Roundtable Session 2 – Table 4 – What Are the Most Critical Bottlenecks in CGT Manufacturing and How Are We Solving Them?

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Abstract:
The mRNA/LNP modality moved from concept to commercial product in record time. As the pipeline expands into rare disease, in vivo gene editing, and extra-hepatic delivery, sponsors are hitting the same recurring bottlenecks: which parts of the package are truly "platform," how to set defensible specifications without precedent, and how to source and characterize the materials the entire modality rests on.
This round table will surface the issues practitioners are facing today and convert them into a shared agenda for the next 12–24 months. Under Chatham House Rule, we will open with a brief go-around to prioritize the topics most pressing to the room, then drive into specifics with the goal of leaving with concrete questions for vendors, sponsors, and regulators.

Discussion Questions:
Platform claims & regulatory leverage. How much of an mRNA/LNP CMC package is truly platform, where do regulators make us re-prove things every program, and has anyone yet used FDA's platform technology designation productively?
Analytical & specification gaps: potency assays based on in-vitro expression and whether they bridge to clinical PD/efficacy for non-vaccine indications; the continued absence of accepted LNP reference standards; and how to justify specifications absent precedent or clinical correlation.
Ionizable lipid supply & impurity qualification: single-source dependencies, IP overhang on proprietary lipids, lot-to-lot variability, and genotoxic assessment of ionizable lipids and their degradants.
Beyond the liver: extra-hepatic targeting (lung, CNS, T-cell, bone marrow) and conjugated or targeted LNPs, including the manufacturing and characterization of the targeting moiety itself.
Participants will leave with a shared map of where the field's pain is concentrated and a short list of analytical and regulatory changes that would unlock the most value.

Notes:

Panel Summary: Bottlenecks in Cell and Gene Therapy Manufacturing

This panel brought together industry experts from various biotech companies (including Beam Therapeutics, TreeFrog, and Lumacyte) to discuss the most critical challenges facing the commercialization and scaling of cell and gene therapies.

The panelists identified several major bottlenecks that must be addressed to make these therapies widely accessible:

1. Patient Access and Logistics

The most pressing bottleneck identified by the panel is patient access and the logistics of delivering therapies.

- The "Bed Issue": There are simply not enough apheresis beds (for collecting patient cells) located near the specialized manufacturing centers. Patients often have to travel across the country, or even internationally, just to receive treatment.
- Geographic Inequality: It was highlighted that patients in regions like Africa or the Middle East often have no realistic path to receiving these therapies due to a lack of local infrastructure and the impossibility of cross-border logistics.

2. High Costs and Scale

The current cost structures are unsustainable for broad patient populations.

- Manufacturing Costs: While some therapies cost $250k on the market, the actual manufacturing cost can be around $25k. However, the panel argued this is still far too high.
- The "First in Human" Problem: The development and clinical trial costs are astronomical. Even before reaching phase 1 trials, companies can spend $15 million, with $4 million dedicated just to licensing fees.
- Lack of Scalability: The current manufacturing paradigm is highly manual and "boutique." The panel agreed that to serve larger patient populations (like those with Parkinson's or diabetes), the industry must transition to highly automated, scalable manufacturing processes.

3. Raw Material Quality and "The Bakery" Analogy

A significant point of discussion centered around the quality of starting materials.

- One panelist used a compelling bakery analogy: "You can automate a bakery with the best robots, but if you don't assess the quality of the starting materials—the flour, the eggs—you'll still have a failed process at the end."
- Moving Beyond Viability: The industry must move past simple cell "viability" (whether the cells are alive or dead) and focus on cell functionality. If the starting cells are functionally deficient, no amount of advanced processing will yield a potent final product.

4. The Autologous vs. Allogeneic Divide

The panel discussed the challenges inherent in autologous (patient-specific) versus allogeneic (off-the-shelf) therapies.

- Autologous Challenges: Creating a custom batch for every single patient is inherently inefficient and expensive.
- Allogeneic Hopes: Moving toward allogeneic, "off-the-shelf" treatments is seen as the ultimate solution for scale. However, this introduces complex biological challenges regarding immune rejection that have yet to be fully solved.

5. Early vs. Late Phase Investment

A persistent theme was the tension between early-stage speed and late-stage scalability.

- The VC Push: Startups are heavily pressured by investors to get to the clinic (First-in-Human) as fast as possible. Because of this rush, they often use unscalable, highly manual processes that have been proven in the past, rather than investing in new, scalable technologies.
- The "Lock-In" Effect: Once a therapy enters clinical trials, it is extremely difficult and expensive to change the manufacturing process. Companies get "locked in" to the inefficient methods they used to rush to the clinic, which ultimately hurts their commercial viability.

Conclusion: The panel largely agreed that while the biological science behind these therapies is incredible, the next major frontier is engineering and logistics: creating automated, closed-system manufacturing that can dramatically lower costs and improve access on a global scale.

Notes Continued:

Panel Summary: Bottlenecks in Cell and Gene Therapy Manufacturing

Comparability – site/process changes

Academic to industry process transfers

Planning for regulatory meeting timelines globally

Cost balance between intended commercial scale and IND needs

Estimating material hold: retains, testing, stability

Scale up with same process (volume) versus changes in process to meet volume (more adherent cells versus switch to suspension cells from adherent cells

Gaps in insight into quality of viral vectors e.g. titers, functional activity, expression

- includes in process

Supply of raw materials, plasmids, etc… Slow timelines

CDMO queue – timing
- outline commitments, responsibilities

Talent development for manufacturing. Retention
- EU has a different educational training i.e. early age enrollment into technical training with job training.
- Required EU handover time

CDMO – BLA readiness
- Advanced assessment. Timelines for raw materials. Agreements for product-specific support. Build relationship
- Perform mock audit

Ensuring process and analytics are sufficient
- Person in plant (PIP): see, understand
- Bring CDMO talent to sponsor site
- Gain experience, remove PIP

Batch – CTO delays to batch release
- New analytical methods – technology
- Additional/layered/orthogonal approach

PPQ – setting expectations
- Evaluation of available data to establish gaps, control

cGMP implementation
- education, planning for implementation, tech transfer gap