Scientific Poster Session

n-lorem FOUNDATION

Nano-rare Patient Colloquium 2025

Monday, October 20 | 5:15 – 6:15 pm EST

Ensuring Quality at Every Step in our ASO Manufacturing and Formulation

Our approach to antisense oligonucleotide (ASO) manufacturing ensures rigorous quality control from lead identification through GMP production. This poster outlines how, once a lead ASO is selected, we assess key development risks and timelines to inform the strategy for GMP drug substance manufacturing—either in parallel with or following toxicology batch production. The selected sequence is transferred to the drug substance CMO, and documentation preparation begins. The GMP process involves several steps: amidite preparation, solid-phase synthesis, cleavage and deprotection, purification, ultrafiltration, and lyophilization.
GMP drug substance is then transferred to the drug product CMO where it is further processed through formulation, sterile filtration, and filling into ready for dosing vials.
Quality is ensured through comprehensive analytical testing, including HPLC purity/impurity profiling, sterility assessment and annual stability testing. These activities are executed in close partnership with trusted CDMOs to ensure consistency and compliance with regulatory standards.

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Introduction

Challenges specific to ASO manufacturing for nano-rare patients

- Typical drug manufacturing takes years for one singular drug; ASOs are patient-specific and require a specialized ASO sequence for each nano-rare patient
- Manufacturing at a nano-rare scale

Our Approach

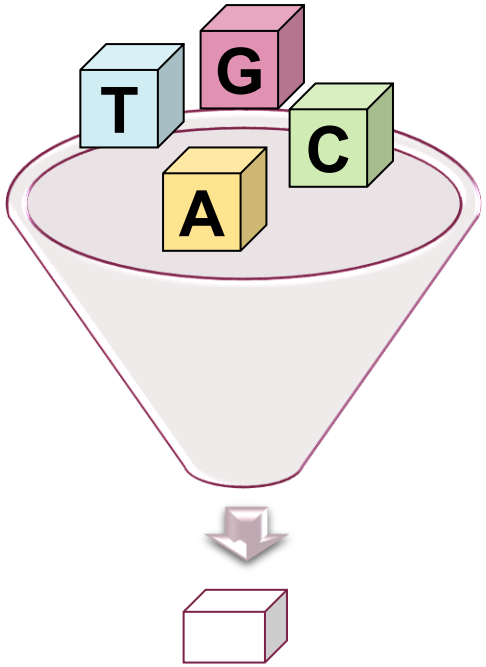
- Careful selection of approved CDMOs with capabilities for our processes
- Utilize a platform approach due to the similar nature of ASOs
  - Base templates, SOPs, and quality documentation to reduce startup time
  - Improves operator efficiency, minimizes oversight errors
  - Standardization of analytical testing across programs

Antisense Oligonucleotide Manufacturing

Amidite Preparation

Amidites are the building blocks for ASOs and are manufactured or procured through the CDMO's qualified vendors.

Once received, the amidites are further tested to confirm they are within specification and in sufficient quantity for the ASO batch.

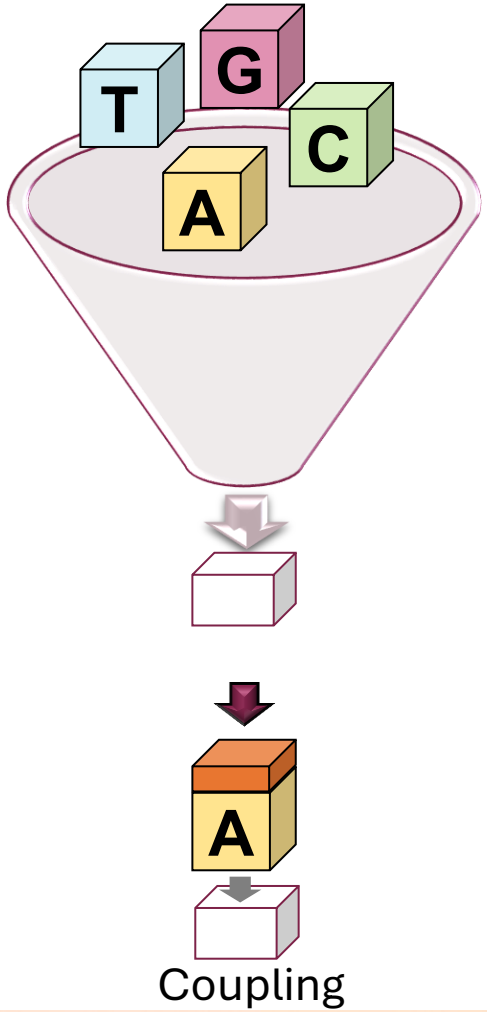


Antisense Oligonucleotide Manufacturing

Oligonucleotide Synthesis – Coupling

(1) A base solid support is selected for the specified oligonucleotide chemistry

(2) A coupling solution of the first nucleotide base of the target sequence is prepared and added to the chain. Coupling solution is prepared in excess to ensure successful coupling. Once coupling is complete, the excess will be washed away using solvent.



