Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
NLM (National Library of Medicine): ID: (101671502)
Index Copernicus Value 2022: 83.058
Volume 13, Issue 4; 2024, 35-46

ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

Review Article

Regulatory and CMC Strategies for Gene and Cell Therapies: Global Perspectives

Krunal Kothari[1], Smit Nayak[2], Saumil Shah[3], Drasti Patel[4], Nishant Madhukar[5], Pooja Dave[6]

[1]Manager, Regulatory Affairs – CMC, Vertex Pharmaceuticals, Boston- MA

[2] Senior Specialist, Quality Assurance – Moderna Therapeutics, Boston- MA

[3]Principal Associate Scientist, bluebird bio, Charlestown- MA

[4]Research Scholar, Government Pharmacy College, Gandhinagar, Gujarat- 382028

[5]Regulatory Affairs Specialist, Baxter, Milwaukee WI

[6]Assistant Professor, Department of Pharmaceutics, Parul Institute of Technology & Research, Parul University Vadodara, Gujarat, India

Article Info: Received: 11-07-2024 / Revised: 27-07-2024 / Accepted: 18-08-2024
Address for correspondence: Krunal Kothari
DOI: https://doi.org/10.32553/jbpr.v13i4.1488
Conflict of interest statement: No conflict of interest

Abstract:

Gene and cell therapies represent a new frontier in modern medicine, offering curative potential for rare, genetic, and otherwise intractable diseases. Unlike conventional biologics or small molecules, these advanced modalities present unique Chemistry, Manufacturing, and Controls (CMC) challenges due to their inherent complexity, patient-specific production workflows, and sensitive functional attributes. Robust CMC strategies are essential to ensure product quality, safety, and efficacy, while also meeting evolving global regulatory expectations. This review provides a comparative analysis of regulatory perspectives from the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency (PMDA, Japan), and harmonized International Council for Harmonisation (ICH) guidelines. Key themes include autologous versus allogeneic manufacturing paradigms, process sensitivity, supply chain logistics, and scalability limitations. Analytical strategies such as potency assay selection, viral vector characterization, and stability assessment are discussed alongside lifecycle management approaches under ICH Q12 and Q14. Case studies of approved therapies—including CAR-T products (Kymriah, Yescarta), AAV-based gene therapy (Zolgensma), and mRNA vaccines—illustrate practical lessons in regulatory engagement, comparability, and accelerated development. Finally, emerging trends such as digital twins, artificial intelligence–enabled analytics, real-time release testing (RTRT), and sustainability considerations are highlighted as future enablers of more efficient and globally harmonized CMC frameworks. By consolidating current regulatory guidance with practical development insights, this review serves as a comprehensive reference for researchers, regulators, and industry stakeholders advancing gene and cell therapies from bench to bedside.

Keywords: Gene therapy; Cell therapy; CMC; Regulatory guidelines; Potency assays; Viral vectors; Advanced Therapy Medicinal Products (ATMPs); ICH harmonization; Real-time release testing; Digital twins

Introduction

Gene and cell therapies have rapidly advanced from experimental concepts to transformative clinical modalities, offering curative potential for rare genetic disorders, oncology indications, and other refractory diseases [1–3]. These products, collectively categorized as Advanced Therapy Medicinal Products (ATMPs) in Europe, differ fundamentally from conventional biologics and small molecules due to their living or genetically engineered components, individualized manufacturing requirements, and heightened sensitivity to environmental and process conditions [4,5]. The complexity of these therapies translates into significant Chemistry, Manufacturing, and Controls (CMC) challenges, where product quality is directly influenced by upstream and downstream manufacturing decisions, analytical characterization strategies, and supply chain logistics [6,7]. Regulatory agencies—including the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency (PMDA, Japan), and the International Council for Harmonisation (ICH)—have established detailed frameworks to guide CMC development, comparability, and lifecycle management [8–11]. Despite these efforts, variability in regional requirements and the novelty of emerging platforms continue to complicate global development [12,13]. This review aims to provide a comprehensive synthesis of regulatory guidance and practical CMC strategies for gene and cell therapies, highlighting key considerations in manufacturing, analytical testing, and lifecycle management [14]. Case studies of approved therapies and emerging technological innovations are used to illustrate best practices, challenges, and future directions toward regulatory convergence and accelerated patient access [15].

