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Strategic regulatory intelligence for cell and gene therapies

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This article is the first of two on strategic regulatory intelligence for cell and gene therapies (CGTs). It will examine how gaps between product approvals and patient access remain despite significant evolutions in the CGT landscape. Longer approval timelines and increasing product withdrawals underscore the need for robust regulatory intelligence frameworks that integrate geopolitical considerations, real-world evidence (RWE), artificial intelligence/machine learning (AI/ML) tools, and multistakeholder collaboration to build an effective regulatory strategy. The article examines the role of regulatory intelligence in advancing effective regulatory strategy across the full CGT and advanced therapy medicinal product (ATMP) lifecycles, including innovative clinical trial designs, chemistry, manufacturing, and controls (CMC) optimizations, and postauthorization surveillance across major global jurisdictions. The second article (p. 65) explores global CGT pricing and reimbursement models.

Keywords – artificial intelligence/machine learning, CGT, CMC, regulatory intelligence, regulatory strategy

Introduction

Regulatory intelligence operations have traditionally focused on collecting, analyzing, and summarizing information to inform regulatory strategy for product development. Regulatory intelligence supports regulatory strategy by providing actionable insights to cross-functional clinical, quality, safety, and commercial stakeholders, enabling evidence-based decisions throughout the product lifecycle while ensuring alignment with the organizational business goals.

However, advances in AI/ML and digital health technologies, alongside rapidly shifting and evolving geopolitics, trade dynamics, innovative clinical trial designs, real-world evidence and real-world data (RWD), adaptive licensing pathways, and payer-reimbursement landscapes are reshaping regulatory intelligence. Current regulatory intelligence activities encompass horizon scanning and analysis of global regulatory trends, evolving policies, and monitoring signals and alerts for a proactive regulatory strategy development to ensure timely execution of product development, launch pathways, pharmacovigilance, and postmarket surveillance.

The CGT field has also undergone scientific innovation and regulatory evolution over the past decade. As of January 2026, the US Food and Drug Administration (FDA) has approved 48 biologics, while the European Medicines Agency (EMA) has authorized 31 ATMPs.[1,2] However, the pace of global technological innovations and product approvals remains discordant with patient access to these therapies. In recent years, China's National Medical Products Administration has emerged as a dominant

force in the CGT space, reflecting its focus on increased investment in research and development infrastructure, supporting domestically developed innovations, efficient clinical trial designs, and progressively reshaping regulatory policies to align with international guidelines to have a global competitive edge.[3]

These regional divergences in approval rates and patient access reflect fundamental differences in evidence expectations, reimbursement architectures, and global regulatory system operations. For CGT and ATMP developers, navigating this landscape requires robust regulatory intelligence frameworks not only for approval requirements but also for patient access paradigms that ultimately determine a product's commercial viability.

In the US, the FDA groups CGTs under biologics, whereas the EU's EMA designates them as ATMPs.[4,5] Globally, CGTs/ATMPs account for the majority of accelerated and conditional approvals intended to address unmet medical needs. CGTs/ATMPs targeting rare diseases qualify for orphan drug designation, which provides benefits such as application fee waivers or reductions, enhanced regulatory interactions, rolling reviews, accelerated approval pathways, grant funding, tax credits, and 7 to 10 years of market exclusivity.[6,7] Of the 48 biologics approved by the FDA, 42 (87.5%) target rare diseases and 6 (12.5%) address non-rare conditions. Similarly, of the 31 ATMPs approved by the EMA, 24 (77.4%) received orphan drug status. The FDA also offers breakthrough therapy designations and regenerative medicine advanced therapy designations, while the EMA and Japan offer priority medicines and Sakigake designations, respectively. These designations facilitate more frequent regulatory interactions, priority and rolling review, and may allow accelerated approvals based on surrogate endpoints demonstrating early clinical efficacy.[8,9]

Despite these incentives, the median total clinical development time for novel orphan-designated drugs is approximately 7.2 years. Moreover, the median regulatory review time is shorter in the US (244 days) than in the EU (353 days).[10] The FDA and EMA require larger randomized controlled trials (RCTs) with confirmatory evidence of superior clinical efficacy over standard of care (SoC) treatments for non-rare indications, while innovative clinical trials using surrogate efficacy endpoints may support accelerated or conditional approvals for serious rare conditions with unmet needs.[11] However, even for conditional approvals, the EMA requires mature, robust, and comprehensive data demonstrating ATMP product quality, safety, and efficacy due to their inherently complex CMC and clinical development. This article examines the current regulatory intelligence paradigm to support effective regulatory strategy across the CGT/ATMP lifecycle.