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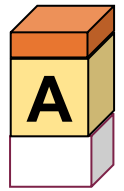
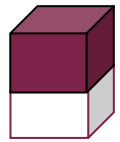
Oligonucleotide Synthesis – Oxidation and Capping

(3a) The chain is treated to aid in stabilizing the new linkage.

(3b) To prevent any unwanted growth, a capping solution is added to ensure no unreactive site remains.



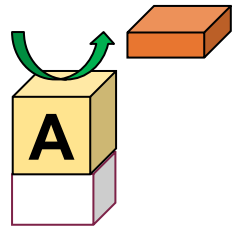
Oxidation



Capping

Antisense Oligonucleotide Manufacturing

Oligonucleotide Synthesis – Deprotection
(4) Deprotection uses an acid to remove the protecting group on the nucleotide base.



Deprotection

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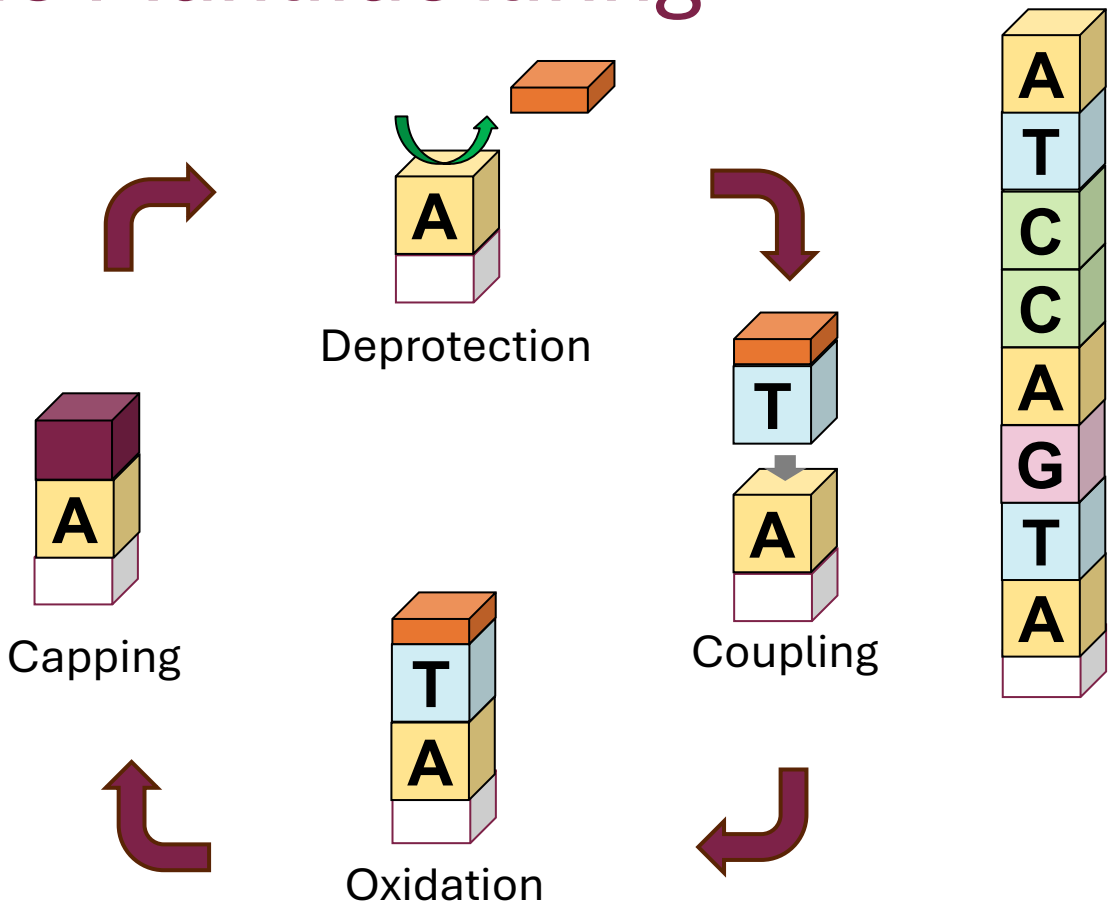
Oligonucleotide Synthesis – Repetition of cycle

