

# Leading Innovation in TIDES

**Aurisco, the first USFDA inspected generic oligonucleotide API manufacturer is innovating in enzymatic ligation, hybrid solid and liquid phase synthesis, GLP-1 peptide recombinant and SPPS technologies, flow-photochemistry and much more.**

Aurisco Pharmaceutical, a leading global oligonucleotide and peptide (TIDES) and small molecule API manufacturer, recently announced that its site in Yangzhou, China has passed the USFDA inspection this June as the first generic Oligonucleotide API manufacturer in the world. The USFDA pre-approval inspection for Inclisiran Sodium API covered cGMP compliance inspection for oligonucleotides, GLP-1 peptides.

## A New Era in Oligonucleotides

Aurisco's announcement marks more than a corporate milestone; it signals a new era for oligonucleotides. As of August 25, 2026, FDA had approved 24 oligonucleotide medicines, including 12 ASOs and 8 siRNAs, yet no generic oligonucleotide had been approved in the US. However, Paragraph IV competition is intensifying: Leqvio (inclisiran) has one ANDA filed, alongside two Spinraza (nusinersen) ANDAs and one Amvuttra (vutrisiran) ANDA. Generic oligonucleotides are moving closer to US patients.

Oligonucleotides are short, synthetic DNA or RNA strands designed to bind specific genetic sequences and regulate gene

expression. Antisense oligonucleotides (ASOs) bind targeted RNA to modify its processing or function, whereas small interfering RNAs (siRNAs) promote RNA degradation and gene silencing. GalNAc conjugation enables efficient, targeted delivery to liver cells. Their sequence-based mechanisms make oligonucleotides a powerful therapeutic platform for genetic and rare disorders, as well as increasingly prevalent diseases.

To help generic companies develop safe and affordable versions of these medicines, USFDA has published 18 product-specific (draft) guidances (PSGs) for generic oligonucleotide drug products with 2 additional planned for February 2027. Most PSGs follow a common regulatory approach that allows applicants to request a waiver of *in vivo* bioequivalence studies based primarily on demonstrating API sameness and manufacturing-process robustness. Patisiran is the principal exception because its formulation incorporates the siRNA within a complex lipid nanoparticle delivery system.

## The Importance of the API

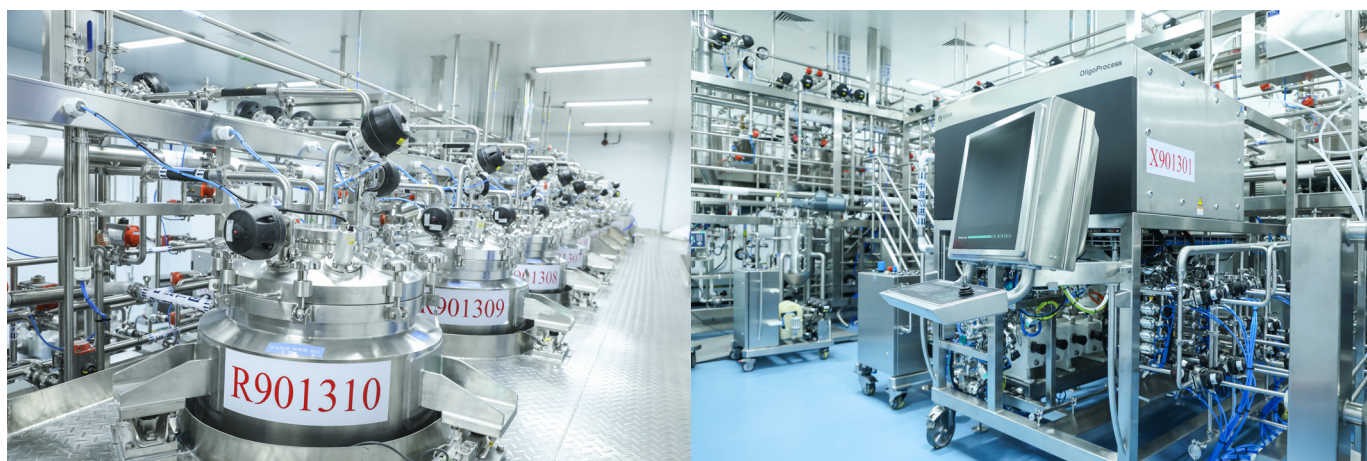
Pre-ANDA meetings are fundamental to ensure the regulatory strategy is adequate and data provided by the API manufacturer is sufficient. Besides Q1/Q2 formulation sameness, the USFDA requires:

- Side-by-side comparative characterisation of at least three test and three RLD batches;
- Confirmation of primary sequence and chemical structure;

- Comparison of diastereomeric composition;
- Evaluation of phosphorothioate-to-phosphodiester ratios, where applicable;
- Orthogonal methods such as MS/MS, NMR, LC and duplex melting temperature;
- Physicochemical characterisation using CD, FTIR, DSC, SEC and SV-AUC or validated alternative analytical methods, as appropriate;
- Comparative impurity profiling;
- Immunogenicity and inflammation-risk assessment.