Methodology

A structured and integrative literature review was conducted to evaluate global regulatory frameworks and Chemistry, Manufacturing, and Controls (CMC) strategies for gene and cell therapies, with a focus on manufacturing complexity, analytical characterization, and lifecycle management of advanced therapy medicinal products (ATMPs).

Literature Sources and Data Collection

A comprehensive search of peer-reviewed scientific literature was performed using electronic databases including PubMed, Scopus, and Google Scholar to identify relevant publications on gene therapy, cell therapy, and associated CMC strategies.

In addition, primary regulatory documents and guidelines were obtained from official sources, including:

- U.S. Food and Drug Administration (FDA) guidance documents on gene and cell therapies
- European Medicines Agency (EMA) guidelines related to Advanced Therapy Medicinal Products (ATMPs)
- Pharmaceuticals and Medical Devices Agency (PMDA, Japan) regulatory frameworks
- International Council for Harmonisation (ICH) guidelines, including Q5A–E, Q6B, Q12, and Q14

Search Strategy

The literature search was conducted using predefined keywords and Boolean operators (AND, OR) to ensure comprehensive coverage. Key search terms included:

- “gene therapy” AND “CMC”
- “cell therapy manufacturing” AND “regulatory guidelines”
- “CAR-T manufacturing” OR “autologous vs allogeneic therapies”
- “viral vector characterization” AND “AAV”
- “potency assays” AND “cell therapy”

Search queries were iteratively refined to capture both foundational knowledge and emerging trends in advanced therapeutics.

Inclusion Criteria

Publications and documents were included based on the following criteria:

- Published between 2015 and2023, with inclusion of foundational regulatory guidelines where necessary
- Peer-reviewed journal articles, regulatory guidance documents, and authoritative industry reports
- Studies focusing on gene therapy, cell therapy, CMC strategies, manufacturing processes, or regulatory frameworks
- Literature providing practical insights into analytical characterization, potency assessment, comparability, and lifecycle management

Exclusion Criteria

The following sources were excluded:

- Non-English publications
- Studies not directly relevant to advanced therapeutics or CMC frameworks
- Publications lacking sufficient scientific rigor or regulatory applicability

Data Extraction and Thematic Analysis

Relevant information from selected sources was systematically extracted and categorized into key thematic domains aligned with the objectives of this review:

- Manufacturing strategies and complexity (autologous vs allogeneic systems, workflow integration, scalability challenges)
- Analytical characterization and potency assessment (functional assays, viral vector analysis, stability studies)
- Regulatory frameworks (FDA, EMA, PMDA, ICH harmonization)
- Comparability and lifecycle management (ICH Q12, Q14, risk-based approaches)
- Supply chain and logistics considerations (cold chain, chain-of-identity, distribution challenges)

A comparative and integrative analysis approach was applied to identify common regulatory expectations, regional differences, and evolving trends in the development of gene and cell therapies.

Critical Appraisal and Synthesis

The selected literature was critically evaluated based on scientific quality, regulatory relevance, and applicability to real-world development and commercialization of advanced therapies. Emphasis was placed on:

- Alignment with global regulatory frameworks
- Strength and reproducibility of analytical and manufacturing approaches
- Relevance to scalability, patient-specific production, and lifecycle flexibility

Findings were synthesized to provide a regulatory-science-driven perspective, integrating both established practices and emerging innovations in gene and cell therapy CMC strategies.

Limitations of the Review

This review is limited by reliance on publicly available literature and regulatory documents. Proprietary industry data and confidential regulatory submissions were not included. Additionally, rapid advancements in gene and cell therapy technologies and evolving regulatory expectations may extend beyond the scope of the reviewed literature.

Manufacturing Complexity in Gene and Cell Therapies

The manufacturing of gene and cell therapies is inherently more complex than that of conventional biologics, largely due to the living nature of the product, patient-specific workflows, and the heightened sensitivity of cells and vectors to environmental conditions. Each step of the manufacturing process—from cell sourcing and genetic modification to formulation, cryopreservation, and delivery—directly influences product quality, safety, and efficacy. Robust control strategies, therefore, are critical to ensuring consistency, regulatory compliance, and scalability across diverse therapy platforms.