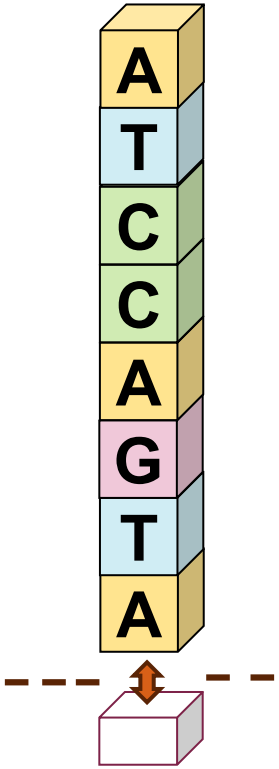
(5-7) Deprotection, coupling, oxidation, and capping steps are repeated to add subsequent nucleotide bases in the sequence until the desired oligonucleotide is synthesized.

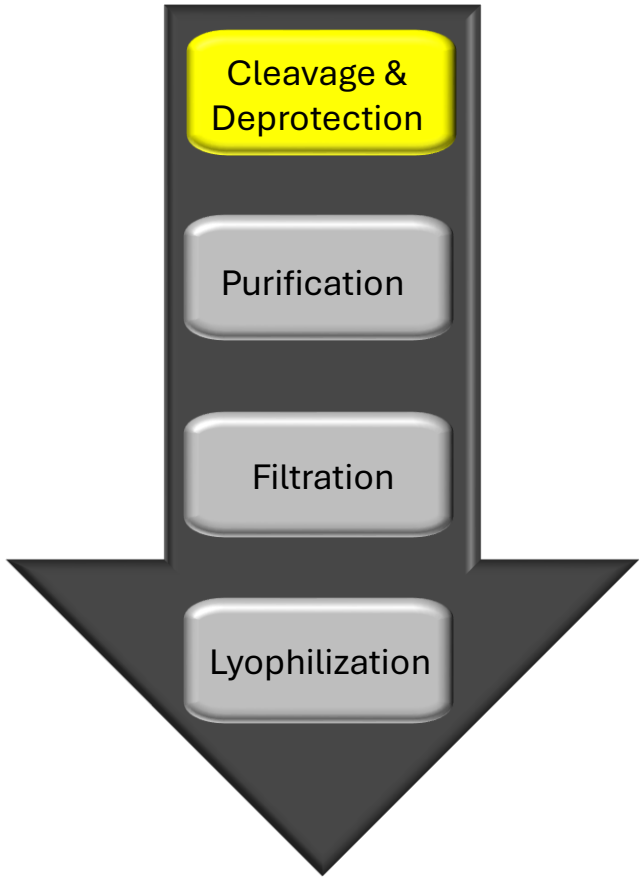


Antisense Oligonucleotide Manufacturing

Downstream Processing

Cleavage and final deprotection removes the amino groups and cleaves the desired oligonucleotide from the solid support.