Strategic framework for CGT clinical development

Increasing healthcare costs, limited budgets, rapid innovation in technologies, and severe unmet medical needs have led to growing regulatory expectations for smarter clinical trial designs. Regulatory intelligence aids in the development of appropriate clinical development, sequencing, and reliance pathways by tracking guidance, pilot programs, and regulatory precedents. This proactive approach can reduce the risk of late-stage regulatory challenges and enhance the efficiency of evidence generation.

Building upon foundational programs, including the Support for Clinical Trials Advancing Rare Disease Therapeutics and Rare Disease Endpoint Advancement Pilot Program, the FDA released three draft guidelines in late 2025 focusing on CGT development for rare diseases.[12-15] These guidelines address innovative trial designs (e.g., single-arm, disease modeling, adaptive approaches, plausible mechanism frameworks), expedited pathways, and postapproval data collection frameworks to accelerate approvals in small patient populations.

In parallel, the pharmaceutical industry has seen a profound shift from being driven by safety and efficacy endpoints and physician-centric drug development, to being driven by patient-centric development models. The EMA, along with the regulatory authorities in Japan, Australia, and Canada, has also increasingly embraced patient participation initiatives in scientific advisory meetings, efficacy endpoint design and evaluation, and benefit-risk assessments, ultimately focusing on developing products with increased patient access.

Since the FDA launched its patient-focused drug development (PFDD) initiative, there has been an unprecedented emphasis on including patient insights in all stages of drug development. This has led to the publication of a series of four PFDD guidance documents from 2020 to 2024.[16-19] The guidelines outline frameworks

for trial design, including rationale and context-specific application of patient-centered approaches. Additionally, the FDA recently announced a policy update outlining an enhanced regulatory flexibility to support pragmatic CGT development addressing unmet needs in rare and ultra-rare diseases, reflecting a shift toward more adaptive, evidence-based regulatory pathways.[20]

Rare and ultra-rare disease clinical development

The successful launch of CGT/ATMP for rare and ultra-rare diseases requires innovative and efficient clinical trial strategies, given the extremely limited global patient population, ethical constraints on control-arm assignment, incomplete understanding of disease pathophysiology, disease heterogeneity, and manufacturing constraints.

Single-arm trials, N-of-1 designs, disease progression models (DPMs), and the plausible mechanism pathway offer distinct and innovative approaches to address structural trial barriers by generating valid evidence of treatment effect through benchmarking against external controls, within-patient crossover comparisons, and incorporating natural history and RWD. Each approach is described in detail in the sections below.

Single-arm trial framework

For chronic rare disorders, patients enrolled in natural history registries with baseline data on disease-specific parameters can serve as their own controls by comparing pre- and posttreatment outcomes using identical measures. This approach can reduce reliance on concurrent control groups and is particularly valuable in generating early phase I/II clinical safety and efficacy evidence for rare and ultra-rare diseases where RCTs are practically and ethically impossible. This approach also opens avenues for cost-effective accelerated/conditional approvals for breakthrough personalized precision therapies and paves the path for the development of platform technologies.[21,22] Additionally, natural history registries and RWD/RWE can identify external controls with matched, context-specific baseline and follow-up parameters for use as comparators in nonrandomized rare disease trials.

N-of-1 trial framework

N-of-1 trials are personalized, single-patient study designs with randomized treatment order, alternating between active treatment and comparator across multiple treatment periods. In the context of CGT and ATMP development for rare and ultra-rare diseases, where conducting clinical trials using conventionally powered cohorts is not feasible, this design offers a scientifically sound alternative to chronic diseases with treatment response heterogeneity and sufficiently well-characterized underlying biological mechanisms. Regulatory agencies, including the FDA and EMA, have increasingly acknowledged such designs as acceptable evidentiary frameworks for rare and ultra-rare conditions.

DPM framework

As a component of the FDA's broader model-informed drug development framework, DPMs use robust mathematical simulations to integrate biomarker, SoC treatments, patient heterogeneity, dropout rates, disease baseline characteristics, disease progression data from patient registries, electronic health records, and RWE to map disease trajectories. This supports clinical trial design optimization, including endpoint selection, patient subgroup stratification, statistical power optimization, and treatment outcome prediction.[23] DPMs based on natural history data help predict patient behavior (e.g., dropout risk), optimize trial duration, justify dosage selections, support patient stratification, and enable extrapolation to pediatric populations when direct trials are infeasible.