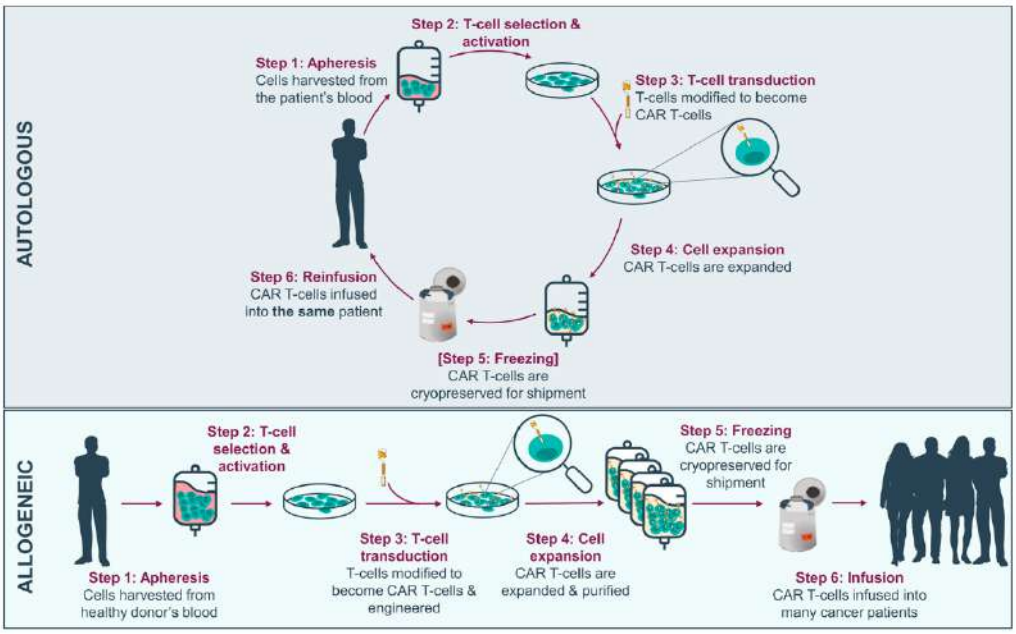

Figure 1 The CAR-T process schematic diagram

Autologous vs. Allogeneic Manufacturing

One of the most significant distinctions in advanced therapy manufacturing lies in the choice between autologous and allogeneic approaches. Autologous products, such as CAR-T therapies (e.g., Kymriah, Yescarta), are derived from a patient's own cells and require individualized, small-scale manufacturing for each patient. This model introduces logistical complexity and demands strict chain-of-identity and chain-of-custody systems to avoid cross-contamination or product mix-ups [16]. In contrast, allogeneic products are manufactured from donor-derived cells, allowing for larger batch production and broader scalability. However, these therapies require extensive donor screening, viral safety testing, and robust strategies to ensure batch-to-batch consistency. Recent advances in allogeneic CAR-T platforms and induced pluripotent stem cell (iPSC)-derived therapies demonstrate the promise of scalable, "off-the-shelf" models, though regulatory scrutiny remains high due to risks of immunogenicity and variability [17].

Process Sensitivity and Control

Gene and cell therapies are highly sensitive to even minor variations in culture conditions, transduction efficiency, and handling procedures. Subtle shifts in temperature, dissolved oxygen, or media composition can profoundly affect cell viability, vector potency, and overall product functionality. For example, studies in CAR-T production have shown that differences in T-cell activation conditions can alter expansion kinetics and final product potency [18,19]. To mitigate operator variability and contamination risks, developers are increasingly adopting closed-system bioreactors and automated manufacturing platforms. These approaches enable more reproducible processes, reduce human error, and enhance regulatory confidence in scalability.

Multi-Step, Complex Workflows

Manufacturing workflows for advanced therapies often involve numerous interdependent stages, including cell isolation, genetic modification (via viral transduction or CRISPR/Cas editing), cell expansion, harvesting, formulation, and cryopreservation. Each stage introduces potential variability and requires robust in-process controls. Integration of real-time monitoring tools and risk-based control strategies is therefore essential to ensure that critical quality attributes (CQAs) are

maintained throughout the process. For viral vector–based products, production platforms such as adeno-associated virus (AAV) require careful control of genome integrity, empty-to-full capsid ratios, and vector potency, which can vary significantly with small process modifications [20].

