Roundtable Session 1 – Table 17 – What Are the New Alternate Lipids for Lipid Nanoparticles?

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Abstract:

Research on lipid nanoparticle (LNP) drug delivery systems remains a key area of focus, following the successful approvals of several LNP-encapsulated RNA therapeutics, including Onpattro®, Spikevax®, and Comirnaty®. LNPs typically consist of four key components: ionizable lipids, PEGylated lipids, helper lipids, and sterols. Despite LNPs being the most promising RNA delivery system due to their efficacy, ease of production and scalability, there are still several limitations. These limitations include restrictive long-term stability conditions and drug targeting challenges. Innovations in lipid chemistry have led to the development of novel lipids designed to enhance the stability, enable targeted drug delivery and increased efficiency of LNPs. Additionally, novel lipids can be tailored to impact the immunogenicity and the safety profile of LNPs, potentially increasing their efficacy and tolerability for various clinical applications. The purpose of this roundtable is to discuss new alternate lipids and the CMC strategies to ensure a robust supply chain, and control of the lipid raw materials as well as the final RNA-LNP drug products.

Discussion Questions:

1. When evaluating new alternate lipids, what is the primary driver (e.g. stability, bioavailability, tolerability, manufacturability etc.)?

2. What are examples of general CMC considerations when implementing novel lipids (e.g. supply chain, raw material impurities, product related impurities etc.)?

3. What are the analytical method considerations for identification and quantitation of individual novel lipids within the LNP, particularly those with similar physiochemical properties?

4. How do you ensure a robust supply chain and raw material control strategy to ensure consistent quality/purity of lipids over time from different vendors?

5. Have you experienced novel lipid raw material impurities that impact your final drug product quality? Where and how in the product lifecycle do you control for this scenario?

6. Do you feel continued development and implementation of alternate novel lipids will drive mRNA as a key therapeutic area beyond the vaccine space?Copy and paste the discussion questions from the online program (if applicable)

Notes:

Question #6 – Do we see changing interest or work on mRNA in the future?

- mRNA vaccines got a lot of visibility – became forefront of discussions
- Fundamental work will need to continue –e.g. novel lipids, targeting different organs
- Question of whether investments are in the direction of novel work, or heading towards maintenance costs with CMC
- Question of whether there are start-ups or academics focusing on challenges of chemically engineering lipids
    - Drug delivery is always the biggest hurdle

Question #1: Evaluating new alternative lipids

- Maintenance of existing lipid platforms (ongoing stability, bioavailability, improving raw material quality)
- Potential for innovation in targeted drug delivery,
    - Needs to go hand-in-hand, if you can't get the drug where it's intended, it is challenging to move forward on indications
- Immunogenicity concerns – need some inherent adjuvant activity; but can be counterproductive
- Toxicity and potency can be impacted if poor stability
- CMC considerations – quality, supply chain
- What are the gaps for innovators?
    - Ensuring high quality, stable, targeted lipids
- How do impurities react with your drug?
    - Identifying gaps in understanding that
    - Can we obtain more mechanistic understanding impurities, causes and watch-outs
    - Opportunity for AI or predictive modeling for risk assessment
- Are there databases of potential degradation pathways for lipids?
- Are there teams that are studying lipidomics that could contribute to this understanding?

- Phase-appropriate considerations for impurity specifications – early vs late stage
- If using a non-compendial, non-novel lipid – what info is needed, what is phase appropriate?
- Is it appropriate to rely on information provided by vendor?
- Having a close relationship with the vendor and having expectations around the lipid
- Is setting specs around the lipid sufficient, or do we need to have a better understanding of the lipid?
  COA usually just states %purity/impurity

- mRNA lipids are critical beyond just vaccine mRNA delivery – gene editing, gene therapy
- mRNA processes tend to be robust, so how well can we target these specifications?

Question #4 – How do you ensure a robust supply chain?

- Supply chain is fixed; few vendors with scale to select
- It is difficult to find a redundant vendor
- Considerations:
    - How do you introduce a second (redundant) supplier for when filing BLA?

    - How quickly do you want it to market? Otherwise put as a post-approval change
    - How do you show comparability of lipids?
    - Should you have to redo formulation development? Or can you just ensure the LNP functions the same
    - Is it appropriate to expand on testing in COA when a new lipid is brought in-house?
    - QA considerations when this comes in – can we negotiate additional tests that meet business quality needs?

Question #3 – Analytical tools used?

- CAD is a popular choice.