CELL & GENE THERAPY PRODUCTS 2026
MANUFACTURING, QUALITY AND REGULATORY CONSIDERATIONS

Driving Concurrent US and EU Approvals for Gene Therapies Using a Reg-CMC Roadmap

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Cell and Gene Therapies – Some Numbers

- In 2019, FDA reported “more than **800** cell-based or directly administered gene therapy INDs” on file with the Agency[1]
- FDA predicted that “by 2025, FDA will be approving **10 - 20** cell and gene therapy products a year….”[1]
- **2,129** gene therapies (including genetically modified cell therapies such as CAR-T cell therapies) are in development[2]
- Growth in clinical trials involving CGT is accompanied by a growth in clinical holds; however, the increase in holds appears to be disproportionate to the increase in overall clinical trials. NIH-listed CGT clinical trials total less than **2%** of all listed clinical trials, yet they are responsible for approximately **40%** of all clinical holds[3]
- Reported causes of clinical holds: Clinical, **70%**; CMC, **21%**; Pre-clinical, **9%**[3]

[1]Statement from FDA Commissioner and CBER Director on new policies to advance development of safe and effective cell and gene therapies (Jan. 15, 2019).
[2]Gene, Cell & RNA Therapy Landscape Report, *ASGCT* Q3 2025 Quarterly Data Report.
[3]Wills *et al*. (2023) *Molecular Therapy* vol 31: 101125.

Approved Gene Therapies

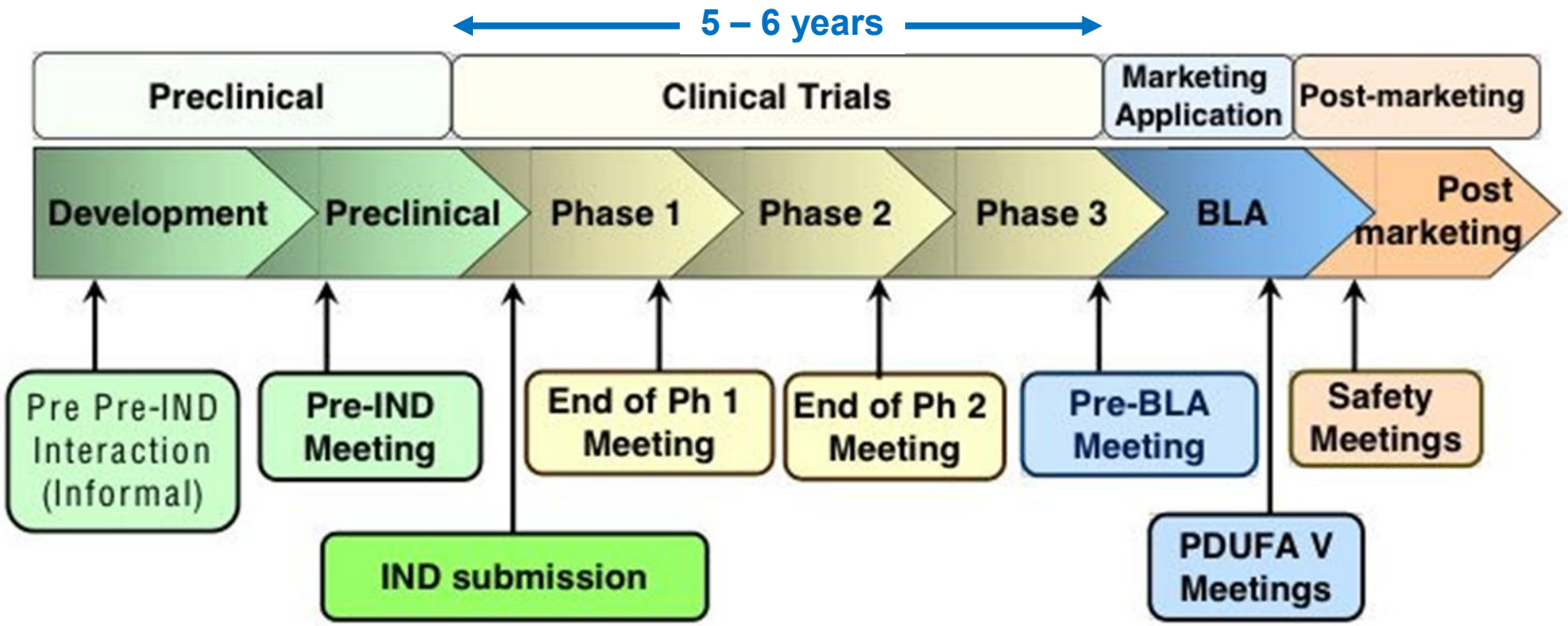
