled syringes has been associated with protein particle formation, aggregation, and potential impacts on product quality attributes. Such interactions highlight the importance of comprehensive compatibility studies during formulation and device development [4,43].

Regulators therefore expect comprehensive compatibility assessments throughout development and commercialization.

Extractables and Leachables:

Extractables and leachables studies are essential components of combination product CMC programs.

Extractables are chemical compounds that can be extracted from device materials under aggressive laboratory conditions, whereas leachables are compounds that migrate into the product under normal storage conditions [10].

Potential sources of extractables and leachables include elastomers, plastics, adhesives, lubricants, and packaging materials used throughout the device and container closure system. Manufacturers must evaluate the toxicological significance of migrated compounds and determine whether they may adversely affect product quality, patient safety, or therapeutic performance [10,13].

Sponsors must evaluate potential toxicological risks and determine whether migrated compounds may affect product safety, efficacy, or quality [10,13].

Stability and Container Closure Integrity:

Biologic-medical device combination products require stability studies that evaluate both pharmaceutical and device performance throughout shelf life.

Stability programs for biologic–medical device combination products should evaluate both biologic quality attributes and device performance characteristics throughout the proposed shelf life. Key parameters typically assessed include potency, purity, protein aggregation, and sterility of the biologic constituent, as well as dose delivery accuracy and device functionality. Regulatory authorities expect manufacturers to demonstrate that the integrated product maintains its safety, efficacy, quality, and performance under anticipated storage, transportation, and use conditions throughout its lifecycle. These evaluations are particularly important because changes in either the biologic or device constituent may affect overall product performance and patient outcomes [5,13,15,22,36–39].

Container Closure Integrity (CCI) testing is particularly important because loss of container integrity may compromise sterility and product quality [5].

Regulatory agencies increasingly expect sponsors to demonstrate maintenance of both biologic quality and device functionality throughout storage, transportation, and intended use conditions. Within the European Union, these expectations are closely aligned with MDR requirements and EMA guidance addressing quality documentation for medicinal products used with medical devices [21,22].

Manufacturing Change Management:

Manufacturing changes present significant regulatory challenges for combination products because modifications to either constituent may impact overall product performance.

Common lifecycle management activities for biologic–medical device combination products include formulation changes, device redesigns, manufacturing site transfers, component supplier changes, and packaging modifications. Because changes to either the biologic or device constituent can influence overall product performance, sponsors must assess potential impacts on product quality, safety, efficacy, usability, and regulatory compliance. A science- and risk-based approach consistent with ICH Q12 principles can facilitate effective change management while maintaining product control throughout the lifecycle [35].

FDA guidance on bridging for biologic-medical device combination products emphasizes the need for scientifically justified comparability assessments whenever significant changes are introduced [15].

In summary, CMC programs for biologic–medical device combination products must address pharmaceutical quality, device performance, and interactions between constituent parts. Compatibility assessments, extractables and leachables studies, stability programs, container closure integrity testing, and scientifically justified change management strategies are critical for ensuring consistent product quality and regulatory compliance throughout the product lifecycle [4,5,13,15,22].

GMP and Quality System Harmonization

Regulatory Need for Integrated Quality Systems:

One of the most significant regulatory challenges associated with biologic–medical device combination products is the integration of pharmaceutical Good Manufacturing Practice (GMP) requirements with medical device quality management systems.

Historically, biologics and medical devices have been regulated under separate quality frameworks. Combination products, however, require manufacturers to

demonstrate compliance with both systems simultaneously [1,6].

FDA Combination Product GMP Requirements:

FDA addressed this challenge through 21 CFR Part 4, which establishes Current Good Manufacturing Practice (CGMP) requirements for combination products [12].

Manufacturers must comply with applicable pharmaceutical current Good Manufacturing Practice (CGMP) requirements together with device quality system requirements established under FDA combination product regulations. The objective is to ensure that both pharmaceutical and device quality principles are appropriately incorporated into manufacturing operations, quality oversight, and lifecycle management activities [12,13].

The objective is to ensure that both pharmaceutical and device quality principles are incorporated into manufacturing operations [12,13].

ISO 13485 and Global Device Quality Systems:

For device constituents, ISO 13485 serves as the internationally recognized quality management standard for medical devices [36].

ISO 13485:2016 provides a structured framework for managing the quality-related activities associated with medical devices and device constituents of combination products. Core requirements include design controls, supplier management, complaint handling, Corrective and Preventive Actions (CAPA), risk management integration, and change control. When integrated with pharmaceutical quality systems and current Good Manufacturing Practice (cGMP) requirements, these elements help manufacturers establish robust quality oversight across development, manufacturing, distribution, and post-market activities. Such integration is particularly important for biologic–medical device combination products because quality issues may arise from either constituent or from interactions between the biologic and device components [12,13,36–38].

Many global regulators reference ISO 13485 when evaluating medical device quality systems.

Harmonization Challenges:

Several operational challenges arise when integrating pharmaceutical and device quality systems:

Design Controls

Medical device regulations require formal design controls, whereas traditional pharmaceutical GMP systems historically emphasized process controls.