Integrating N-of-1 studies with DPMs enhances drug development by providing natural history, treatment response grade, and placebo or SoC response data to evaluate treatment effects in small patient pools without a control arm. DPMs also have the potential to enhance N-of-1 studies by using delayed-start or wait-listed crossover designs for chronic rare diseases where disease progression remains relatively stable, and the goal is to assess disease modification rather than an immediate, permanent cure. This allows patients to act as their own controls, maximizing statistical power and trial efficiency despite limited patient populations, with promising findings that can be combined via DPM-based meta-analysis to extrapolate population-level efficacy.

Plausible mechanism pathway

In 2026, the FDA's Center for Biologics Evaluation and Research released draft guidance describing a plausible mechanism pathway as an accelerated approval route for CGTs for rare and ultra-rare diseases. Under this pathway, accelerated approval may be granted if a CGT functionally corrects an established molecular or cellular anomaly underlying a rare disease, without requiring demonstration

of clinical benefit on a fully validated surrogate endpoint. The evidentiary standard rests on three elements: a well-characterized disease pathophysiology with a defined mechanistic target; functional correction of a specific target demonstrated through biomarker or cellular assay data; and a scientifically plausible link between mechanistic correction and expected clinical benefit.

This pathway is most applicable where disease is severe and rapidly progressive, with very small patient populations, where conventional endpoint-driven trials are not feasible, and mechanistic correction constitutes the most direct available evidence of therapeutic effect.[15] Sponsors pursuing this pathway are expected to generate confirmatory evidence of clinical benefit and safety through postapproval studies, structured long-term follow-ups (LTFU) programs, and patient registries within agreed timelines for full marketing approvals. **Table 1** (p. 55) shows some of the recent approvals using these innovative trial approaches.

Adaptive, Bayesian, and master protocol trials

A key challenge in rare disease trials is to derive robust and valid inferences from small, heterogeneous datasets, which conventional statistical approaches designed for large randomized studies do not address effectively. Approaches such as Bayesian methods, adaptive trial designs, and master protocols offer innovative approaches to trial design that are more efficient, flexible, and capable of producing evidence that meets regulatory standards despite limited patient populations.

Adaptive trials. Integration of model-informed drug development, DPM, and RWD strategies enables adaptive clinical trials in which predefined design elements may be prospectively modified based on pre-specified criteria using interim analysis of the current trial. This approach facilitates patient subtype enrichment, dosing optimization based on responses, sample size re-estimation, reduction of redundancy, and value-based decision making for trial continuation.[24,25]

Bayesian trials. Bayesian approaches incorporate adaptive design features but follow flexible, intuitive, continuously adjustable trial designs based on real-time data and probability data using prior knowledge from external controls, natural history registries, and RWE.[26] Adaptive and Bayesian designs allow modifications (e.g., sample size, randomization) during the study based on interim data, improving efficiency and enabling earlier go/no-go decision making.

Master protocol designs. Master protocol designs (including basket, umbrella, and platform trials) aim to evaluate multiple diseases, disease subtypes, or treatments under a single overarching clinical protocol.[27] Master protocols leverage prior knowledge from natural history studies, RWE, external controls, and patient registries while incorporating Bayesian and adaptive features to enhance operational efficiency, reduce costs, accelerate patient recruitment, enable more robust comparisons through shared control arms, and improve personalized treatment options.

Basket trials test one intervention across multiple diseases or subtypes sharing a common mutation or biomarker. *Umbrella trials* evaluate multiple therapies for one disease or subtype. *Platform trials* are long-term, adaptive trials that typically adopt Bayesian frameworks and common control arms, thereby reducing patient sample sizes and costs. These innovative trial design modalities are being currently used for dose optimization and interim efficacy analysis in ongoing clinical trials.[28-30]

Decentralized trials as part of the PFDD framework provide another paradigm to increase patient enrollment and retention while generating clinical data representative of geographically, ethnically, and socioeconomically diverse populations. These approaches leverage telemedicine follow-up visits, home phlebotomy and testing, local testing centers, AI-enabled digital health monitoring devices, online pharmacies, and mobile research units. Patient-reported preferences and outcomes, RWE/RWD, and natural history records provide invaluable insights for developing effective clinical protocols, including patient-preferred efficacy endpoints, which may improve the likelihood of regulatory approval in rare disease trials.[31,32]