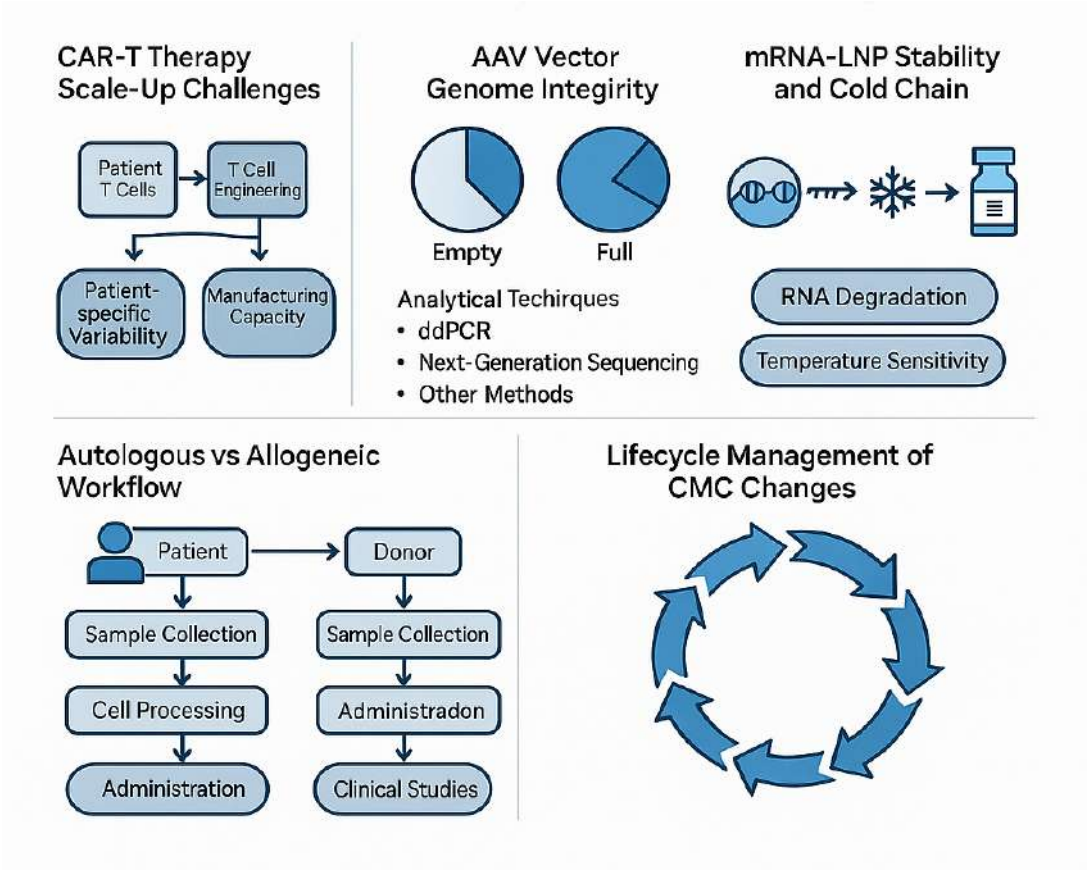

Figure 2: Research developments in cell and gene therapy manufacturing

Supply Chain and Logistics

The supply chain for advanced therapies is particularly challenging, especially for autologous products that demand patient-specific manufacturing. Coordination between clinical sites, collection centers, and centralized manufacturing facilities requires meticulous planning to meet patient treatment timelines. Cryopreservation and cold-chain logistics are critical for preserving cell viability and viral vector stability, with products often requiring ultra-low temperature storage (≤ –150°C) during transport. Failures in cold-chain management can compromise potency and lead to product rejection, emphasizing the need for robust logistics networks and contingency planning [21].

Scalability Challenges

Scaling advanced therapies is not linear. Autologous therapies face inherent limitations in throughput and cost efficiency, while allogeneic products must address variability introduced by larger-scale production. Risk-based comparability studies are essential to ensure that process modifications during scale-up do not alter critical quality attributes or compromise clinical efficacy. Platform-based approaches, such as modular bioreactor systems or standardized viral vector platforms, are emerging as solutions to facilitate scalability while maintaining product quality [22,23].

Regulatory Implications

The complexity of manufacturing translates into heightened regulatory scrutiny. Agencies such as the FDA and EMA expect detailed documentation of manufacturing steps, validation of process controls, and robust comparability data to support changes. Lifecycle management principles outlined in ICH Q12 are increasingly applied to advanced therapy products, allowing sponsors to predefine change management protocols (PACMPs) and ensure post-approval flexibility without compromising patient safety [24].