The ANDA holder and API manufacturer should be able to provide comprehensive method validation data to demonstrate the adequacy (e.g., sensitivity, resolution and discriminative power) of the selected methods in demonstrating the sameness between the test and reference product. The demonstration of resolution of the analytical methods and comparative impurity profiling requires the synthesis and characterisation of a significant number of potential process impurities. When solid-phase synthesis is used, each step can generate at least N-1 and N+1 impurities, on top of degradation impurities. As such, an ASO may require over 50 impurity standards, and a siRNA may require over 100 impurity standards to be synthesised and characterised. Behind every oligonucleotide DMF there is a ton of analytical work.

Another challenge for generics is the access and cost of the RLD batches to support the API and FDF development and sameness



cGMP Oligonucleotide Manufacturing at Yangzhou Aurisco

| Active Ingredient or revised | RLD        | Modality                                       | Dosage form/route      | PSG issued or revised | PSG_NDA |
|------------------------------|------------|------------------------------------------------|------------------------|-----------------------|---------|
| Nusinersen sodium            | Spinraza   | ASO, 2'-MOE phosphorothioate                   | Intrathecal solution   | Feb 2022              | 209531  |
| Eteplirsén                   | Exondys 51 | PMO antisense oligonucleotide                  | IV solution            | Nov 2022              | 206488  |
| Patisiran sodium             | Onpattro   | Lipid nanoparticle-formulated siRNA            | IV solution            | Nov 2022              | 210922  |
| Inotersen                    | Tegsedi    | ASO; 2'-MOE phosphorothioate                   | Subcutaneous solution  | Nov 2022              | 211172  |
| Golodirsén                   | Vyondys 53 | PMO antisense oligonucleotide                  | IV solution            | Feb 2023              | 211970  |
| Viltolarsén                  | Viltepso   | PMO antisense oligonucleotide                  | IV solution            | Feb 2023              | 212154  |
| Givosiran sodium             | Givlaari   | GalNAc-conjugated siRNA                        | Subcutaneous solution  | May 2023              | 212194  |
| Casimersen                   | Amondys 45 | PMO antisense oligonucleotide                  | IV solution            | May 2023              | 213026  |
| Lumasiran sodium             | Oxlumo     | GalNAc-conjugated siRNA                        | Subcutaneous solution  | Aug 2023              | 214103  |
| Vutrisiran sodium            | Amvuttra   | GalNAc-conjugated siRNA                        | Subcutaneous solution  | Aug 2023              | 215515  |
| Inclisiran sodium            | Leqvio     | GalNAc-conjugated siRNA                        | Subcutaneous solution  | May 2023;             | 214012  |
| Tofersen                     | Qalsody    | ASO, 2'-MOE phosphorothioate                   | Intrathecal solution   | Nov 2023 (rev)        | 215887  |
| Nedosiran sodium             | Rivfloza   | GalNAc-conjugated siRNA                        | Injectable solution    | Aug 2024              | 215842  |
| Eplontersen                  | Wainua     | GalNAc-conjugated ASO; 2'-MOE phosphorothioate | Subcutaneous solution  | Aug 2024              | 217388  |
| Avacincaptad pegol sodium    | Izervay    | PEG-conjugated RNA aptamer                     | Intravitreal solution  | Nov 2024              | 217225  |
| Fitusiran sodium             | Qfittia    | GalNAc-conjugated siRNA                        | Subcutaneous solution  | Feb 2026              | 219019  |
| Imetelstat sodium            | Rytelo     | Lipid-conjugated ASO phosphorothioate          | Powder for IV solution | May 2026              | 217779  |
| Olezarsén                    | Tryngolza  | GalNAc-conjugated ASO; 2'-MOE phosphorothioate | Subcutaneous solution  | May 2026              | 218614  |
| Donidalorsén                 | Dawnzera   | GalNAc-conjugated ASO; 2'-MOE phosphorothioate | Subcutaneous solution  | Aug 2026              | 219407  |
| Plozasiran                   | Redemplo   | GalNAc-conjugated siRNA                        | Subcutaneous solution  | Planned Feb 2027      | 219947  |

demonstrations. In certain oligos, the sourcing of 3 vials of 3 independent batches can easily exceed USD1.5M, a significant upfront investment that deters smaller generic companies.