Patient-reported outcomes collect patient health information to assess symptoms, quality of life, and overall well-being, helping gauge treatment effectiveness from the patient's perspective. Patient preference studies reveal patient values and quantify willingness to make trade-offs between benefits and risks, outcomes and convenience, and efficacy and side effects, and therefore play an important role in the effective clinical trial designs. Both PFDD and guidance on innovative trial designs advocate for broadening patient inclusion criteria by reducing overly restrictive eligibility requirements that hinder enrollment in limited patient populations. These policies also prioritize pediatric-focused clinical trial strategies in early development, reflecting the

Table 1. List of approved CGTs/ATMPs with innovative clinical trial designs

Product	Disease	Technology platform	Trial design features	Regulatory pathways
K-abe	CPS1D	In vivo base editing	– Natural history data – N-of-1 design for control group – Plausible mechanism pathway	– FDA emergency IND – Compassionate use
Waskyra	Severe WAS	Autologous HSC-based gene therapy	– Single-arm trial – Natural history data	– FDA accelerated approval – BT – Orphan drug – EMA conditional approval
BE-CAR7[a]	T-cell ALL	Base-edited allogeneic CAR-T	– Natural history data	– UK specials pathway
Zolgensma	Infantile-onset SMA Type 1	AAV9-based gene therapy	– Natural history data	– FDA accelerated approval – EMA conditional approval
Luxturna	LCA, RP	AAV2-based gene therapy	– Natural history data and natural history studies – Phase 3 delayed crossover RCT	– FDA accelerated approval – BT – Orphan drug – Rare pediatric disease designations – EMA conditional approval
Lenmeldy	Early onset MLD	Autologous HSC-based gene therapy	– Natural history data – Single-arm trial historical controls	– FDA accelerated approval – EMA conditional approval
Elevidys	DMD	AAV-based gene therapy	– External control group trials – Natural history data – DPM	– FDA accelerated approval
Kymriah	B-cell ALL (pediatric/young adult), DLBCL, FL	Autologous anti-CD19 CAR-T	– Natural history data	– FDA accelerated approval – EMA conditional approval
Yescarta	R/R LBCL, DLBCL, PMBCL, HGBL	Autologous anti-CD19 CAR-T	– Single-arm trials – Natural history data	– FDA accelerated approval – EMA conditional approval
Amtagvi	Unresectable or metastatic melanoma	Autologous TIL therapy	– Natural history data – Response rates – Single-arm trials	– FDA accelerated approval
Hemgenix	Hemophilia B	AAV5-based gene therapy	– Natural history data – single-arm trials	– FDA accelerated approval – EMA conditional approval

AAV, adeno-associated virus; **ALL,** acute lymphoblastic leukemia; **ATMP,** advanced therapy medicinal product; **BT,** breakthrough designation; **CAR-T,** chimeric antigen receptor T-cell therapy; **CGT,** cell and gene therapy; **CPS1D,** carbamoyl phosphate synthetase 1 deficiency; **DLBCL,** diffuse large B-cell lymphoma; **DMD,** Duchenne muscular dystrophy; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration; **FL,** follicular lymphoma; **HGBL,** high-grade B-cell lymphoma; HSC, hematopoietic stem cell; **IND,** investigational new drug application; **LCA,** Leber congenital amaurosis; **MLD,** metachromatic leukodystrophy; **PMBCL,** primary mediastinal B-cell lymphoma; **RCT,** randomized controlled trial; **RP,** retinitis pigmentosa; **R/R LBCL,** relapsed/refractory large B-cell lymphoma; **SMA,** spinal muscular atrophy; **TIL,** tumor-infiltrating lymphocyte; **WAS,** Wiskott-Aldrich syndrome.

[a]First-in-human but not true N-of-1 (therapy designed for broader CD7+ T-ALL population).

FDA's strategic shift toward personalized, flexible, evidence-supported approaches for rare disease products.

Regulatory intelligence related to innovative clinical trial designs – including adaptive, Bayesian, master protocol, single-arm, N-of-1 studies, decentralized designs, and plausible mechanism-based frameworks – can help sponsors select evidentiary strategies aligned with regulatory requirements, payer expectations, and reimbursement frameworks. As global regulatory authorities expand the use of model-informed drug development and consider mechanism-based and RWE, particularly in rare and ultra-rare diseases, up-to-date intelligence on precedents and regulatory guidance can support the design of fit-for-purpose pivotal programs.

