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Addressing oligonucleotide development challenges from a CRDMO's perspective

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In today's oligonucleotide therapeutic development, to make oligonucleotides "druggable" with enhanced PK/PD properties has always been the focus. There are several promising approaches. Chemistry modifications offer the solution with modified oligonucleotides with enhanced characteristics. Conjugation chemistry utilizes peptides, GalNAcs, antibodies, or lipids to improve stability and uptakes. Formulation designs improve the delivery of fragile oligonucleotides, such as lipid nanoparticles (LNP) and Adeno- associated virus vectors (AAV).

LNP to deliver oligonucleotides

Among the breakthrough formulation designs, LNP delivery is particularly successful. Today, drug formulations incorporating LNP delivery are surging in new oligonucleotide drug development, for example, Onpattro® has been the 1st FDA- approved siRNA drug. LNP has several advantages – First, it offers protection for the pH-sensitive oligonucleotide API; Second, it has been able to access different tissues and can even cross the blood-brain barrier (BBB) to reach the central nerve system (CNS); Third, it can be modified to target different cell types; Finally, it can release the oligonucleotide to the cytoplasm via endosomal escape.

Despite these advantages, LNP formulation development and manufacturing for oligonucleotide therapeutics require "state-of-the-art" capabilities and capacities that are very challenging to build, especially for middle/ large-scale GMP manufacturing for clinical development and commercialization.

With the rapidly increasing amount of clinical-stage oligonucleotide projects, few CDMOs have GMP LNP manufacturing facilities at this moment. The cost of building a new LNP facility, for most other service providers, is high. From the technical aspect, LNP requires additional small molecule chemistry capabilities, as well as customizable lipid synthesis to efficiently handle the diverse lipid design and synthesis requirements. In addition, the corresponding process team and analytical teams are necessary for a functional LNP manufacturing platform.

For a large CRDMO, these problems are out of concern. Building upon a platform that integrates all the capabilities mentioned above, a "one-stop" solution for LNP formulation, including R&D and manufacturing, as well as sterile fill-finish manufacturing, is what oligonucleotide drug developers expect from us.

Oligonucleotide Conjugates

Another hotspot for oligonucleotide drug designs is conjugation. Conjugate designs are ever-changing and increasingly require more integration of capabilities of multiple molecular modalities. This is one of the key advantages of WuXi TIDES that integrates all the necessary chemistry R&D and manufacturing capabilities for monomer/linker, oligonucleotide, peptide, and all related synthetic conjugates under one roof.

For oligonucleotide conjugates, the platform incorporates various conjugation strategies, including PPMO, GalNAc-oligonucleotide, lipid-oligonucleotide, peptide-oligonucleotide, 'drug'-oligonucleotides and dye-labeled oligonucleotide, etc. The principle of our conjugate platform is "custom-tailored" – clients have access to all the necessary expertise for any oligonucleotide designs with comprehensive linker chemistry and topology capabilities. For example, peptide-oligonucleotide conjugate (POC) is gaining increasing popularity. Peptides and peptoids grant pharmacodynamic enhancement to oligonucleotide APIs via their flexible structure and functions. However, these peptides have extensively diverged from the traditional concept of the single-chain short amino acid chain. In this case, large CRDMOs with both strong peptide and oligonucleotide platforms, as well as corresponding linker selection, can provide advanced peptide solutions for POC R&D and manufacturing.

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Especially for the trending new designs, such as glacogon-like peptide (GLP), cell- penetrating peptide (CPP), and cyclic-RGD peptides, clients require more customized solutions. For the sake of timeline, the "ready-to-go" service for conjugation chemistry provided by large CRDMOs is crucial for their outsourcing needs.

Technologies for Sustainability

Furthermore, incorporating new technologies can greatly benefit the project in terms of cost, speed, and sustainability. A wide array of enabling technology often impresses clients. Thin film evaporation (TFE), for example, is an advanced distillation process that is especially suitable for oligonucleotides. Its less heat-intensive drying process protects the stability of fragile molecules such as oligonucleotides and peptides and consumes less energy and costs compared with lyophilization. Based on our experience, other technologies, such as spray-dried dispersion and biocatalysis had also proven effective in enabling clients' projects for faster, greener, and more efficient solutions, and our client did appreciate these options.

Manufacturing Capacity

Throughout our experience, we have observed that capability and capacity constraints are impairing many new oligonucleotide therapeutics' development. The available resources are highly scarce that often require long lead times. When outsourcing, customers should consider not only the experience and expertise but also the team size and large-scale manufacturing capacity to ensure a seamless scale-up for success at later stages.