Supplier Qualification

Combination products frequently rely on multiple specialized suppliers for biologic substances, device components, packaging materials, and software systems.

CAPA Systems

Integrated CAPA systems must address deviations originating from biologic manufacturing processes, device assembly operations, or user-related complaints.

Documentation

Manufacturers must maintain comprehensive documentation throughout the lifecycle of biologic–medical device combination products to demonstrate compliance with applicable regulatory and quality system requirements. Such documentation typically includes device design history files, pharmaceutical batch records, risk management files, validation reports, and change control records. These records provide objective evidence that the product has been designed, manufactured, tested, and

maintained in accordance with established specifications and regulatory expectations. Effective documentation management also supports regulatory inspections, product lifecycle management, deviation investigations, corrective and preventive actions (CAPA), and post-market surveillance activities. Given the complexity of combination products, maintaining traceability across both biologic and device constituents is essential to ensure continued product quality, safety, and regulatory compliance [12,13,36–38].

Regulatory inspections frequently focus on the interfaces between these documentation systems [24,36].

Successful harmonization requires integration of pharmaceutical quality system principles described in ICH Q10 with device quality management requirements described in ISO 13485 and risk management principles outlined in ISO 14971. Regulatory inspections increasingly evaluate how effectively manufacturers manage interfaces between these systems rather than assessing each framework independently [34,36,37].

Lifecycle Quality Management:

Modern regulatory frameworks increasingly emphasize lifecycle quality management rather than one-time compliance activities.

Effective lifecycle management for biologic–medical device combination products requires continuous monitoring and improvement activities throughout commercialization. Key lifecycle activities include continuous process verification, trending and signal detection, complaint analysis, periodic risk reviews, supplier performance monitoring, and post-market quality investigations. These activities enable manufacturers to identify emerging quality or safety concerns, evaluate the effectiveness of existing control measures, and implement timely corrective and preventive actions when necessary. By integrating these processes into a comprehensive pharmaceutical and device quality system, manufacturers can maintain product quality, support ongoing regulatory compliance, and ensure that the benefit–risk profile of the combination product remains favourable throughout its lifecycle [12,13,35–38].

This lifecycle approach aligns closely with ICH Q10 and ICH Q12 principles and supports continual improvement throughout commercialization [34,35].

Table 4. QbD, CMC, and Quality System Considerations for Combination Products

Development Area	Biologic Focus	Device Focus	Combination Product Consideration
Critical Quality Attributes (CQAs)	Potency, purity, stability	Functional performance	Integrated product performance
Risk Management	ICH Q9	ISO 14971	Combined risk management strategy
Design Controls	Limited traditional requirement	Mandatory under device regulations	Integrated design history documentation
Stability Studies	Biologic stability	Device functionality	Simultaneous assessment required
Change Management	Comparability protocols	Design change controls	Bridging assessments may be required
Supplier Qualification	API and biologic suppliers	Device component suppliers	Cross-functional supplier oversight
Lifecycle Management	ICH Q10/Q12	ISO 13485	Harmonized quality system

References: [32–39]

Regulatory Implications:

Integrated quality systems are essential for successful development and commercialization of biologic–medical device combination products. Regulators increasingly expect sponsors to demonstrate seamless integration of pharmaceutical GMP requirements, medical device quality systems, risk management processes, and lifecycle quality management principles. Organizations that establish harmonized quality systems early in development are generally better positioned to support global approvals and long-term regulatory compliance [12,13,24,34–37].

Human Factors Engineering and Usability Considerations

Introduction:

Human Factors Engineering (HFE), also referred to as usability engineering, has become a critical component of biologic–medical device combination product development. As biologic therapies increasingly shift from healthcare-provider administration to self-administration in home settings, regulators have placed greater emphasis on ensuring that intended users can safely and effectively operate combination products under real-world conditions [7–9,18,19].

Historically, many biologics were administered exclusively in hospitals or clinics by trained healthcare professionals. However, advances in drug delivery technologies have enabled the development of prefilled syringes, autoinjectors, wearable injectors, and infusion systems that can be used by patients and caregivers outside traditional healthcare environments [7–9,43]. While these delivery systems improve convenience and treatment adherence, they also introduce risks associated with user interaction, device misuse, and administration errors.

Consequently, regulatory agencies now expect manufacturers to systematically evaluate how users interact with combination products throughout development and commercialization [18,40].

Regulatory Framework for Human Factors Engineering:

The FDA has established comprehensive guidance on the application of human factors and usability engineering principles to medical devices and combination products. The guidance, Applying Human Factors and Usability Engineering to Medical Devices, emphasizes the identification and mitigation of use-related risks throughout product development [18].

In addition, FDA issued Application of Human Factors Engineering Principles for Combination Products: Questions and Answers, which specifically addresses biologic-medical device and drug-device combination products [19].

Within the European Union, usability requirements are incorporated into MDR 2017/745 and supported by IEC 62366-1, which provides internationally recognized requirements for usability engineering in medical devices [21,40].