For instance, single-arm trials that may be considered for pathways such as accelerated approval, integrated regulatory intelligence across clinical development, marketing authorization, and health technology assessment can help sponsors anticipate and address evidentiary gaps by planning for external or synthetic control arms, natural history data, or incorporation of platform trial elements, in line with evolving regulatory and payer expectations.

Non-rare disease development pathways

Given the complexity of CGT, traditional rigorous RCTs remain the recommended gold standard for non-rare disease indications. Dose selection and escalation studies are typically evaluated in Phase I trials (approximately 10-20 patients), followed by Phase II exploratory studies for efficacy assessment in expanded cohorts (approximately 50-100 patients).

For expedited programs such as breakthrough therapy designation and priority medicines designation, primary endpoints such as overall response rate from Phase II studies have served as evidence for conditional market approval.[33] However, Phase III confirmatory trials (typically 300-500 patients) are required to establish therapeutic benefit-risk profiles. Regulatory authorities increasingly require progression-free survival, event-free survival, and overall survival rate as evidence for therapeutic benefit in randomized, placebo/SoC-controlled trials. Recent trends also indicate the overall survival rate as an important evidentiary factor even for conditional or accelerated approval pathways.

CMC strategic framework

The majority of approved CGTs for oncology are chimeric antigen receptor T-cell (CAR-T) therapies, whereas gene therapies predominate in rare disease indications. 74% of the rejections of biologics license applications, clinical trial dossiers, and marketing authorization are due to manufacturing and CMC compliance issues. These issues are also a major reason for postlaunch viability failures.[34] CGT/ATMP CMC challenges include starting material heterogeneity, process and batch-to-batch variability, limited reference material availability, short product shelf-life, lack of validated potency assays reflecting clinical efficacy, insufficient stability data, manufacturing site inspection findings, technology transfer complexities, shortages of skilled personnel, and implementation of effective control strategies.

Regulatory authorities expect stringent adherence to current good manufacturing practice (cGMP) guidelines under 21 CFR Part 211, which requires robust process and product validation for clinical trials and marketing application approvals.[35] The FDA recently introduced flexibility for CGTs through a case-by-case assessment of CMC requirements.[20] For Phase I trials, the FDA made the cGMP guidelines optional for CGT manufacturing, creating advantages for small- and mid-size enterprises that traditionally invest heavily in in-house process development and in partnerships with contract development and manufacturing organizations (CDMOs). This flexibility extends to commercial process validation, including the potential for reduced manufacturing batches in certain circumstances.

Despite these flexibilities, the increasing issuance of complete response letters and nonapprovals based on CMC deficiencies is concerning. Most CGTs receive breakthrough or accelerated approvals based on early clinical efficacy endpoints that subsequently face challenges in confirmatory trials and postapproval success due to manufacturing and CMC validation barriers. CGT/ATMP CMC strategy development necessitates risk-based quality-by-design implementation with an end-in-sight approach by defining the target product profile at the program initiation stage. This is followed by risk-based identification of critical quality attributes and the development of manufacturing processes that consistently produce safe, efficacious, quality products that are comparable to pivotal trial products derived from a late-stage cGMP-compliant, validated process.

The advent of AI/ML-based technologies, closed automated systems, and in-process analytics that enable real-time process monitoring has expanded the scope of proactive,

cost-effective design, development, and control strategies for CMC manufacturing. Given the biological material's dynamics and heterogeneity, it is critical to prioritize robust control strategy development from early CGT process development stages, with meticulous real-time monitoring of critical process parameters linked to product critical quality attributes. Implementation of stricter starting material testing and traceability, quality raw materials, robust risk-based pre- and postchange process comparability testing, refined release test specifications, multiple potency assays reflecting mechanism of action, extensive product characterization assays, and comparable stability and sterility testing with cold-chain distribution, container closure, and shipping validation studies for multisite trials are highly recommended by regulatory authorities, as the product matures through clinical experience.

Manufacturing models and strategy

For small to mid-sized enterprises, resource-constrained, timeline-sensitive environments necessitate diligent regulatory and CMC strategy in weighing options between establishing in-house cGMP facilities or partnering with commercial contract research organizations and CDMOs, which may offer advantages through effective regulatory authority communications, comparability and control strategy development and implementation, regulatory intelligence expertise, skilled cGMP compliance professionals, process and analytical validation capabilities, and inspection-ready manufacturing services.