Regulatory Landscape: Global Perspectives for Cell and Gene Therapies

The regulatory oversight of gene and cell therapies varies across regions but converges on a common goal of ensuring product quality, safety, and efficacy through robust Chemistry, Manufacturing, and Controls (CMC) frameworks. In the United States, the Food and Drug Administration (FDA), through its Center for Biologics Evaluation and Research (CBER), regulates these products under the Investigational New Drug (IND) and Biologics License Application (BLA) pathways. FDA guidance emphasizes comprehensive product characterization, potency assessment, and comparability exercises, with distinct expectations for autologous and allogeneic therapies. For autologous products, detailed process validation is required to account for patient-specific variability, whereas allogeneic therapies must demonstrate consistency across larger batch productions. In addition, the FDA mandates rigorous viral vector safety testing, including replication-competent virus assays, and outlines expectations for managing post-approval manufacturing changes [25, 26].

In Europe, the European Medicines Agency (EMA) classifies these products as Advanced Therapy Medicinal Products (ATMPs) and provides a centralized framework for Marketing Authorization Applications (MAAs). The EMA emphasizes a risk-based approach to manufacturing and comparability, requiring developers to demonstrate consistent product quality, stability, and safety across batches. Specific attention is given to viral vector integrity and cell viability, both of which are critical for ensuring reproducibility in autologous and allogeneic product platforms [27].

In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has established a regulatory pathway that allows for conditional or time-limited approvals, particularly fortherapies addressing high unmet medical needs. CMC requirements in this framework include detailed product characterization, potency and identity assessments, comparability studies, and comprehensive stability data. The PMDA also strongly encourages early consultation with sponsors to align development strategies and streamline both clinical progression and post-marketing commitments [28].

Beyond regional authorities, the International Council for Harmonisation (ICH) plays a critical role in promoting global convergence. ICH guidelines provide harmonized expectations that reduce redundancy and facilitate multinational development. Among the most relevant are Q5A–E, which address viral safety, comparability, and the quality of biotechnological products; Q6B, which defines specification and acceptance criteria for biologics; and Q12, which establishes principles for lifecycle management and structured post-approval change strategies [29]. Collectively, these guidelines serve as a unifying framework that supports consistent regulatory standards worldwide, enabling developers to design robust CMC programs applicable across multiple jurisdictions [30].

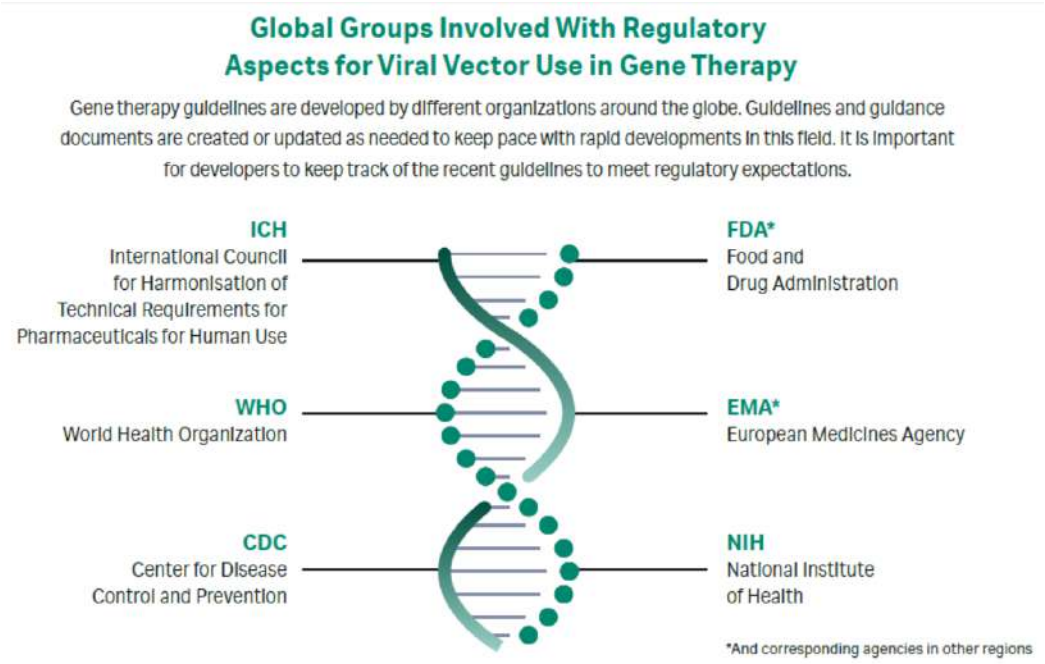

Figure 3 Global organizations involved in regulatory oversight of gene therapy and viral vectors

CMC Strategies for Advanced Therapeutics

The harmonization facilitated by ICH enables developers to design robust CMC programs that meet multiple regulatory expectations simultaneously, reducing redundancy and accelerating patient access.