Collectively, these regulatory frameworks require manufacturers to adopt a systematic and user-centered approach to product design and evaluation. This includes identifying the intended users, defining the anticipated use environments, analysing user–device interactions, and assessing potential use-related hazards that could affect product safety or effectiveness. Manufacturers are also expected to conduct usability validation studies under representative use conditions and demonstrate that any residual risks associated with product use have been

reduced to acceptable levels. Through these activities, human factors engineering helps ensure that biologic–medical device combination products can be used safely and effectively by the intended user population throughout the product lifecycle. Regulators increasingly view usability data as an essential component of the overall benefit-risk assessment for combination products [18,21,40].

Use-Related Risk Analysis:

Use-related risks arise when product design characteristics contribute to user errors that may affect safety or effectiveness.

Common use-related hazards include incorrect dose administration, incomplete injections, failure to activate the device correctly, premature device removal, improper storage conditions, needle-stick injuries, and misinterpretation of instructions for use. These risks may compromise both therapeutic effectiveness and patient safety and therefore require systematic evaluation during usability engineering activities [18,19].

For biologic therapies, administration errors may have particularly significant consequences because biologics often exhibit complex dosing regimens, specialized administration requirements, and potential immunogenicity concerns. Consequently, human factors engineering plays an important role in ensuring safe and effective product use [4,43].

risk assessment methodologies throughout product development and lifecycle management. Commonly used approaches include Use-Related Risk Analysis (URRA), Failure Mode and Effects Analysis (FMEA), Task Analysis, and Hazard Analysis. These methodologies help manufacturers systematically evaluate user interactions with the product, identify potential failure modes and sources of use error, assess the severity and likelihood of associated risks, and implement appropriate risk control measures. The resulting information supports product design optimization, usability validation planning, and regulatory submissions by demonstrating that use-related risks have been adequately evaluated and controlled [18,19,37,40].

These tools support identification of critical tasks and guide development of risk mitigation strategies [7,8,37].

User-Centered Design Principles:

Modern regulatory expectations encourage adoption of user-centered design principles early in development.

User-centered design involves the systematic consideration of user capabilities, physical limitations, cognitive characteristics, environmental conditions, and workflow requirements throughout product development. The objective is to ensure that the design of the combination product supports safe, effective, and intuitive use under anticipated real-world conditions. Intended users of biologic–medical device combination products may include patients, caregivers, nurses, pharmacists, physicians, and emergency responders, each of whom may possess different levels of training, experience, and physical or cognitive abilities. Consequently, human factors programs should evaluate the specific needs, capabilities, limitations, and use environments associated with each user group to ensure that the product can be operated safely and effectively in clinical and non-clinical settings [7–9,18,19,40].

Particular attention should be given to populations that may be more susceptible to use-related errors, including individuals with reduced dexterity, visual impairments, cognitive limitations, limited health literacy, or age-related functional decline. These factors may influence a user's ability to

understand instructions, prepare the device correctly, administer the intended dose, interpret device feedback, or respond appropriately to warnings and alerts. Addressing such considerations during product design and usability testing can improve accessibility, reduce the likelihood of use errors, and enhance overall product safety and effectiveness across diverse patient populations [18,19,40].

Failure to adequately consider user characteristics can significantly increase the likelihood of administration errors and product complaints [7–9].

Human Factors Validation Studies:

Human factors validation studies are designed to demonstrate that intended users can safely and effectively perform critical tasks under expected use conditions.

Regulators generally expect human factors validation studies to be conducted using representative user populations operating under realistic use conditions. Validation programs should incorporate representative product labeling, simulated use environments, and use scenarios that closely reflect real-world clinical practice. Particular emphasis is placed on evaluating critical tasks that directly influence product safety and effectiveness. For biologic–medical device combination products, these tasks commonly include device preparation, dose administration, needle disposal, product storage, and interpretation of device indicators or feedback mechanisms. Successful completion of these tasks demonstrates that intended users can operate the product safely and effectively without patterns of use-related errors that could result in patient harm or compromised therapeutic outcomes [18,19,40].

FDA recommends that validation studies focus on residual risks that remain after implementation of design controls and other risk mitigation measures [18].

The quality of human factors data can significantly influence regulatory review timelines and approval decisions for biologic-medical device combination products [19].

Human Factors Challenges in Emerging Technologies:

Emerging delivery technologies introduce additional usability considerations.

Digital health technologies are increasingly being integrated into biologic–medical device combination products to enhance treatment delivery, patient engagement, and real-world performance monitoring. Examples include connected autoinjectors, wearable delivery systems, smart infusion pumps, mobile application interfaces, and software-enabled dosing support platforms. These technologies can improve adherence, facilitate remote monitoring, and support data-driven healthcare decisions; however, they also introduce additional regulatory and technical considerations. Regulatory authorities increasingly expect manufacturers to evaluate user interactions with software components, alarm management systems, data interpretation processes, cybersecurity-related workflows, and remote monitoring functionality. Such assessments are essential to ensure that digital features support safe and effective product use while maintaining data integrity, system reliability, and patient privacy throughout the product lifecycle [41,42].