Increasingly, successful rare disease-targeting CGTs have been developed in small and academic settings focusing on personalized, cost-effective, timely therapeutic interventions through accelerated approvals (e.g., K-abe, Waskyra). Some European centers have manufactured patient-specific CAR-T products under Article 28 hospital exemptions using essentially N-of-1 treatment frameworks.[36] However, challenges persist in commercial translation and wider patient access due to scalability, development costs, and payer-mediated issues.

Recognizing severe unmet needs and a lack of suitable SoC for patients with rare and bespoke diseases, the FDA and EMA have initiated several programs. The FDA initiated the CMC Development and Readiness Pilot Program, which aims to accelerate complex product development, including CGTs, by increasing FDA-sponsor communication through FY 2027;[37] the Collaboration on Gene Therapies Global Pilot to advance global regulatory convergence on complex gene therapy development;[38] and the Platform Technology Designation program, which streamlines development pathways for validated delivery systems, allowing sponsors to reference precedent platform CMC and nonclinical data for new indications. The FDA and EMA jointly launched the Parallel Scientific Advice program and orphan drug cluster meetings. Both agencies have also explored decentralized manufacturing models, including point-of-care, distributed, and regional distribution models, to overcome supply chain and patient access challenges. **Table 2** (p. 58) presents key points of the FDA and EMA convergence and minor divergence regarding CMC manufacturing strategies.

Table 3 (p. 60) illustrates the major areas of divergence in CMC strategy across the two agencies. For starting materials and GMP requirements, early-stage trials in the EU involve higher costs and earlier implementation timelines due to the EMA's expectation for GMP compliance from the outset. Likewise, the divergence in potency assay expectations for first-in-human studies means that global sponsors must have a suitable potency assay developed before initiating Phase 1 studies.

Proactive regulatory intelligence is important for navigating these evolving frameworks. Continuous monitoring of the FDA's CMC flexibility frameworks, complete response letter trends, and CMC deficiency patterns can inform manufacturing investment decisions and CDMO selection without compromising inspection readiness or product quality. Furthermore, intelligence on the FDA's Collaboration on Gene Therapies Global Pilot program and platform technology precedents can help sponsors leverage established CMC data packages across new indications, thereby compressing development timelines, reducing duplicative validation efforts, and costs. As decentralized and point-of-care manufacturing models mature, global regulatory intelligence on GMP expectations will be essential for sponsors for developing multisite CGT manufacturing networks.

Postapproval benefit-risk monitoring

For full marketing approval, supplemental evidence and post-marketing safety and efficacy studies are necessary. In oncology indications, improvements in event-free survival, progression-free survival, and, in some cases, overall survival rate compared with SoC therapies are required beyond overall response

Table 2. FDA and EMA CMC strategy convergences and minor divergences

CMC criteria	FDA	EMA	Convergence or divergence
Cell viability specifications	Minimum acceptable viability is 70%, with supporting data needed if < 70%	Minimum acceptable viability is 70%	**Convergent**
Extractables/ eachables from single-use systems – bDtBPP	Testing required for bDtBPP	Testing required for bDtBPP	**Convergent**
RCV testing for retroviral vectors	Testing required for: – Vector producer cells – End-of-production cells – Vector stock – LV-modified cells Ex vivo cells cultured ≥4 days: RCV required as a release assay	Testing required for – Vector producer cells – End-of-production cells – Vector stock – LV-modified cells Same ≥ 4-day threshold as FDA: extensive RCV testing required	**Highly convergent** Both require a 15-year patient follow-up
CAR-T starting material collection (leukapheresis)	Excluded from cGMP: – Leukapheresis collection – Initial cell processing – Cryopreservation Subject to cGTP (21 CFR 1271)	Excluded from GMP: – Donation and collection of cells – Testing of cells GMP applies beginning at vector manufacture, cell purification/ processing, and MCB/viral seed stocks	**Convergent** Both exclude GMP requirements from early collection steps
Product nomenclature:	CGTs: – Cell therapy – Gene therapy – Tissue-engineered therapy	ATMPs: – GTMP – sCTMP – TEP – cATMPs	**Minor divergence**
Potency assay validation for pivotal trials	Quantitative functional potency assay required for release; must be validated according to ICH guidelines	Validated analytical methods; recommended but not strictly required; surrogate assays acceptable (e.g., functional characterization with demonstrated correlation)	**Minor divergence** EMA slightly more flexible; both require functional assay by MAA/ BLA
Manufacturing changes and comparability	Data-driven approach emphasizing: – Process performance qualification – Detailed control material documentation – Excipient specifications	Science-based, continuous improvement approach emphasizing: – Overall manufacturing strategy – Risk management – Lifecycle comparability	**Minor divergence** Both cite ICH Q5E (comparability)