#### NEW Oligo Synthesis Platform

Most approved oligonucleotide medicines still target rare or ultra-rare diseases but

improving knowledge of disease mechanisms is expanding their potential into larger cardiovascular, degenerative and metabolic indications. Inclisiran and vutrisiran illustrate this shift toward substantially larger patient populations. These indications will require greater manufacturing capacity, lower costs, and more sustainable production technologies.

Enzymatic ligation emerges as an alternative to fully solid-phase synthesis for long and complex oligonucleotides. Short, chemically synthesised fragments are joined using ligases or polymerases, avoiding cumulative coupling inefficiencies, declining yields, and increasing impurity burdens associated with conventional solid-phase synthesis. Assembling shorter high-purity fragments can improve final

product quality, scalability, and manufacturing robustness while reducing synthesis cycles and purification demands. This approach can also improve sustainability. Conventional oligonucleotide synthesis consumes substantial quantities of acetonitrile, activators, oxidants, and protecting-group reagents. Fewer chemical coupling cycles can reduce solvent consumption, process mass intensity, and hazardous waste. Progress in enzyme engineering, template-directed ligation, and enzymatic error correction is expanding the industrial applicability of hybrid chemical-biological processes.

To combine chemical synthesis with enzymatic ligation, Aurisco is developing intelligent design and directed evolution methods for non-natural nucleic acid ligases. Its scientists use AI-assisted enzyme design to enable recognition and ligation of modified phosphorothioate-containing substrates, while optimising ligase expression and production for reactions conducted at high substrate concentrations. These capabilities will support efficient manufacturing of increasingly long, modified, and structurally complex therapeutic oligonucleotides at commercially relevant scale while improving product consistency and reducing environmental burdens across the overall manufacturing global lifecycle.

## Continuous Flow Phosphoramidite Synthesis

A key contributor to the COGS of oligonucleotide medicines is the phosphoramidite cost. Due to the inherent inefficiency of standard solid-phase synthesis and extensive purification, each kilo of a 20-mer ASO consumes between 5kg and 15kg of amidites and siRNAs require double of that. Leveraging years of experience in the development of flow-chemistry processes, Aurisco has developed continuous flow process technology and equipment to efficiently manufacture customized amidites, eliminating the use of expensive catalysts, bases and reducing the consumption of expensive reagents, solvents and water. With increased yields and reduced cycle-times, continuous flow is the most sustainable and cost-efficient way to manufacture phosphoramidites.

## Synthetic and Recombinant Peptide Synthesis Platforms

Recent advances in structural biology, recombinant biologics, and new synthetic and analytic technologies have significantly accelerated the discovery process. As of March 2024, there were 119 peptides with

FDA approval for therapeutic or diagnostic purposes, with six approved in 2025 alone with more than 150 peptides in clinical trials and another 400–600 peptides in preclinical studies.

The choice between recombinant and synthetic peptide manufacturing has significant implications for development timelines, production capacity and costs, environmental sustainability, and the regulatory approval pathways applicable to both innovative and generic products.

Recombinant synthesis uses biotechnology to introduce a plasmid containing DNA encoding a semaglutide precursor into host cells such as *S. cerevisiae* or *E. coli*. The engineered host translates the recombinant DNA into the intended peptide chain. The resulting intermediate is then recovered and purified using biochemical, chromatographic, and filtration techniques that remove biological contaminants and process-related byproducts. This recombinant route, selected by Novo Nordisk for commercial semaglutide production, supports efficient biosynthesis followed by downstream purification.

In solid-phase peptide synthesis (SPPS), amino acids are sequentially added to a peptide chain anchored to a solid resin. After the first amino acid is attached, repeated protection, deprotection and coupling cycles extend the sequence. Each cycle removes an Fmoc or Boc protecting group to expose the reactive amine, which is coupled with the next protected amino acid. Once the target sequence is complete, the peptide is cleaved from the resin and purified. Hybrid processes use SPPS to produce shortmers and then combine them into the final peptide by liquid-phase peptide synthesis (LPPS). Eli Lilly uses this kind of route to produce tirzepatide at commercial manufacturing scale.