The development of gene and cell therapies demands a highly integrated CMC strategy due to the inherent complexity, heterogeneity, and patient-specific nature of these products. **Manufacturing considerations** differ markedly between autologous and allogeneic therapies; autologous products require individualized processing, strict chain-of-identity control, and robust closed-system bioreactors, whereas allogeneic products emphasize large-scale reproducibility and batch consistency. For viral vector-based gene therapies, production must ensure high vector potency, accurate genome copy numbers, and minimal contamination with replication-competent particles [29].

Analytical characterization is a cornerstone of CMC strategy. It encompasses identity, purity, potency, and safety testing using orthogonal and high-resolution techniques. Potency assays are particularly critical, often employing cell-based functional readouts aligned with the mechanism of action, complemented by binding or molecular assays. Risk-based comparability strategies are employed during process scale-up, site transfers, or post-approval changes, typically following a tiered approach: detailed analytical assessment, orthogonal confirmation, and, if necessary, bridging clinical data [30].

Stability and storage considerations further complicate CMC development. Cryopreservation for cellular therapies and cold-chain management for viral vectors are essential to maintain viability, potency, and overall product integrity. Forced-degradation and stability-indicating studies inform shelf-life, transportation conditions, and real-time release strategies.

Overall, a successful CMC strategy integrates **risk-based design, robust analytical characterization, process control, and regulatory alignment**, ensuring that advanced therapeutics meet safety and efficacy standards while supporting accelerated development and global market access [31,32].

Risk-Based and Lifecycle Management

Risk-based and lifecycle management approaches are central to CMC development for gene and cell therapies. The identification of **critical quality attributes (CQAs)** and **critical process parameters (CPPs)** allows developers to prioritize analytical focus on parameters that directly impact safety, potency, and efficacy. Regulatory guidance, including **ICH Q12 and Q14**, promotes a structured framework for post-approval changes, comparability assessments, and ongoing verification. Advanced analytics, real-time monitoring, and **process analytical technologies (PAT)** facilitate proactive quality control, enabling adaptive responses to manufacturing variability and ensuring consistent product performance across batches [33,34].

Tables

Table 1. Summary of Global Regulatory Guidance for Gene and Cell Therapies

Regulatory Body	Classification	Key CMC Requirements	Potency & Analytical Expectations	Post-Approval Change Approach
FDA (USA) [8]	Gene therapy, Cell therapy	IND/BLA submission, GMP compliance	Functional potency assays, orthogonal methods	Risk-based comparability, bridging clinical data
EMA (EU) [9]	Advanced Therapy Medicinal Products (ATMPs)	MAA submission, batch consistency	Potency assays, viral vector characterization	Risk-based comparability, analytical bridging
PMDA (Japan) [10]	Regenerative & cellular therapies	Conditional approval, GMP	Potency, identity, safety assays	Time-limited post-marketing studies, comparability
ICH [11]	Harmonization	Q5A–E, Q6B, Q12 guidelines	CQAs, CPPs, analytical validation	Lifecycle management, post-approval changes

Case Studies and Lessons Learned

Several approved advanced therapeutics illustrate the importance of integrated CMC strategies. **CAR-T therapies** such as Kymriah and Yescarta highlight the complexities of autologous manufacturing, including patient-specific workflow management, potency assay selection, and comparability across small batch sizes. **AAV-based gene therapies**, exemplified by Zolgensma, underscore challenges in viral vector characterization, empty/full capsid ratio assessment, and genome integrity analysis. Additionally, **mRNA vaccines** demonstrate accelerated development facilitated by robust analytical characterization and regulatory flexibility, providing lessons in stability management, high-throughput potency assays, and global regulatory coordination. These case studies reinforce that early integration of risk-based CMC strategies and regulatory engagement is critical for timely approval and patient access.