Gene Therapy	Manufacturer	FDA Approval	EMA Approval
GLYBERA	Amsterdam Molecular Therapeutics	NA	Oct-12[a]
STRIMVELIS	Orchard Therapeutics (Europe) Limited	NA	May-16
KYMRIAH	Novartis Pharmaceuticals	Aug-17	Aug-18
YESCARTA	Kite Pharma, Inc.	Oct-17	Aug-18
LUXTURNA	Spark Therapeutics, Inc.	Dec-17	Nov-18
ZOLGENSMA	Novartis Gene Therapies, Inc.	May-19	May-20
TECARTUS	Kite Pharma, Inc.	Jul-20	Dec-20
LENMELDY	Orchard Therapeutics (Europe) Limited	Mar-21	Dec-20
ABECMA	Celgene Corporation (BMS)	Mar-21	Aug-21
IMLYGIC	BioVex, Inc., a subsidiary of Amgen Inc.	Dec-21	Dec-15
CARVYKTI	Janssen Biotech, Inc.	Feb-22	May-22
BREYANZI	Juno Therapeutics, Inc. (BMS)	Jun-22	Apr-22
ZYNTEGLO	bluebird bio, Inc.	Aug-22	May-19[b]
SKYSONA	bluebird bio, Inc.	Sep-22	Jul-21[c]
HEMGENIX	CSL Behring LLC	Nov-22	Feb-23
ADSTILADRIN	Ferring Pharmaceuticals A/S	Dec-22	pending
VYJUVEK	Krystal Biotech, Inc.	May-23	Feb-25
ELEVIDYS	Sarepta Therapeutics, Inc.	Jun-23	NA
ROCTAVIAN	BioMarin Pharmaceutical Inc.	Jun-23	Aug-22
CASGEVY	Vertex Pharmaceuticals Inc.	Dec-23	Feb-24
LYFGENIA	bluebird bio, Inc.	Dec-23	NA
BEQVEZ	Pfizer, Inc.	Apr-24[d]	Jul-24[d]
KEBILIDI / UPSTAZA	PTC Therapeutics	Nov-24	Jul-22
ZEVASKYN	Abeona Therapeutics, Inc.	Apr-25	NA
PAPZIMEOS	Precigen, Inc.	Aug-25	pending
ITVISMA	Novartis Gene Therapies, Inc.	Nov-25	pending
WASKYRA	Fondazione Telethon	Dec-25	Nov-25
OTARMENI	Regeneron Pharmaceuticals, Inc.	Apr-26	pending

