Roundtable Session 1 – Table 4 - What are the Most Critical Bottlenecks in CGT Manufacturing, and How Are We Solving Them?

Facilitator: Bo Yan, *Beam*
Scribe: Diane Blumenthal, *Dianthus Biopharma Consulting, LLC*

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 will center on:

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:

Cost Drivers

- Critical raw materials particularly in gene editing.
    - The need to conduct in depth CMC activities on 4 drug substances/components is costly
    - Limited vendors for critical materials increase the cost of these components due to supply and demand as well as capacity limitations.
- CDMOs are saying more is needed but is this truly the case? Are the CDMOs taking advantage of their clients?
- Keeping pace with potency assays development is both costly and time consuming
- Production needs for CMC activities due to the product requirements

Potential Solutions

- Use of platform allows for a streamlined approach
- Form a Rare disease consortium and where data sharing is freer.
    - Encourage vendors/suppliers to do more pro bono work to give back
- Conduct clinical trials overseas where they can be less costly
- Harmonization of release specifications in each of the various modalities so that excessive testing is not being performed.