Table 2: Advanced Therapy Approval

Year	Therapy	Company
2017	Kymriah (tisagenlecleucel) – First FDA-approved CAR-T therapy [35]	Novartis
	Yescarta (axicabtagene ciloleucel) – Second CAR-T approved by FDA [36]	Kite/Gilead
2018	Luxturna (voretigene neparvovec) – First FDA-approved in vivo gene therapy (AAV-based) [37]	Spark Therapeutics
2019	Zolgensma (onasemnogene abeparvovec-xioi) – AAV-based gene therapy for spinal muscular atrophy [38]	Novartis
2020	Tecartus (brexucabtagene autoleucel) – CAR-T therapy for mantle cell lymphoma [39]	Kite/Gilead
	First mRNA vaccines – Emergency approvals for COVID-19; milestone for RNA-based therapeutics [40]	Pfizer/BioNTech, Moderna
2021	Abecma (idecabtagene vicleucel) – First FDA-approved CAR-T for multiple myeloma [41]	Bristol Myers Squibb/bluebird bio
	Breyanzi (lisocabtagene maraleucel) – CAR-T for large B-cell lymphoma [42]	Bristol Myers Squibb/Juno
2022	Carvykti (ciltacabtagene autoleucel) – CAR-T for multiple myeloma [43]	Janssen/Legend Biotech
	EMA approval of additional CAR-Ts and expansion of mRNA vaccine authorizations	–
2023	Hemgenix (etranacogene dezaparvovec) – First FDA-approved gene therapy for hemophilia B [44]	CSL Behring/UniQure
	Roctavian (valoctocogene roxaparvovec) – Gene therapy for hemophilia [45]	BioMarin

Future Directions

The regulatory future of gene and cell therapies is moving toward greater global convergence, with FDA, EMA, PMDA, and ICH working to harmonize requirements for potency assays, viral safety, and lifecycle management. This alignment will reduce duplicative studies and streamline multinational submissions, enabling faster patient access. At the same time, regulators are introducing adaptive pathways such as conditional approvals, rolling reviews, and reliance on real-world evidence, requiring sponsors to prepare robust and flexible CMC packages. Emerging tools such as multi-attribute methods (MAM), single-cell analytics, and real-time release testing (RTRT) will further strengthen product characterization and release strategies, while digital twins and AI-enabled process models promise predictive control of manufacturing variability. Clear regulatory frameworks for data integrity, validation, and model governance will be essential for these technologies to be fully integrated into compliant CMC programs [26,27,45].

Looking ahead, sustainability and supply chain resilience are expected to become integral to CMC strategy. As advanced therapeutics increasingly rely on single-use systems, specialized raw materials, and complex logistics, regulators are placing greater emphasis on supply chain qualification, extractables/leachables testing, and environmental considerations. Post-approval change management protocols (PACMPs), established conditions (ECs), and harmonized lifecycle documentation will provide the agility needed to address raw material shortages, facility expansions, and evolving global demands while maintaining compliance. Collectively, these trends highlight a future in which regulatory harmonization, digital innovation, and sustainability converge to create more resilient, efficient, and patient-focused CMC strategies for gene and cell therapies.

Digitalization and artificial intelligence (AI) are poised to transform the regulatory and CMC landscape for gene and cell therapies by enabling data-rich, predictive, and adaptive quality management systems. The integration of digital twins, process simulation models, and AI-driven analytics allows real-time monitoring of critical process parameters (CPPs) and predictive assessment of critical quality attributes (CQAs). These technologies can anticipate deviations, optimize manufacturing conditions, and support continuous improvement, thereby reducing process variability and accelerating product release. For autologous therapies, where time-sensitive patient delivery is essential, AI-enabled scheduling and logistics platforms enhance coordination across collection centers, manufacturing sites, and clinical facilities, minimizing risks associated with chain-of-identity and chain-of-custody management [46].

From a regulatory perspective, digital and AI-driven systems introduce both opportunities and challenges. Regulators are increasingly open to the use of digital models and advanced analytics as supportive or primary tools for CMC submissions, provided that robust governance frameworks are in place. Key requirements include validation of predictive algorithms, lifecycle management of machine learning models, and compliance with data integrity standards under GxP frameworks (e.g., 21 CFR Part 11, EU Annex 11). Digital audit trails, transparency of model training datasets, and defined recalibration triggers are expected to form the foundation of regulatory acceptance. As these frameworks mature, digital and AI-driven approaches will not only streamline regulatory submissions but also redefine post-approval lifecycle management, enabling adaptive control strategies, real-time release testing (RTRT), and predictive pharmacovigilance. Ultimately, the convergence of digitalization, AI, and regulatory science will drive more efficient, agile, and globally harmonized CMC strategies for advanced therapies [47].

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