NATIONAL ACADEMIES *Sciences Engineering Medicine*

Recognizing the Platform: A Reliance Framework for Contract Development & Manufacturing Organizations (CDMOs) in Gene Therapy

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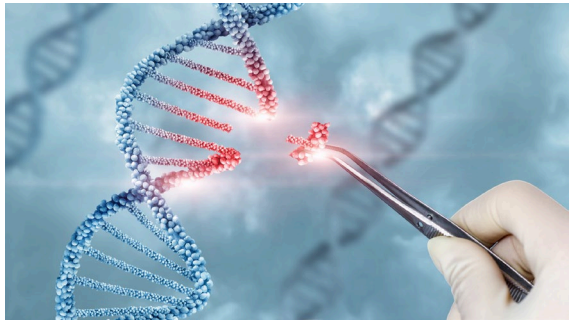
Our Central Question

How can we align the competing incentives in gene therapy manufacturing, so the field can move toward a platform-based approach?

What is a Gene Therapy

- Fixes the genetic cause of disease, not the symptom
- Rooted in monogenic rare diseases; moving towards common and acquired conditions
- Ex: Casgevy (sickle cell), Elevidys (DMD), Otarmeni (deafness)
- The delivery vehicle (viral or non-viral) sets how the therapy is made



Method

What is done to the genome

- Gene addition
- Gene silencing
- Gene editing
- Combined modality

Approach

Site of modification

- *In vivo* — Modified within the body
- *Ex vivo* — Cells removed, modified, & returned

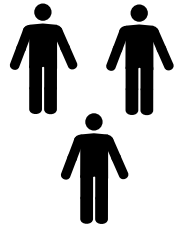
Delivery

The vehicle carrying the payload

- AAV
- Lentivirus
- Adenoviral / HSV
- Lipid nanoparticle

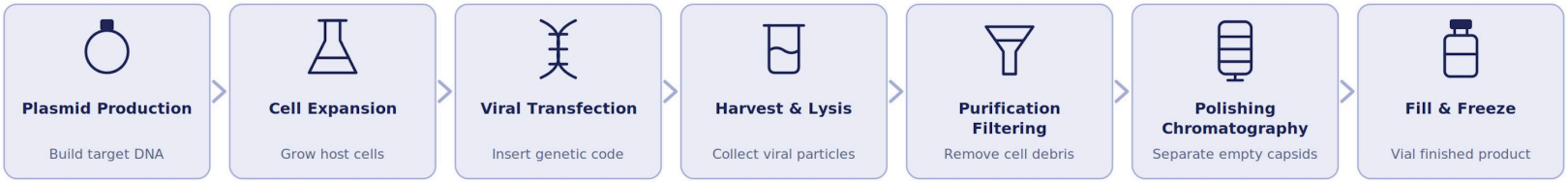
Gene Therapy Is Its Own (Tricky) Market

- Usually treats rare diseases, so only a small number of doses are made
- Often one, irreversible dose (higher stakes)
- Very different from other biologics/drugs:
  - Ex 1: Monoclonal antibodies are made continuously, at volume, for a large population
  - Ex 2: Small-molecule drugs are chemically synthesized at massive scale and taken repeatedly, for years
- That steady production is what makes their manufacturing worth building well



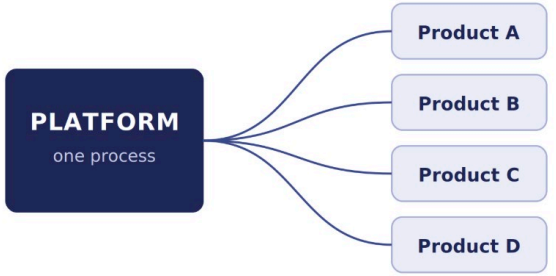
Gene Therapies Require Bespoke Manufacturing

- Chemistry, Manufacturing, and Controls (CMC) is the proof that a gene therapy can be made reproducibly, at consistent quality, from characterized inputs
- Different vector, transgene, and targets require a bespoke manufacturing process → **slow and costly process**
- Thus, every gene therapy manufactured re-establishes these steps



Industry is Moving Towards Platforms

- **Process platform** - one pre-qualified process, the cell line, backbone, purification, and analytics, reused across a family of products
- Reusing it instead of rebuilding improves consistency, lowers risk, and speeds development
- **Key problem:** the FDA still reviews each product individually, so the “platform” components are re-reviewed in full every time



The Pivotal Stakeholder: Contract Development and Manufacturing Organizations (CDMOs)

- While some larger sponsors have internal manufacturing capabilities, **50-60% of manufacturing** in the gene therapy space is outsourced to **CDMOs**
- The CDMO develops and runs the process, but the FDA regulates it only **indirectly through the sponsor**'s IND or BLA
- **AI vendors** are new players with even less oversight: software companies whose models support manufacturing but fall outside FDA oversight
- **Key problem:** the reusable capability lives with the CDMO and its vendors, yet recognition still attaches only to the sponsor's product

CDMOs in Biologic Development

Misaligned Incentives Make CMC the Bottleneck in Gene Therapy Development

- **Manufacturing** is where gene therapy applications **fail the most**
  - Most CRLs cite CMC issues, not clinical efficacy
- Inefficiencies are due to **structural differences in stakeholder needs:**

Small/Rare Disease Sponsors:
Need platforms to support accelerated manufacturing

Vertically Integrated Sponsors:
Want to keep platform and manufacturing capabilities internal