As digital health technologies become increasingly integrated into combination products, regulators are expected to expand human factors requirements to address software-enabled interactions and connected healthcare ecosystems [41,42].

In summary, human factors engineering has evolved from a supplementary design activity to a core regulatory requirement for biologic–medical device combination products. Regulatory agencies increasingly recognize that product safety and effectiveness depend not only on device performance but also on the ability of intended users to interact with products correctly under real-world conditions. Early incorporation of usability engineering principles can reduce use-related risks, improve patient outcomes, and facilitate regulatory approval [18,19,40].

Clinical Development Strategies for Biologic–Medical Device Combination Products

Introduction:

Clinical development programs for biologic–medical device combination products are inherently more complex than those for standalone biologics or medical devices. Regulatory authorities require evidence supporting not only the therapeutic effectiveness of the biologic constituent but also the safety, reliability, and usability of the integrated product system [3,13,14].

Clinical development programs for biologic–medical device combination products must evaluate multiple dimensions of product performance beyond traditional measures of therapeutic efficacy and safety. Because the biologic and device constituents function as an integrated system, regulatory authorities expect sponsors to demonstrate not only clinical benefit and an acceptable safety profile but also reliable device functionality, consistent product performance, and effective user interaction. Clinical studies may therefore incorporate assessments of device operation, dose delivery performance, product reliability, and human factors outcomes in addition to conventional clinical endpoints. This integrated approach helps ensure that the combination product can be used safely and effectively by the intended user population under real-world conditions while consistently delivering the intended therapeutic effect [3,18,19,43].

Integrated development strategies are increasingly encouraged by regulators because they allow simultaneous evaluation of biologic and device performance under intended use conditions [14,43].

Clinical Development Planning:

Successful clinical development begins with a clearly defined regulatory strategy that incorporates both pharmaceutical and device considerations.

To support efficient development and regulatory approval, sponsors should establish a comprehensive development strategy early in the product lifecycle. This strategy typically includes a Target Product Profile (TPP) that defines the intended clinical and performance characteristics of the combination product, a clinical development plan outlining the evidence required to demonstrate safety and effectiveness, and a human factors strategy designed to address usability and use-related risks. In addition, sponsors should develop a risk management plan that integrates biologic, device, and user-related risks throughout development and commercialization, as well as a regulatory interaction plan that identifies opportunities for scientific advice, regulatory consultations, and jurisdiction-specific engagement. Collectively, these planning activities help align development objectives with regulatory expectations and facilitate a more efficient pathway to global approval [11–24,33–35].

Early consultation with FDA, EMA, NMPA, Health Canada, and other relevant regulatory authorities can reduce uncertainty regarding clinical evidence expectations, study design

considerations, and regulatory submission requirements [14,21,25,29].

Clinical Endpoints:

Clinical endpoints for combination products generally encompass therapeutic outcomes, device performance measures, and user-performance assessments. Therapeutic endpoints may include disease activity scores, biomarker responses, remission rates, or survival outcomes. Device-related endpoints frequently evaluate dose delivery accuracy, administration success, reliability, and failure rates, while user-performance measures assess successful completion of critical tasks, administration errors, training requirements, and user confidence. Together, these endpoints provide an integrated assessment of the biologic and device constituents as a unified therapeutic system [3,43].

Sponsors should ensure that endpoints appropriately capture both biologic and device contributions to overall product performance [3,43].

Bridging and Comparative Studies:

Changes to device constituents frequently require bridging studies to demonstrate that modifications do not adversely affect safety or effectiveness.

Examples of post-approval changes for biologic–medical device combination products include device redesigns, material changes, manufacturing process modifications, and software updates. Although these changes may enhance product performance or manufacturing efficiency, they can also influence critical quality attributes, device functionality, usability, or overall therapeutic performance. Consequently, manufacturers should apply science- and risk-based change management principles consistent with ICH Q12 and applicable quality management system requirements to evaluate potential impacts and ensure continued compliance throughout the product lifecycle [35–39,41].

FDA guidance specifically addresses bridging for drug-device and biologic-medical device combination products and recommends risk-based approaches to determine the scope of additional clinical or nonclinical evidence required [15].

Real-World Evidence in Clinical Development:

Regulatory agencies increasingly recognize the value of Real-World Evidence (RWE) in supporting lifecycle management and post-approval decision-making.

Real-world evidence (RWE) is becoming an increasingly important component of regulatory decision-making and lifecycle management for biologic–medical device combination products. Potential sources of RWE include patient registries, electronic health records, healthcare claims databases, device-generated data, and digital health platforms. These sources can provide valuable information regarding long-term safety, product performance, treatment adherence, utilization patterns, and clinical outcomes in routine healthcare settings. Regulatory authorities are increasingly recognizing the value of such data for supporting post-market surveillance, benefit–risk assessments, label expansions, and lifecycle management activities. When collected and analysed using appropriate scientific and methodological standards, RWE can complement traditional clinical trial data and provide important insights into the real-world performance of combination products across diverse patient populations [21,41,42].

For connected combination products, real-world data may provide valuable insights regarding device performance, patient adherence, and long-term safety [41,42].