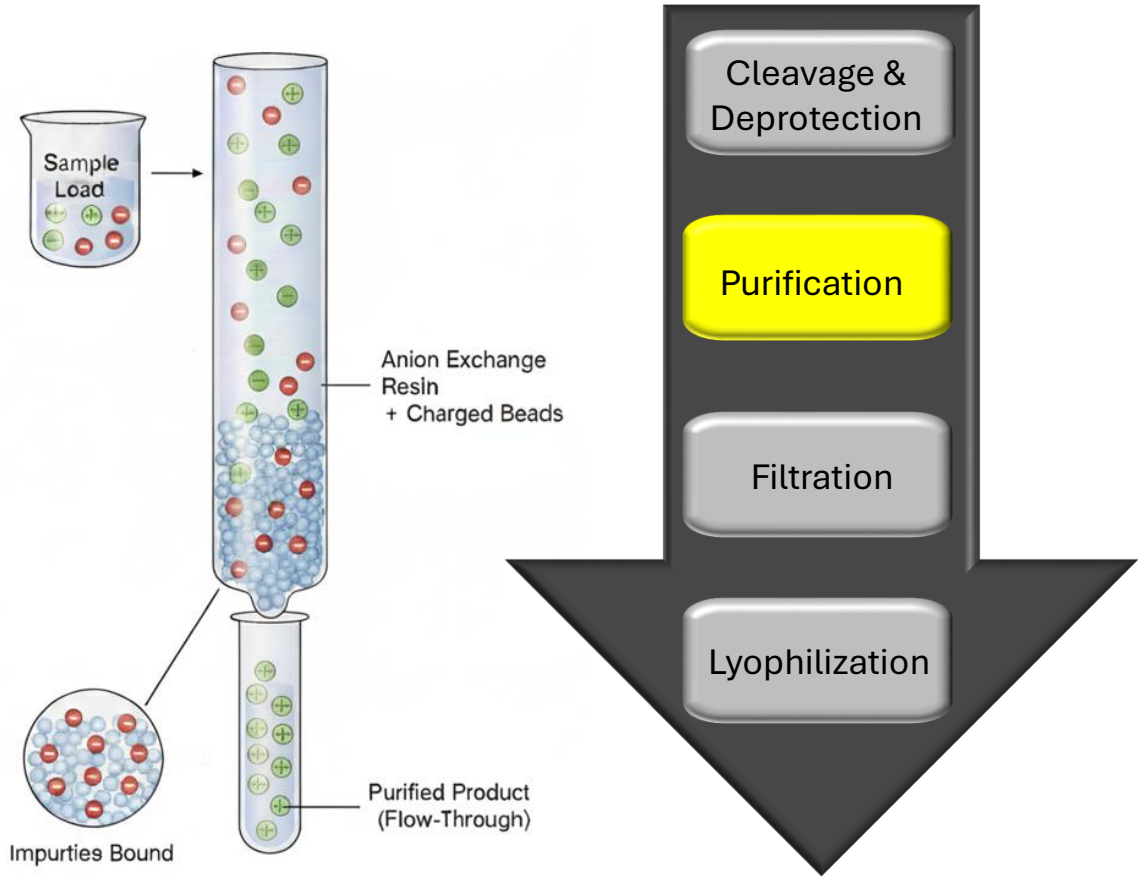


Antisense Oligonucleotide Manufacturing

Downstream Processing – Purification

Anion exchange (AEX) purification uses a chromatography system such as a Cytiva AKTApure where the oligo solution is loaded onto a column and eluted using various buffers.

Purification uses a technique called fractionation which separates the solution based on different biophysical properties such as size, charge, solubility.