## Generic GLP-1 Peptides

Generic peptides require extensive characterisation of primary and secondary structure, oligomeric and aggregation states, and biological activity to demonstrate sameness with the reference listed drug (RLD). Primary amino acid sequence and disulfide-bond positions are critical for establishing drug-substance sameness. Generic formulations are usually qualitatively and quantitatively identical to the RLD because new excipients may alter stability and promote dimers, higher-order aggregates, or other species that could affect efficacy, safety, and immunogenicity. Peptides exhibit predominantly random-coil conformations

with varying proportions of alpha-helices or beta-sheets. Because structural organisation can influence biological activity, secondary structure should be evaluated during comparative characterisation. However, many peptides are highly conformationally flexible, and their higher-order structures are governed primarily by thermodynamic equilibrium rather than kinetic folding. Consequently, when a generic peptide has the same amino acid sequence and an equivalent qualitative and quantitative formulation, its higher-order structure can generally be inferred to match that of the RLD.

The USFDA Guidance for Industry “ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin” defines requirements for generic synthetic peptides referencing recombinant DNA-derived drugs. For semaglutide, FDA has issued PSGs for oral and injectable generics, including the possibility of waiving *in vivo* bioequivalence studies for the injectable product. The principal challenge is demonstrating comparable quality and safety because manufacturing may introduce impurities absent from the reference product. The July 2026 revised semaglutide PSG\_209637 requires sameness to be demonstrated at release and at the end of shelf life, emphasising control of API-related and non-API-related impurities. This revision may favour recombinant semaglutide because recombinant production can reduce process-related impurities and lower the risk of higher-order structural changes and aggregation during storage. These controls are particularly important because peptide-related impurities often closely resemble the active peptide in sequence and physicochemical properties, making them difficult to detect, characterise, quantify, and control throughout the product lifecycle.

Beyond analytical comparison of peptide-related impurities and the primary and secondary structures of the generic and RLD, FDA may require comparative *in vitro* studies, animal studies, clinical pharmacokinetic and pharmacodynamic equivalence studies, or clinical trials to establish the safety and effectiveness of a synthetic peptide. *In vitro* bioassays linking structure to activity are essential for characterising higher-order structure and biological function in complex peptides. Biological activity may be assessed through animal-based, cell-based, biochemical, or immune-response assays, particularly when confirmatory evidence is needed to demonstrate sameness. FDA's tirzepatide PSG recommends comparative



assessment of secondary structure, oligomeric and aggregation states, and biological activity. If clinical evidence is necessary, submission under section 505(b) of the FD&C Act may be required.

Outside the US, some generic peptides may follow biosimilar pathways, requiring high similarity in manufacturing quality, biological activity, clinical safety and efficacy, and immunogenicity. EMA guidance requires applicants to quantify differences between chemically synthesised and recombinant peptides and demonstrate comparability using a broad panel of side-by-side analytical methods applied to the synthetic product and the EU-sourced recombinant reference product. The overall evidence package

must therefore integrate physicochemical characterisation, functional testing, impurity assessment, and, where justified, targeted comparative clinical confirmation studies.

#### Conclusion

The generic landscape in new modalities such as peptides and oligonucleotides is changing fast and companies like Aurisco are leading the way, offering demonstrated experience, regulatory knowledge and compliance in the manufacturing of peptide and oligonucleotide APIs for both generic and innovators. Using modern facilities and advanced science, Aurisco is a CDMO collaborating with the best pharmaceutical companies in the world and with regulators to make new and generic medicines accessible to patients.



**Rafael  
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Rafael Antunes is the Vice President of Marketing and Business Development of Aurisco Pharmaceutical in Europe. He has over 20 years of Pharma Industry Experience, working in International European and Chinese, Generic and CDMO companies. Broad experience in multiple roles in Process Chemistry R&D, Tech-Transfer, Scale-up, Pilot-Scale and Commercial cGMP Manufacturing, Procurement, Management, Product Development and Licensing and Business Development. Strong Scientific and Business Management backgrounds and relevant HSE, Quality and Regulatory experience. Has been a qualified cGMP and ISO14001 auditor and participated as industry representative in RX360 and EFCG (European Fine Chemicals Group – a pharma industry CDMO lobby group, member of the broader European Chemical Industry Council (CEFIC). He represented the EFCG at USFDA GDUFA II implementation meetings and Regulatory Science meetings. Championed the adoption of Science Based targets (SBTi), Ecovadis Sustainability ranking and joined the Sustainable Procurement Pledge (SPP).