Clinical Challenges for Advanced Therapies:

Advanced therapy medicinal products (ATMPs), including cell and gene therapies, present unique clinical development challenges because therapeutic success often depends on specialized delivery systems.

Advanced biologic therapies frequently require specialized delivery systems to ensure safe and effective administration. Examples include cell therapy administration devices, gene therapy injection systems, implantation platforms, and customized delivery technologies designed to meet product-specific clinical and technical requirements. These systems often play a critical role in maintaining product integrity, ensuring accurate delivery, and supporting complex administration procedures. Consequently, regulatory authorities may require additional evidence demonstrating the compatibility, reliability, usability, and performance of both the biologic and device constituents as an integrated therapeutic system throughout development and lifecycle management [4,5,43].

Clinical programs must therefore evaluate both therapeutic performance and device functionality as an integrated system [4,5,43].

Regulatory Implications:

Clinical development strategies for biologic–medical device combination products should be designed to generate integrated evidence supporting safety, efficacy, usability, and device performance. Sponsors that proactively address device-related risks and incorporate human factors considerations into clinical programs are more likely to achieve efficient regulatory review and successful commercialization [14,15,43].

Post-Market Surveillance and Lifecycle Management

Introduction:

Regulatory oversight of biologic–medical device combination products extends far beyond initial approval. Modern regulatory frameworks increasingly emphasize lifecycle management and continuous monitoring of product performance following commercialization [12,34,35].

Because adverse events may originate from biologic constituents, device constituents, user interactions, or combinations of these factors, post-market surveillance systems for combination products must be more comprehensive than those typically required for standalone products [13].

Regulatory Requirements:

FDA, EMA, NMPA, Health Canada, and other regulatory authorities require manufacturers to establish systems for monitoring product safety and performance following market authorization [12,21,25,26,29,30].

Post-market surveillance obligations generally include adverse event reporting, complaint handling, corrective and preventive actions (CAPA), trend analysis, risk management updates, and field safety corrective actions. Because safety signals may originate from either the biologic or device constituent, manufacturers must maintain integrated surveillance systems capable of identifying and investigating multifactorial product issues [12,21].

Under MDR 2017/745, European manufacturers must maintain robust Post-Market Surveillance (PMS) systems and periodically update safety documentation throughout the product lifecycle [21].

Pharmacovigilance and Device Vigilance Integration:

One of the greatest challenges associated with combination products is integration of

pharmacovigilance and device vigilance systems.

Effective post-market surveillance programs are essential for identifying and managing emerging safety concerns associated with biologic–medical device combination products. Potential safety signals may originate from a variety of sources, including biologic adverse reactions, device malfunctions, administration errors, product quality defects, and software failures associated with connected or software-enabled products. Because these events may arise from individual constituent parts or from interactions between the biologic and device components, manufacturers must employ integrated surveillance systems capable of evaluating multifactorial safety issues. Timely identification, investigation, and assessment of potential safety signals support ongoing benefit–risk evaluations, facilitate corrective and preventive actions, and help ensure continued product safety and regulatory compliance throughout the product lifecycle [12,21,35–38,41,42].

Manufacturers must establish integrated investigation processes capable of determining the root cause of reported events and implementing appropriate corrective actions [12,13].

Complaint Handling and CAPA Systems:

Effective complaint management systems are essential components of post-market surveillance programs.

Complaint management is a critical component of post-market surveillance and quality system oversight for biologic–medical device combination products. Manufacturers should systematically evaluate complaints to determine whether they are associated with product defects, device failures, labeling deficiencies, use-related errors, or emerging safety signals. Comprehensive complaint investigations can help identify recurring issues, assess potential risks to patients, and determine whether corrective and preventive actions (CAPA), product modifications, field safety actions, or regulatory reporting activities are warranted. By integrating complaint analysis with risk management and post-market surveillance processes, manufacturers can support continuous product improvement and maintain compliance with applicable regulatory requirements throughout the product lifecycle [12,13,21,36–38].

CAPA systems should ensure timely implementation of corrective and preventive measures while maintaining compliance with pharmaceutical GMP and device quality system requirements [6,12,36].

Real-World Performance Monitoring:

Real-world performance monitoring has become increasingly important for biologic-medical device combination products.

Increasingly, manufacturers are leveraging multiple sources of real-world data to support post-market surveillance and lifecycle management activities. Potential data sources include patient support programs, product registries, connected devices, remote monitoring systems, and digital health platforms. These data streams can provide valuable insights into product performance, user behaviour, treatment adherence, and real-world safety outcomes across diverse patient populations. Regulatory authorities are placing greater emphasis on the use of such information to support signal detection, update risk management activities, identify opportunities for product improvement, and fulfil post-market regulatory reporting obligations. When appropriately collected and analysed, real-world data can strengthen ongoing benefit–risk assessments and support evidence-based decision-making throughout the product lifecycle [12,21,41,42].

Regulators increasingly encourage manufacturers to leverage real-world data to strengthen lifecycle management activities [41,42].