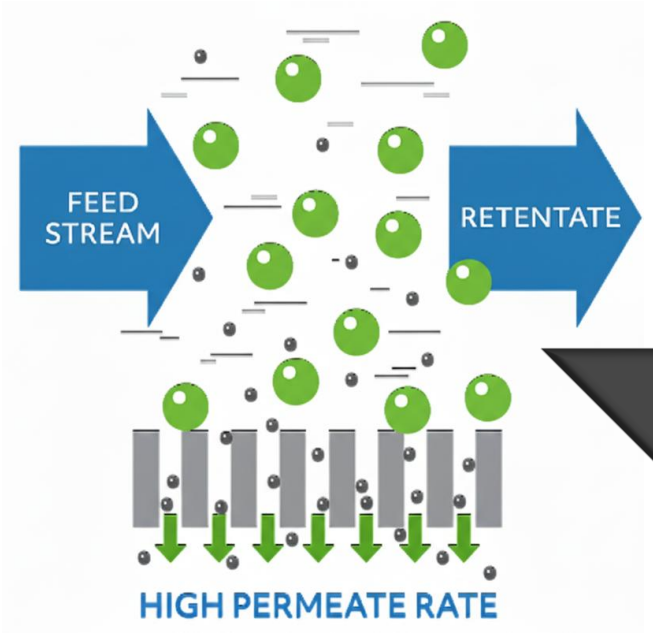


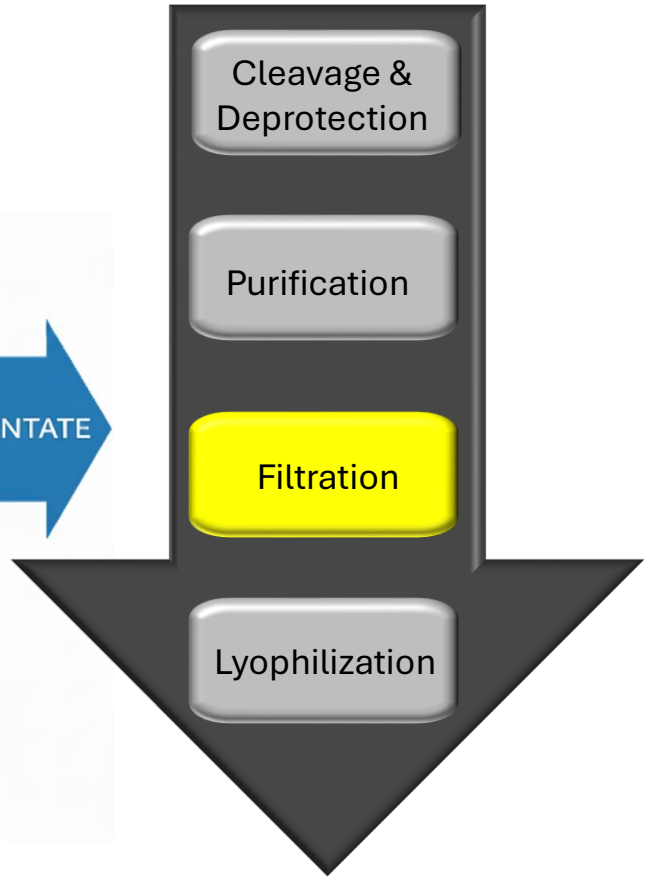
Antisense Oligonucleotide Manufacturing

Downstream Processing – Filtration

Fractions containing product peak are collected and tested on analytical U/HPLC. The ones that pass criteria are taken for ultrafiltration.

Filtration removes salts and smaller impurities while retaining the desired oligonucleotide.



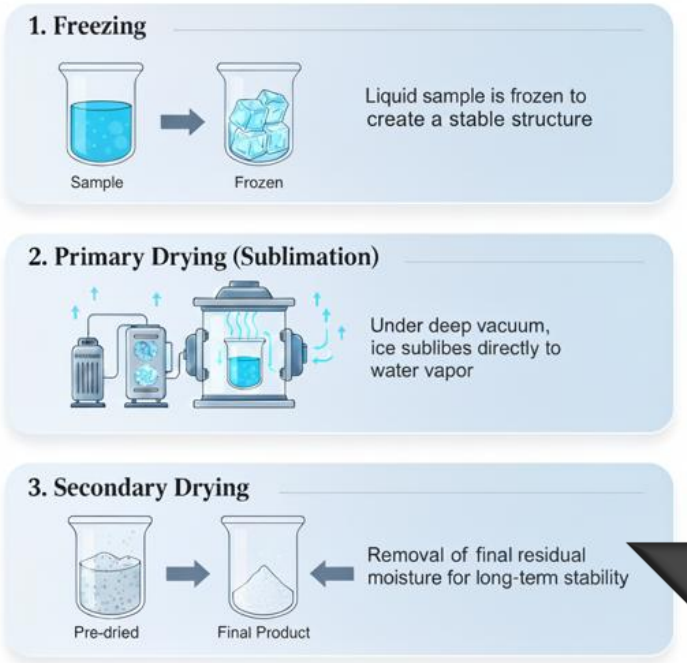


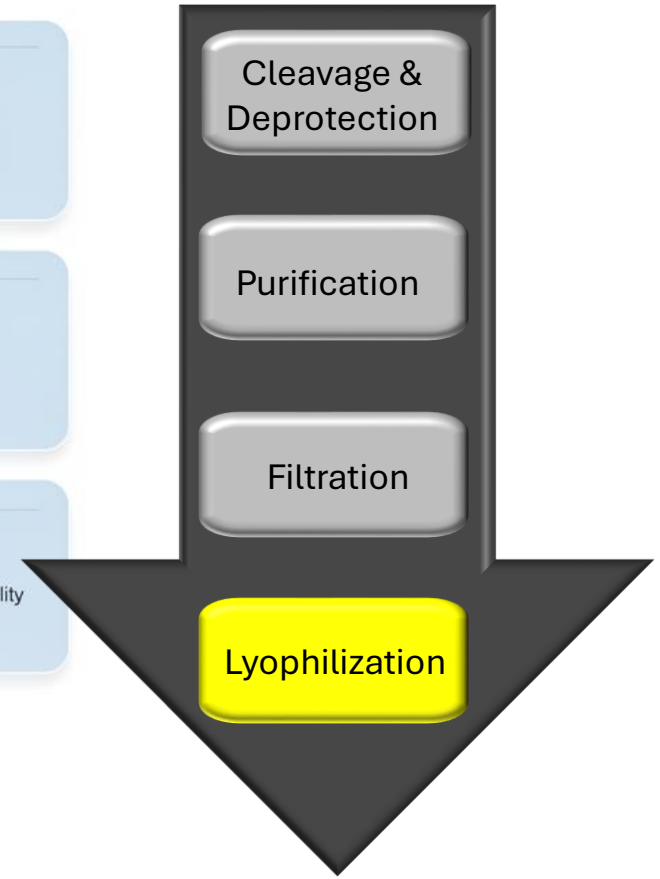
Antisense Oligonucleotide Manufacturing

Downstream Processing – Lyophilization

Lyophilization freeze dries the collected liquid solution into a dried solid by removing water while the solution is under vacuum.

The final isolated oligonucleotide, now in powder form, is tested analytically for tests such as purity, water content, identity, sodium content, and microbiological.