FDA Reviewers:
Need enough evidence to trust quality and safety

CDMOs/Manufacturers:
Want to protect their IP and maximize profit from sponsors

The Cycle Keeping Gene Therapy Manufacturing Stuck

- Federal response has been substantial (statutes, guidances, facility programs, engagement teams, pilots), but **hasn't changed what actually gets reviewed**
  - These mainly speed up **step 4**
- This capstone works further upstream: highlighting and addressing **steps 2 and 3 as the larger drivers of CMC inefficiencies**

Areas of Focus

1) The Sponsor-CDMO Relationship
2) Hidden Manufacturing Evidence
3) Governing the Platform
4) Encouraging Manufacturing Collaboration

Problems and Recommendations

1. **<u>The Sponsor-CDMO Relationship:</u> give sponsors the visibility and contract tools to choose and work with CDMOs well**
2. Hidden Manufacturing Evidence: enable swifter technology transfer between CDMOs and a tiered master file for sponsors
3. Governing the Platform: create a home for platforms that, with AI, are constantly changing and improving
4. Encouraging Manufacturing Collaboration: support rare-disease sponsors and incentivize data sharing/shared learning

1) The Sponsor-CDMO Relationship

Problem	Why It Persists	Recommendation	Who Does It
There are no ways to perceive the quality or capabilities of CDMOs	Its process is its main competitive asset	Adapt the Quality Management Maturity (QMM) rating for advanced therapies: the market sees the rating, no competitor sees the process	FDA

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2) Hidden Manufacturing Evidence

Problem	Why It Persists	Recommendation	Who Does It
A technology transfer requires a full comparability exercise	ICH Q5E assumes nothing is known, even when the process is unchanged	Calibrate comparability to development phase, and adopt a structured, machine-readable transfer package	FDA, ICH, SCB

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3) Governing the Platform

Problem	Why it persists	Recommendation	Who Does It
Platforms are not clearly defined, so what can be reused is never fixed	No shared definition of a platform's fixed core and its allowed variation exists	Define and qualify a platform envelope once: its fixed core and bounded range of permitted variation, with a scoped finding	FDA

How a Platform Could Change Regulatory Review

PRODUCT-SPECIFIC Reviewed in full	• Construct identity and potency • Disease pharmacology and dose • Clinical protocol and follow-up
SHARED-VECTOR SAFETY Confirmed vs. baseline	• Capsid toxicology • Biodistribution and shedding • Insertional risk, immunogenicity
BOUNDED VARIATION Checked against limits	• Transgene within a size limit • Promoter class and dose range • AI model updates
FIXED CORE No re-review	• Capsid and vector backbone • Cell line and transfection • Process train and analytics

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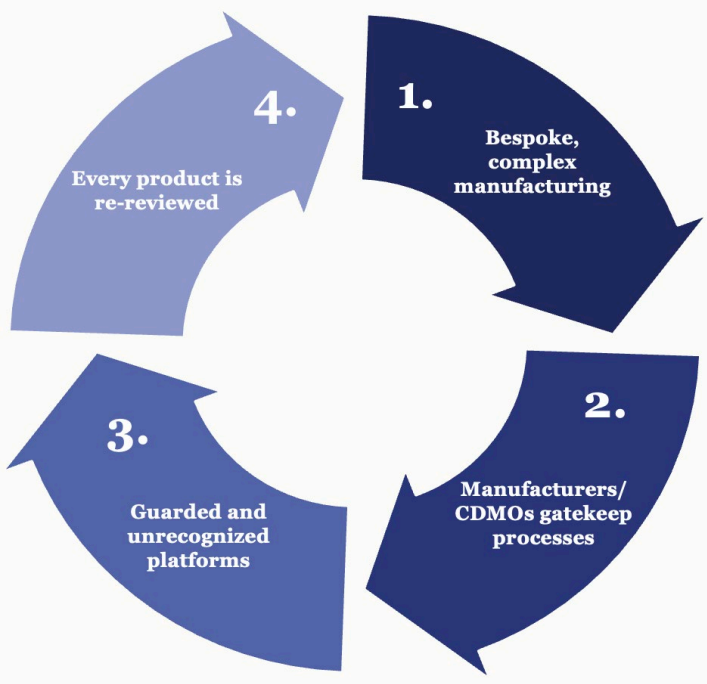
4) Encouraging Manufacturing Collaboration

Problem	Why it persists	Recommendation	Who Does It
The rare disease sponsors that would aid most from a platform cannot always access one	Sharing a platform means exposing private manufacturing data, and there's no neutral entity to host it	NCATS should hold a standing primary IND for a rare-disease platform; sponsors file substudy INDs that reference its shared manufacturing and analytics	NCATS, FDA

Conclusion: Recognizing the CDMO's Role in Enabling Gene Therapy Manufacturing Platforms

Complements and enhances federal initiatives and programs!!



1) The Sponsor-CDMO Relationship
→ select and contract with the right CDMOs

2) Hidden Manufacturing Evidence
→ smoother transfer & more visible master files

3) Governing the Platform
→ gives the platform a home

4) Encouraging Manufacturing Collaboration
→ indirectly learn from each other's processes

Looking Ahead: Future of Gene Therapies

The science is expanding:

- Delivery i… …ing
- Newer mo… writing) a…

Manufactu…

- Some ther… …peat productio…
- Production is moving toward closed, automated, continuous systems that only work on a standardized platform

Defining the platform now, and the mechanisms needed to maintain it, is what the future of the field will build on

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Thank you!

Any questions?