Cybersecurity and Digital Health Considerations:

Connected biologic–medical device combination products introduce additional post-market surveillance and lifecycle management responsibilities beyond those associated with traditional combination products. Manufacturers must address issues related to cybersecurity vulnerabilities, software maintenance, data integrity, and privacy protection throughout the product lifecycle. Because connected devices frequently collect, transmit, store, or process patient and product performance data, ongoing monitoring and maintenance activities are necessary to ensure system reliability, protect sensitive information, and maintain compliance with applicable regulatory requirements. Regulatory authorities and international organizations, including the International Medical Device Regulators Forum (IMDRF), continue to expand guidance and regulatory expectations in these areas as digital health technologies become increasingly integrated into healthcare delivery systems [41,42].

Lifecycle Management and Continuous Improvement:

Lifecycle management principles outlined in ICH Q10 and ICH Q12 emphasize continual improvement and proactive quality oversight throughout product commercialization [34,35]. Consistent with these principles, manufacturers should maintain robust systems for continuous process verification, periodic risk reassessment, change management, supplier monitoring, and ongoing product optimization. These activities enable organizations to identify emerging trends, evaluate the effectiveness of existing control strategies, manage post-approval changes in a science- and risk-based manner, and ensure the continued reliability of both biologic and device constituents. By integrating these lifecycle management practices into the overall quality system, manufacturers can support regulatory compliance while maintaining product quality, safety, and effectiveness throughout the commercial lifecycle [12,13,34–38].

Table 5. Human Factors, Clinical Development, and Post-Market Surveillance Requirements

Regulatory Area	Key Objective	Regulatory Expectations	Supporting Standards/Guidance
Human Factors Engineering	Safe and effective use	Usability validation studies	FDA HFE Guidance, IEC 62366
User Risk Assessment	Minimize use errors	Critical task analysis	ISO 14971
Clinical Development	Demonstrate safety and efficacy	Integrated biologic-medical device evidence	FDA Early Development Guidance
Device Performance Evaluation	Reliable delivery	Dose accuracy, failure analysis	FDA Combination Product Guidance
Pharmacovigilance	Monitor biologic safety	Adverse event reporting	Regional PV regulations

Device Vigilance	Monitor device failures	MDR/MDR reporting requirements	MDR, FDA MDR requirements
Real-World Evidence	Support lifecycle management	Registry and observational data	FDA and EMA RWE initiatives
Cybersecurity Monitoring	Protect connected products	Continuous monitoring and updates	IMDRF, FDA Cybersecurity Guidance

References: [18,19,37,40–42]

Section Summary:

Post-market surveillance represents a critical component of combination product regulation. Modern regulatory frameworks require integrated systems capable of monitoring biologic performance, device functionality, user interactions, and emerging safety signals throughout the product lifecycle. Effective surveillance programs support patient safety, regulatory compliance, and continuous product improvement [12,21,34–42].

Digital Health Technologies and Advanced Therapy Combination Products

Introduction:

The convergence of biologics, medical devices, software, and digital health technologies is reshaping the regulatory landscape for combination products. Traditionally, biologic-medical device combination products consisted primarily of delivery systems such as prefilled syringes, autoinjectors, and infusion pumps. However, recent advances in digital health, connected medical devices, gene therapies, and cell-based therapies have expanded the complexity of these products and challenged existing regulatory paradigms [4,41,42].

Modern healthcare systems increasingly emphasize personalized medicine, remote patient monitoring, decentralized clinical care, and real-time data collection. Consequently, combination products are evolving beyond simple delivery devices into integrated therapeutic platforms capable of monitoring patient behaviour, collecting clinical data, providing adherence support, and facilitating clinical decision-making [41-43].

Regulatory authorities worldwide are actively adapting their frameworks to address these emerging technologies while maintaining patient safety, product quality, and clinical effectiveness.

Connected Drug Delivery Systems:

Connected drug delivery devices represent one of the fastest-growing segments of combination product development. These products combine biologics or pharmaceuticals with electronic components, sensors, wireless communication technologies, and software applications.

Examples of connected combination products include smart autoinjectors, wearable infusion pumps, Bluetooth-enabled inhalers, digital adherence tracking systems, and remote monitoring platforms. These technologies can improve patient adherence, enhance engagement, facilitate remote monitoring, support collection of real-world performance data, and enable personalized treatment strategies. However, they also introduce new regulatory challenges related to software validation, cybersecurity, interoperability, and data governance [41,42].

FDA, EMA, IMDRF, and other regulatory organizations increasingly require manufacturers to demonstrate that software components function reliably and do not introduce unacceptable risks to patients [18,41].

Software as a Medical Device (SaMD) Considerations:

Many modern combination products incorporate software components that may independently qualify as Software as a Medical Device (SaMD). IMDRF defines SaMD as software intended for medical purposes that performs these functions without being part of a hardware medical device [41].