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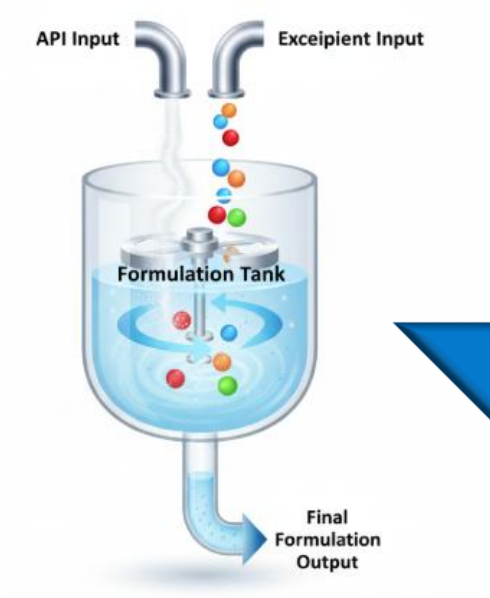
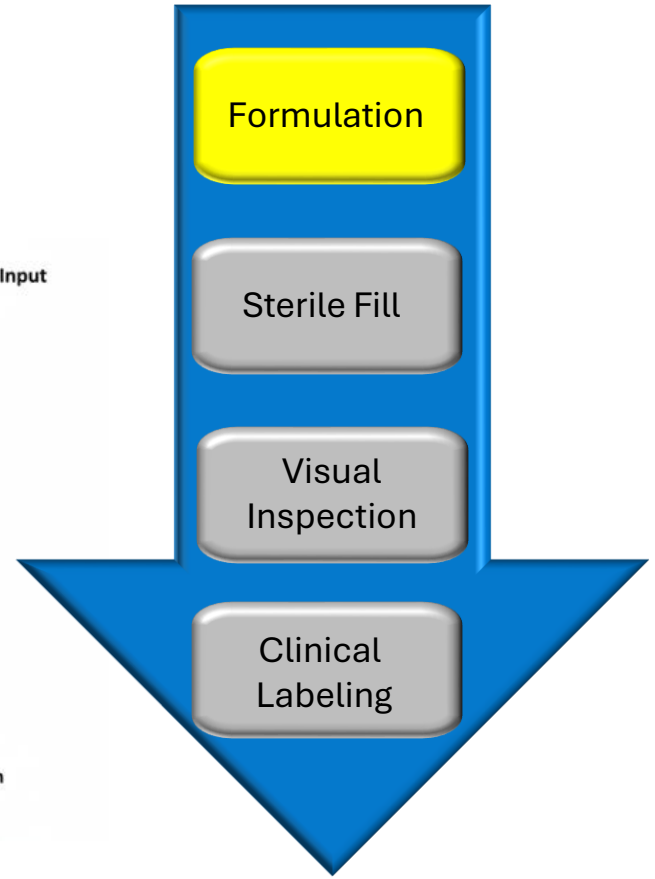
Drug Product Formulation

The dried drug substance or active pharmaceutical ingredient (API) is then reconstituted in a formulated buffer which would be more ideal for drug product administration.

Formulated buffers and any intermediate solution undergo in-process testing to verify specifications for pH, concentration, osmolality, density are met prior to sterile fill.