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Table 2. (cont.) FDA and EMA CMC strategy convergences and minor divergences

CMC criteria	FDA	EMA	Convergence or divergence
		Specific guidance for GM cells: full vector sequencing, RCV absence, impurity comparison for starting materials	
Overall regulatory philosophy	Risk-based and pragmatic, emphasizing: – Graduated GMP compliance – Flexibility for Phase 1 – Data-driven decision making – Process performance qualification	Science- and quality driven, emphasizing – GMP compliance from early stages – Comprehensive lifecycle approach – Continuous improvement – Holistic risk management	**Minor divergence**

ATMP, advanced therapy medicinal product; **bDtBPP,** bis(2,4-di-tert-butylphenyl) phosphate; **BLA,** biologics license application; **cATMP,** combined advanced therapy medicinal product; **cGMP,** current good manufacturing practice; **CGT,** cell and gene therapy; **cGTP,** current good tissue practice; **CMC,** chemistry, manufacturing, and controls; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration [US]; **GM,** genetically modified; **GTMP,** gene therapy medicinal product; **ICH,** International Council for Harmonisation; **MAA,** marketing authorization application; **MCB,** master cell bank; **RCV,** replication-competent virus; **sCTMP,** somatic cell therapy medicinal product; **TEP,** tissue-engineered product.

rate alone. Consequently, the Prescription Drug User Fee Act dates have increasingly been extended to incorporate additional confirmatory evidence. The recent review of serious, adverse postapproval events of a high-profile gene therapy application for a rare pediatric condition highlighted the FDA's policy shift toward requiring stringent safety and efficacy endpoints for complex gene therapy approvals.[39,40]

For final approvals, the EMA requires extensive, more stringent confirmatory data from additional late-stage clinical trials that are generalizable across multiple EU regions. While the FDA primarily focuses on postmarketing safety (36.1%), the EMA also places significantly greater emphasis on postauthorization efficacy studies (47.1%), acknowledging that sustained clinical benefit and cure evidence for ATMPs require several years of monitoring.[41,42] CGTs/ATMPs approved under accelerated and conditional pathways are also subject to postmarketing monitoring. Both the FDA and EMA require 15 or more years of mandatory safety monitoring as part of pharmacovigilance and pharmacosurveillance programs, with risk-based approaches used to determine the duration of LTFU monitoring.[43] Factors such as DNA integration potential, duration of transgene expression, in vivo product persistence, and administration route influence regulatory decisions on LTFU duration and stringency. For example, therapies using genome-editing products and integrating vectors require 15 years of LTFU, whereas low-risk adeno-associated vectors require about 5 years of LTFU.

The FDA enforces a centralized approach using risk evaluation and mitigation strategy plans for high-risk CGTs, making decisions on the implementation and elimination based on postapproval benefit-risk surveillance. The EMA utilizes a decentralized pharmacovigilance system with region-specific compliance requirements across EU member states, requiring postauthorization safety and efficacy studies and a risk management plan that incorporates postmarketing surveillance of both efficacy and safety, with appropriate traceability systems. The EMA relies heavily on the European Network of Centers of Pharmacoepidemiology and Pharmacovigilance guidelines and registry-based studies for data gathering, especially when single-arm trials are the only feasible option. Both the FDA and the EMA recommend registry-based postapproval monitoring to assess the effectiveness of adaptive trial designs in clinical practice and to evaluate the effectiveness of these designs in smaller subsets and more heterogeneous patient populations.

Sponsors should perform feasibility assessments, collect continuous and uninterrupted data, transparently address missing data, and consider linking multiple data sources. Registries, electronic medical records, and claims data – capturing clinical, laboratory, demographic, genetic, histopathology, imaging, and digital health technology inputs – constitute common RWD sources. Key challenges include missing covariate data, patient dropout, unstructured data, and inconsistent or fragmented patient records.