[a]MA ended Oct-17 (not renewed)
[b]MAA withdrawn Mar-22
[c]MAA withdrawn Nov-21
[d]Discontinued Feb-25

Challenges to Concurrent US and EU Gene Therapy Approvals

- Different clinical trial designs and endpoint(s) requirements for FDA vs EMA can cause delays and create submission inconsistencies requiring separate applications for each agency
- FDA's flexible approach can create uncertainties; EMA's multi-step process can create roadblocks
- Manufacturing and quality requirements are not harmonized across the agencies, with varying definitions and guidelines for CMC

Development of Biologics – the usual course



Exciting, Breakthrough “Early” Data

Akouos reports positive data from gene therapy trial for hearing loss

Initial results from the clinical trial indicate that AK-OTOF gene therapy restored hearing in patients with profound loss.

January 24, 2024

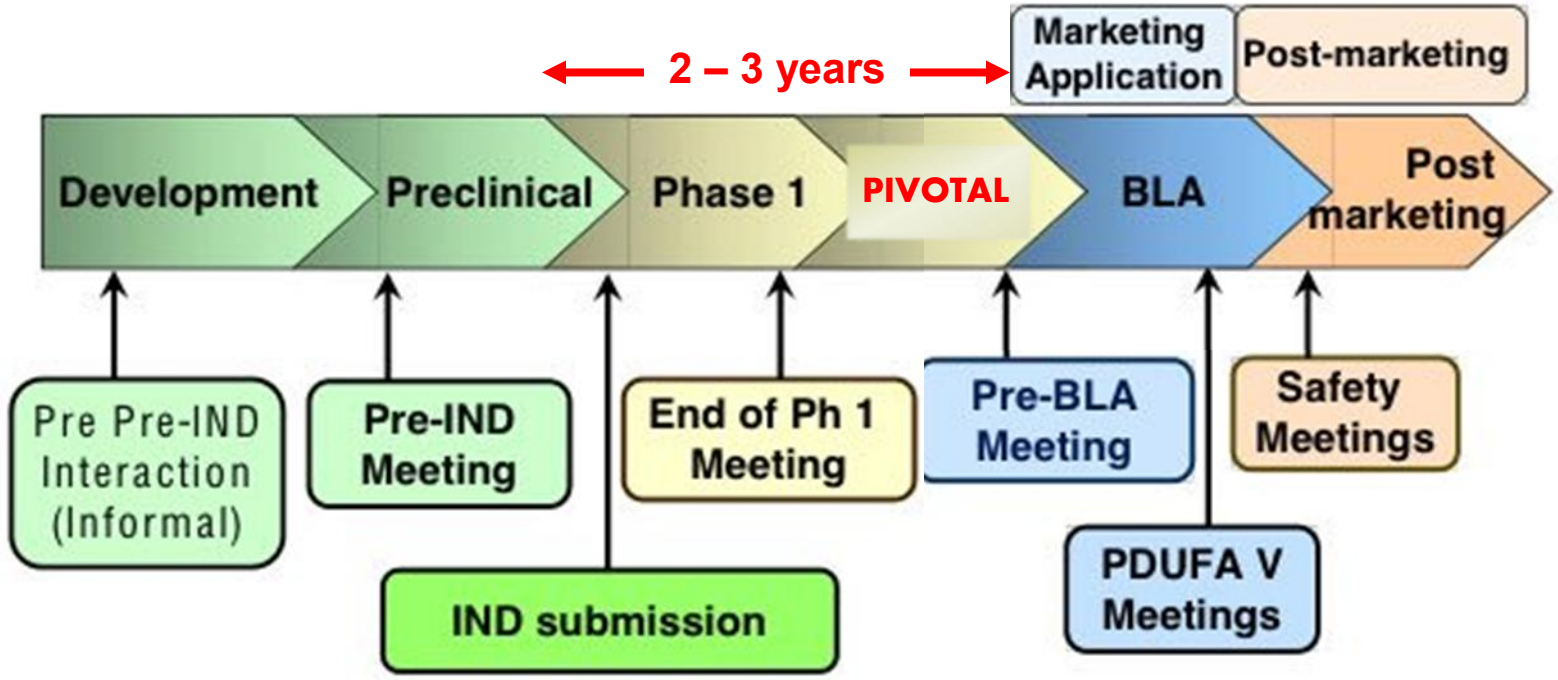
The New York Times

Gene Therapy Allows an 11-Year-Old Boy to Hear for the First Time

The genetic treatment targeted a particular kind of congenital deafness and will soon be tried in children who are younger.

- Eli Lilly and Akouos reported encouraging initial data from the Phase I/II AK-OTOF-101 clinical trial of its investigational gene therapy, AK-OTOF, for genetic hearing loss.
- The trial has demonstrated pharmacologic hearing restoration within 30 days of administration in the first participant, who had a history of profound hearing loss for more than a decade.
- A dual adeno-associated viral (AAV) vector-based gene therapy, AK-OTOF is in the developmental stage for treating sensorineural hearing loss due to mutations in the otoferlin gene (OTOF).
- The therapy uses AAVAnc80, a capsid known for its increased transduction efficiency in inner hair cells, and a promoter to ensure that otoferlin expression is confined to the target cells.

Development of Gene Therapies – likely accelerated course



- Early ‘breakthrough’ data can place development on an accelerated course to licensure, reducing essential CMC timelines

FDA and EMA Regulatory Governance for Gene Therapies

	US-FDA	EU-EMA
Governed by	Center for Biologics Evaluation and Research (CBER)	Committee of Advanced Therapies (CAT); regulated as Advanced Therapy Medicinal Products (ATMPs)
Key laws/legislation	Section 505 of the Food, Drug, and Cosmetic Act (1938) and Sections 351 and 361 of the Public Health Service Act (1944)	ATMP regulation 1394/2007/EC and Directive 2009/120/EC
Expedited pathways	**RMAT, Fast Track**, **Breakthrough Therapy**; pathways allow earlier market access, but can introduce potential unpredictability **CDRP** program – CMC readiness for accelerated development timelines	**Accelerated Assessment**, **Conditional Marketing Authorization**, **Approval Under Exceptional Circumstances** **Priority Medicines** (PRIME) initiative offers enhanced support and accelerated assessment for gene therapies that address unmet medical needs
Review timelines	Standard BLA: ~10 months Priority review: ~6 months	Standard review: 210 days (excluding clock stops); Accelerated Assessment: 150 days for high-value products
Post-market surveillance	Requires monitoring of gene therapy recipients for 15+ years	Follows a risk-based approach, generally with shorter follow-up requirements