Software increasingly serves as an important component of biologic–medical device combination products, supporting functions such as dose calculation, treatment adherence monitoring, patient management, and clinical decision support. Examples include dose calculation algorithms, treatment adherence applications, patient monitoring platforms, clinical decision-support tools, and software-enabled dosing support systems. Although these technologies offer opportunities to improve treatment outcomes and patient engagement, they also introduce additional regulatory considerations. Manufacturers must assess whether software functions influence treatment decisions, control device operation, modify dosing recommendations, or affect patient monitoring activities, as these functions may significantly influence the safety and effectiveness of the overall product. Consequently, software components should be evaluated using appropriate risk management, usability engineering, cybersecurity, and lifecycle management principles to ensure reliable performance throughout the product lifecycle. Depending on functionality, regulators may require additional software validation, cybersecurity documentation, usability testing, and post-market monitoring activities [41,42].

Advanced Therapy Medicinal Products (ATMPs):

Advanced therapy medicinal products (ATMPs), including gene therapies, cell therapies, and tissue-engineered products, represent an increasingly important area of biologic–medical device combination product development [4,5,43].

These products often require specialized delivery systems because therapeutic success depends on precise administration techniques.

Advanced Therapy Medicinal Products (ATMPs) frequently rely on specialized delivery technologies to ensure safe and effective administration. Examples include gene therapy injection systems, cell therapy infusion devices, tissue-engineered scaffold delivery platforms, and customized implantation technologies designed to meet product-specific clinical requirements. Unlike conventional biologics, ATMPs often require highly specialized handling procedures, customized administration protocols, cryogenic storage systems, and complex supply chain controls to maintain product identity, potency, viability, and sterility throughout distribution and clinical use. As a result, manufacturers must carefully coordinate biologic development, device engineering, manufacturing operations, and clinical administration strategies to ensure that both the therapeutic product and associated delivery system perform reliably as an integrated treatment platform. These considerations add significant complexity to product development, regulatory review, and lifecycle management activities for advanced biologic–medical device combination products [4,5,43].

As a result, device performance may become increasingly important to therapeutic success,

creating additional regulatory complexity regarding classification, quality systems, and clinical evaluation [41].

Regulatory Challenges for Digital and Advanced Therapy Products:

Several common regulatory challenges emerge across digital health and advanced therapy combination products.

Product Classification

The integration of software, biologics, and devices may complicate determination of the Primary Mode of Action (PMOA) and lead regulatory authority [11,16].

Cybersecurity

Connected biologic–medical device combination products are increasingly exposed to cybersecurity risks that may affect the safety, performance, and reliability of the overall system. Potential cybersecurity threats can compromise patient safety, data integrity, device functionality, and, in some cases, clinical decision-making processes that depend on accurate and timely information. As healthcare systems become more interconnected and reliant on digital technologies, manufacturers are expected to implement comprehensive cybersecurity risk management programs that address vulnerability assessment, threat monitoring, software maintenance, incident response, and security updates throughout the product lifecycle. Regulatory authorities increasingly recognize cybersecurity as an essential component of product safety and quality and expect manufacturers to incorporate cybersecurity considerations into product design, risk management, post-market surveillance, and lifecycle management activities [41,42].

Data Privacy

Collection of patient-generated health data introduces privacy and data protection considerations that may be subject to jurisdiction-specific regulations.

Lifecycle Management

Frequent software updates and algorithm modifications require robust change management systems capable of maintaining regulatory compliance while supporting innovation [35,41].

Future Regulatory Trends:

Future developments are expected to focus on greater integration of connected devices, remote monitoring technologies, real-world data collection, software-enabled healthcare solutions, and digital health platforms that support patient-centered care and lifecycle management [41,42].

Organizations that proactively integrate these considerations into development strategies will likely achieve greater regulatory success and competitive advantage.

In summary, digital health technologies and advanced therapy medicinal products are transforming the combination product landscape. While these innovations offer substantial opportunities to improve patient outcomes, they also introduce new regulatory challenges involving software validation, cybersecurity, digital health technologies, data governance, and complex delivery systems. Regulatory agencies worldwide continue to adapt existing frameworks to support innovation while ensuring patient safety and product effectiveness [41–43].

Table 6: Emerging Regulatory Challenges for Digital Health and Advanced Therapy Combination Products

Emerging Technology	Regulatory Challenge	Key Regulatory Guidance
Connected Autoinjectors	Cybersecurity	FDA Cybersecurity Guidance, IMDRF
Wearable Injectors	Software validation	IEC 62304, MDR
Gene Therapy Delivery Systems	Device-biologic interaction	FDA CBER Guidance
Digital Therapeutics	Software lifecycle management	IMDRF SaMD Guidance

Reference: [41-43]

Discussion

Biologic–medical device combination products occupy a unique position at the intersection of pharmaceutical, biologic, medical device, and increasingly digital health regulation. As demonstrated throughout this review, successful development and commercialization require a multidisciplinary approach that integrates scientific, engineering, clinical, quality, and regulatory expertise [1,3].

One of the most significant observations across global regulatory frameworks is the increasing convergence toward risk-based and lifecycle-oriented regulatory approaches. Although FDA, EMA, NMPA, and Health Canada continue to maintain jurisdiction-specific requirements, many fundamental regulatory principles have become increasingly aligned through the influence of ICH, ISO, IEC, and IMDRF standards [32–42].

