Four Considerations when Planning for an RNA Manufacturing Facility

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RNA MANUFACTURING PROCESSES

RNA is manufactured through a multi-step process that necessitates a multi-product facility approach to design. Plasmid DNA (pDNA) is used in the Ribonucleic Acid (RNA) Invitro Synthesis (IVT) reaction and is most commonly manufactured through an E.coli-based bacterial fermentation process. Synthetic manufacture of pDNA is possible but is still in the early development stages for commercial manufacturing. Most manufacturers desire to isolate the bacterial fermentation process from the rest of the RNA drug substance manufacturing process to address contamination and potential quality concerns, requiring dedicated gowning, airlocks, access corridors, and cleanroom suites.

Manufacturing of the drug substance is completed through two distinct process steps, often conducted in separate cleanroom suites: RNA synthesis and encapsulation in the Lipid Nanoparticle (LNP). First, RNA is produced through a multi-step process where it is synthesized, the reaction quenched, and then the RNA chain modified for stability. Numerous purification and concentration steps are required for the RNA process, placing demands on suite size and utility systems. Second, the Lipid Nanoparticle is formed, and an RNA molecule is encapsulated within it. Formation of the LNP particle requires additional larger pieces of equipment for the mixing process and subsequent purification of the encapsulated RNA/LNP particle.

DESIGN CONSIDERATIONS FOR AN RNA MANUFACTURING FACILITY

DPS is routinely engaged in early-stage site selection discussions with our clients and prospective clients in response to the recent growth in RNA manufacturing due to the COVID-19 virus. Throughout these evaluations, we have gained unique insight into the requirements including site selection and design for RNA manufacturing facilities.

Here are four points of consideration when planning for your RNA manufacturing facility:

1

Process Separation

Multiple isolated manufacturing areas may be required to properly separate the pDNA's bacterial fermentation process from the RNA/LNP synthesis process. Further separation of the RNA and LNP processes may be required to mitigate electrical classification zones present. Isolated manufacturing areas require segregation of HVAC systems and additional floor space for gowning areas, corridors, and airlocks. Space for all of these elements and the quality impact of not providing them requires careful upfront planning.

2 Hazardous Material Handling

Unlike many other biologic modalities, preparation of the LNP requires the use of 100% ethanol, a flammable fluid with special handling and storage characteristics. Depending on the process, preparation of the lipid stock solution may occur at elevated temperatures compounding safety concerns. Flammable handling requirements introduce electrical classification challenges complicating equipment layout that is generally not designed for use in classified environments (i.e., intrinsically safe non-sparking components). Similar concerns and design challenges are present due to the storage of flammable materials and managing control areas within the facility. Alternately, some elements may require design as high hazard spaces under the building code if maximum quantities are exceeded.

3 Facility Layout

Building on the needs for Process Separation is the need for careful planning on how available space will support both the overall facility adjacency and layout of systems within the manufacturing suite. For example, larger buffer preparation suites are often required to support the process, and being able to locate buffer preparation central to the RNA/LNP suites minimizes traffic in corridors. Pass-throughs from buffer areas into processing suites can help minimize equipment in the processing suites and optimize tubing management when chromatography/TFF skids can be located opposite the same wall.

The layout of the process suites is important to minimize tubing management challenges and ensure good operability of multiple purification steps within a single suite. The layout of the LNP suite can be especially onerous to manage due to the previously discussed electrical classification challenges, especially when locked into room geometries constraints if an existing facility is to be used for the process. When reviewing an existing facility or planning how to fill an empty building shell, additional considerations should be given for:

- Process suite size, adjacency, and geometry
- Requirements for supply/return corridors, including uni vs. bi-directional flow
- The ability to expand mechanical space to meet utility system demands, including bump-ups if necessary, for tall equipment
- Space for freezer farms, including HVAC considerations for heat rejection
- Location of high hazard rooms requiring exterior walls to meet code

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Site Utilities

When identifying a manufacturing facility for RNA production, special consideration is required for the utility systems necessary to support the process and their impact on building services (i.e. gas, electric, sewer). Commercial-scale RNA processing uses large volumes of Water for Injection (WFI) due to the amount of buffer required for multiple chromatographies and diafiltration steps. Additional WFI is needed to support clean-in-place (CIP) systems. Most of this water must also be disposed of to a pH treatment system and the site sewer. Support of larger WFI systems requires plant steam and process chilled water, both of which place demands on-site services.

Care must be taken to ensure that the facility has the space for the required utility systems and that the site has sufficient gas, power, and sewer capacity to support these systems. Building service upgrades such as power can often take 12-18 months, depending on the municipality. Additional utilities required include Nitrogen, Process Air, Vacuum, carbon dioxide, and sometimes oxygen. It is important to make sure that sufficient mechanical room space is allotted to support these systems.

PLANNING AHEAD IS KEY

Careful and upfront planning is critical to understanding the considerations and requirements of an RNA facility. Whether pre-clinical or commercial manufacturing, our experienced team will help identify and design the essential requirements for your GMP facility.