Comparing FDA and EMA CMC Guidelines for Gene Therapies

- Starting Materials
- Potency / Efficacy Assessment
- Comparability

Comparing FDA and EMA Guidelines for Gene Therapies:

Starting Materials

US-FDA	EU-EMA
No specific definition; the term '*critical raw materials'* is often used	Defined as those that will become part of the drug substance, e.g., vectors
Allows for a broader range of starting materials, including those not fully defined by the International Council for Harmonization (ICH)	Requires a more stringent definition of starting materials, often based on ICH guidelines
Guidance emphasizes the importance of defining critical raw materials, drug substance and drug product clearly before regulatory submissions to ensure implementation of quality requirements and control strategies	Starting material (e.g., plasmids) manufacture can follow GMP principles; manufacturer is expected to apply a risk-based approach
Raw material covered by a DMF does not need to be described with the same level of detail in regulatory submissions	Level of information provided for critical starting material(s) is expected to be the same as that for the active substance

Comparing FDA and EMA Guidelines for Gene Therapies:

Potency / Efficacy Assessment – recognized as CQA by both agencies, but differ in method validation requirements, timing, and regulatory expectations across clinical phases

US-FDA	EU-EMA
Accepts real-world experience, surrogate endpoints, particularly for rare or life-threatening diseases	Requires more comprehensive clinical data; demonstration of long-term efficacy for approval
Full validation of drug product potency assays is not required for Phase 1	Mandates an appropriate degree of method validation at each stage of development
Potency testing is mandatory for each batch; flexibility in assay design	Potency testing is mandatory for each batch; assay is expected to reflect the products MOA accurately

FDA and EMA Guidelines for Gene Therapies:

Comparability – both agencies agree on several key aspects

- **Comparability Protocols**
  - Design of comparability protocols should satisfy the most stringent requirements to ensure global market readiness
- **Risk Assessment**
  - Sponsors should conduct a thorough risk assessment of proposed manufacturing changes to ensure that product quality is not adversely affected
- **Analytical Testing**
  - In designing comparability exercises and selecting testing or quality attributes, both agencies agree that the extent of testing included should increase with the stage of clinical and product development
  - Extended characterization testing, if applicable, should be added to support comparability
  - Potency should be included as part a of the comparability testing panel

Sources: Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products | FDA (2023)

Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP) - Scientific guideline | European Medicines Agency (EMA)

FDA and EMA Guidelines for Gene Therapies:

Comparability – Divergence in stability assessment

- US comparability guidance specifies that a thorough assessment of stability (often including real-time study data) should be included in support of comparability following changes to formulation, container, or shipping conditions
- EU guidance states that real-time stability data is not needed. However, following manufacturing site changes, the applicant for Casgevy® (cell-based gene therapy for SCD) was required to commit to evaluating comparability for the drug product once real-time stability studies were complete[1], despite EU guidance stating that these data are not required

[1]Casgevy; INN-exagamglogene autotemcel

Concluding Remarks (1)

Strategies to Address Regulatory-CMC Challenges for Concurrent US and EU Gene Therapy Approvals

- Start early, develop a phase-appropriate reg-CMC strategy
- Engage in preliminary / consultation meetings with both agencies
  - INTERACT, pre-IND, pre-CTA meetings can
    - Provide an early assessment of IND-enabling strategy and plans
    - Ensure better allocation of resources
    - Help in developing realistic timelines
    - Jump-start the process of collecting and organizing essential documents, e.g., development reports for process and methods

Concluding Remarks (2)

Strategies to Address Regulatory-CMC Challenges for Concurrent US and EU Gene Therapy Approvals

- Invest in a Reg-CMC strategy that meets regulatory requirements for both agencies
  - Focus: Raw materials, analytical testing, comparability, process and analytical validation
- Keep up with evolving regulatory guidance
  - While the FDA's inclination to be more flexible with CMC requirements for CGTs[1] is desirable, sponsors should evaluate the flexibilities in the context of the therapies they are developing
    - Some of the noted flexibilities could impede progress and/or cause delays
    - Focus on safety and efficacy should not be compromised

[1]Flexible Requirements for Cell and Gene Therapies to Advance Innovation | FDA

Thank you!