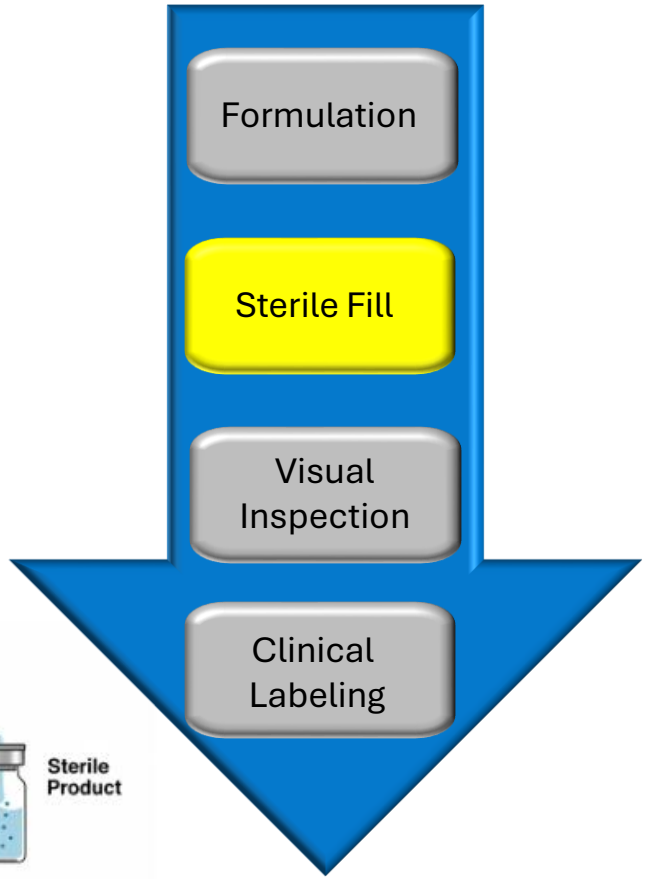


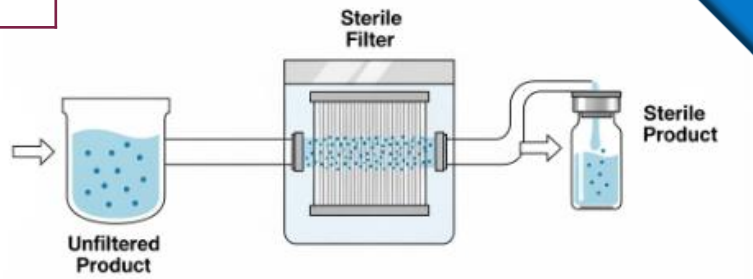


Antisense Oligonucleotide Manufacturing

Sterile Fill and Finish

Sterile filtration is a process step which removes or reduce microbial contaminants from liquids. It typically involves utilizing specific filters with extremely small pore sizes.





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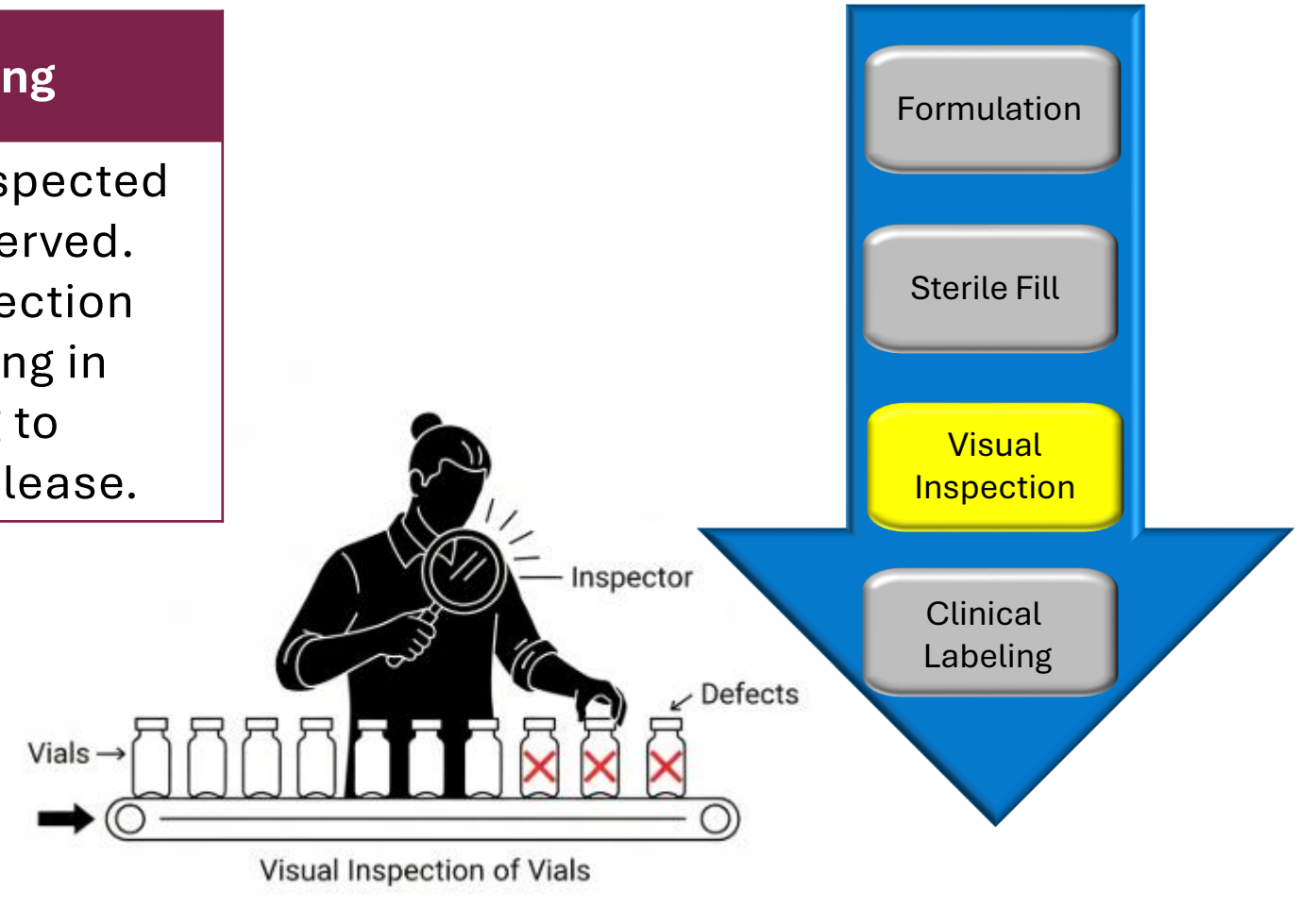
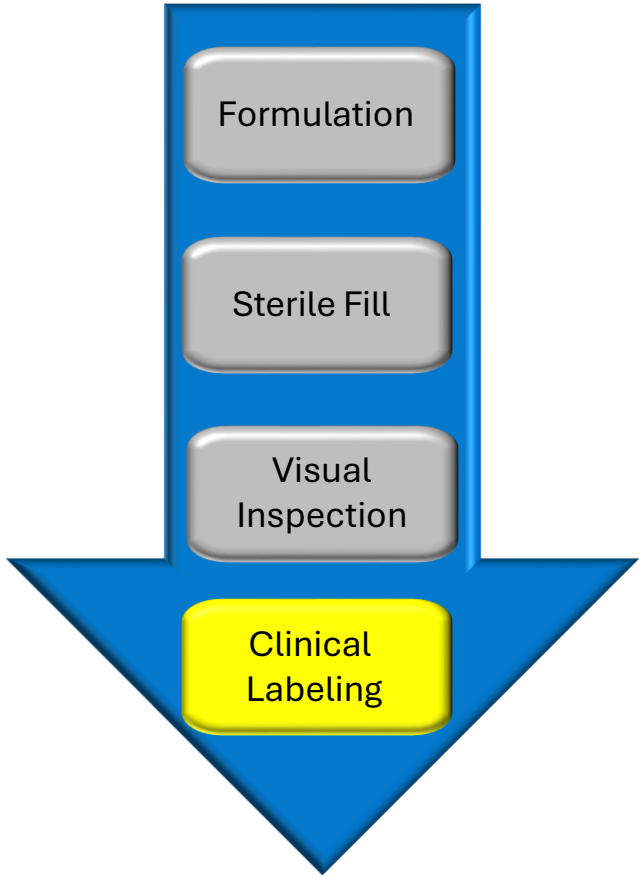
Downstream Processing