Table 3. Major areas of divergence between FDA and EMA CMC strategies

CMC criteria	FDA	EMA	Divergence
Starting materials definition	Guidance refers to materials forming an integral part of the active substance, but does not provide a formal definition	Formally defined as materials that will become part of the drug substance (e.g., vectors, gene-editing components, cells)	**Major divergence**
Starting material (genome-editing components such as plasmids, mRNA, proteins); GMP requirements	Risk-based, flexible approach; non-GMP acceptable for Phase 1 with proper justification, step-wise increase in GMP compliance; full qualification and GMP validation at BLA and pre-license inspection	Stricter from outset, starting materials must follow GMP principles from early development; manufacturin sites subject to inspection; QP must ensure starting material quality	**Major divergence** EMA requires GMP from start while the FDA allows risk-based approach
Potency assay at FIH clinical trial	Flexible: if a potency assay is not available for release testing, other aspects of the control strategy may be accepted for potency assurance, including: – Manufacturing process controls – In-process testing – Material controls	Mandatory: a suitable potency assay must be in place when material for the FIH clinical trial is produced	**Major divergence** EMA requires potency assay earlier in development

BLA, biologics licensing application; **CMC,** chemistry, manufacturing, and controls; **EMA,** European Medicines Agency; **EU,** European Union; **FDA,** Food and Drug Administration [US]; **FIH,** first-in-human; **GMP,** good manufacturing practice; **QP,** qualified person.

Moreover, the FDA has provided draft guidance on decentralized data collection methods, including remote monitoring, telehealth, and local clinic assessments, to reduce patient burden as part of LTFU.[44]

Unless waived or deferred, the FDA requires sponsors to submit pediatric assessments per the Pediatric Research Equity Act. This act provides initial pediatric study plan exemptions for orphan designation applications, except for rare pediatric cancers under the amended Research to Accelerate Cures and Equity Act. As many rare disease CGTs/ATMPs target childhood-onset conditions, both the FDA and EMA require pediatric study plan submissions.[45] Deferred pediatric studies are mandated in pediatric populations after adult patient marketing approval.

Studies of drugs or biological products for life-threatening or severely debilitating pediatric diseases lacking adequate therapy could begin earlier than adult studies when urgency may justify early initiation despite limited adult safety and effectiveness information. The EMA requires a pediatric investigation plan submission for every new marketing application.[46] These submissions can be deferred until adult clinical efficacy data generation. Additionally, the EMA's 2023 pilot program allows sponsors to continue development with a partial pediatric investigation plan rather than waiting for more adult clinical trial data to support a full plan.

Conclusion

The CGT landscape demands a sophisticated, proactive regulatory intelligence framework. Higher FDA regulatory approval success rates alone are insufficient to ensure commercial viability; integrated strategies that address CMC robustness, RWE generation, multistakeholder collaboration, and region-specific market access are required. The convergence of AI/ML technologies, decentralized trial methodologies, patient-centric development frameworks, and regulatory flexibility initiatives creates unprecedented opportunities for accelerating CGT development.

However, success requires early, strategic, and proactive planning with an end-in-sight approach – particularly for CMC development, where 74% of regulatory failures occur. Emerging global dynamics necessitate comprehensive international regulatory intelligence that encompasses diverse regulatory frameworks, manufacturing paradigms, and market access strategies. The future of CGT development will be defined by

organizations that effectively integrate regulatory intelligence into strategic decision making across the entire product lifecycle, from early development through long-term postmarket surveillance, while maintaining flexibility to adapt to evolving regulatory landscapes as well as scientific and technological advances.

Ultimately, an effective regulatory strategy for CGTs requires balancing innovation with rigorous safety and efficacy standards, leveraging novel trial designs and RWE, and maintaining robust quality systems. Success also depends on fostering collaborative relationships among regulatory authorities, sponsors, patient advocacy groups, and healthcare systems to ensure these transformative therapies reach patients who need them most.

Abbreviations

AI/ML, artificial intelligence/machine learning; **ATMP,** advanced therapy medicinal product; **CAR-T,** chimeric antigen receptor T-cell; **CDMO,** contract development and manufacturing organization; **CGT,** cell and gene therapy; **CMC,** chemistry, manufacturing, and controls; **DPM,** disease progression model; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration [US]; **LTFU,** long-term follow-up; **PFDD,** patient-focused drug development; **RCT,** randomized controlled trial; **RWD,** real-world data; **RWE,** real-world evidence; **SoC,** standard of care; **cGMP,** current good manufacturing practice.

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