The FDA's PMOA-based classification model remains one of the most mature approaches for assigning regulatory responsibility to combination products [11,16]. In contrast, the European Union's implementation of MDR Article 117 has strengthened device oversight within medicinal product applications and increased expectations regarding device conformity documentation [21–23]. While these differences create challenges for global development programs, they also encourage sponsors to adopt integrated development strategies that address both biologic and device considerations from the earliest stages of development.

The increasing use of biologics for chronic disease management has accelerated demand for patient-centric delivery systems such as autoinjectors, wearable injectors, and connected devices. Consequently, human factors engineering has evolved from a supplementary design consideration to a central component of regulatory decision-making [18,19,40]. Regulatory authorities increasingly recognize that product safety depends not only on device performance but also on the ability of intended users to interact with products correctly under real-world conditions.

Similarly, Quality by Design (QbD), risk management, and lifecycle quality systems have become essential elements of modern combination product regulation. Regulatory agencies increasingly expect sponsors to demonstrate deep understanding of product attributes, manufacturing processes, and constituent interactions rather than relying solely on end-product testing [32–37].

Perhaps the most significant future challenge involves the emergence of digital health technologies, connected medical devices, and advanced therapies. These innovations blur traditional regulatory boundaries and require new approaches to classification, validation, cybersecurity, and post-market oversight [41–43]. Regulatory frameworks developed for conventional products may require substantial adaptation to effectively oversee continuously learning algorithms, connected

healthcare ecosystems, and personalized therapeutic platforms.

Ultimately, organizations that adopt globally harmonized, science-based, and risk-based development strategies are likely to achieve greater efficiency in regulatory interactions and commercialization activities. Early regulatory engagement, robust quality systems, comprehensive risk management, and proactive lifecycle planning remain the most effective tools for navigating the increasingly complex combination product environment.

Conclusion

Biologic–medical device combination products have become an essential component of modern healthcare and represent one of the most dynamic areas of therapeutic innovation. By integrating biologics with advanced delivery technologies, these products offer significant benefits including improved treatment adherence, enhanced patient convenience, optimized dosing accuracy, and expanded access to home-based therapies [1,4,43].

Despite these advantages, combination products present substantial regulatory challenges because they must satisfy requirements applicable to multiple regulated constituents simultaneously. Differences among FDA, EMA, NMPA, and Health Canada frameworks create additional complexity, particularly with respect to classification, quality systems, clinical evidence requirements, and lifecycle management [11–31].

Successful global approval of biologic–medical device combination products depends on the implementation of several interconnected regulatory and development principles. These include early and proactive engagement with regulatory authorities, accurate product classification, integration of Quality by Design (QbD) principles, and the application of robust risk management practices throughout the product lifecycle. Equally important are comprehensive human factors engineering programs, effective Chemistry, Manufacturing, and Controls (CMC) and compatibility strategies, harmonized pharmaceutical and device quality systems, and strong post-market surveillance programs. Collectively, these elements support regulatory compliance, facilitate efficient global development, and help ensure the continued safety, efficacy, quality, and performance of combination products throughout commercialization and lifecycle management [11–42].

International harmonization efforts led by ICH, IMDRF, ISO, and other organizations continue to reduce regulatory divergence and support more efficient global development programs [32–42]. Nevertheless, sponsors must remain attentive to jurisdiction-specific requirements and evolving regulatory expectations.

Looking forward, digital health technologies, connected medical devices, digital health technologies, and advanced therapy medicinal products are expected to further transform the combination product landscape. These innovations will create new opportunities for personalized medicine and improved patient outcomes while simultaneously introducing novel regulatory challenges [41–43].

As the field continues to evolve, organizations that embrace integrated, science-based, and lifecycle-oriented regulatory strategies will be best positioned to achieve successful approvals, maintain regulatory compliance, and deliver innovative therapies to patients worldwide.

Abbreviations

Abbreviation	Definition
ATMP	Advanced Therapy Medicinal Product
CAPA	Corrective and Preventive Action
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CCI	Container Closure Integrity
CMC	Chemistry, Manufacturing, and Controls
CQA	Critical Quality Attribute
dFMEA	Design Failure Mode and Effects Analysis
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
FMEA	Failure Mode and Effects Analysis
GMP	Good Manufacturing Practice
GSPR	General Safety and Performance Requirement
HACCP	Hazard Analysis and Critical Control Point
HFE	Human Factors Engineering
ICH	International Council for Harmonisation
IEC	International Electrotechnical Commission
IFU	Instructions for Use
IMDRF	International Medical Device Regulators Forum
ISO	International Organization for Standardization
MDR	Medical Device Regulation
NBOp	Notified Body Opinion
NMPA	National Medical Products Administration
OCP	Office of Combination Products
pFMEA	Process Failure Mode and Effects Analysis
PMOA	Primary Mode of Action
PMS	Post-Market Surveillance
PSUR	Periodic Safety Update Report
QbD	Quality by Design
QMS	Quality Management System
QMSR	Quality Management System Regulation
RFD	Request for Designation
RWE	Real-World Evidence
SaMD	Software as a Medical Device
URRA	Use-Related Risk Analysis

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