Samples are then visually inspected to assure no defects are observed. Samples passing visual inspection are pulled for analytical testing in parallel with clinical labeling to reduce turnaround time of release.



Antisense Oligonucleotide Manufacturing

Downstream Processing
Clinical labeling and packaging appropriately identifies the drug product and manufacturing information.



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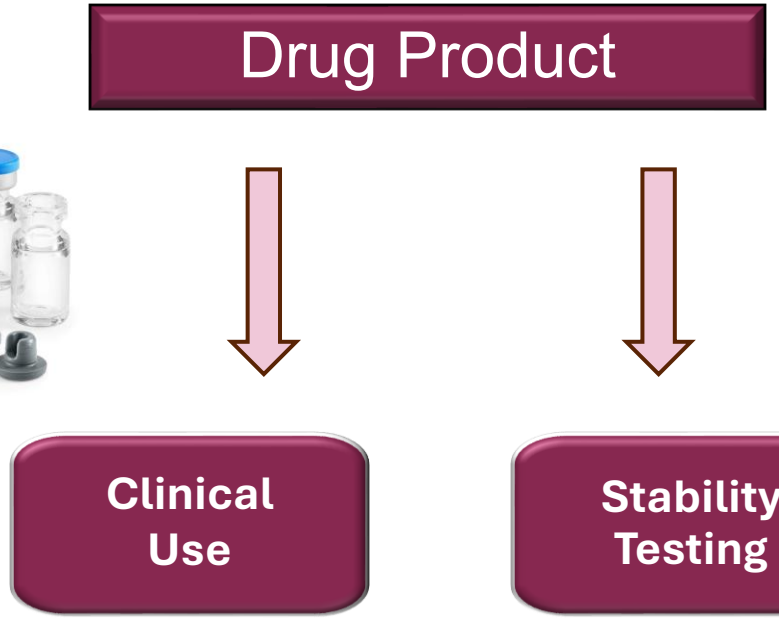
Clinical Use and Ongoing Stability

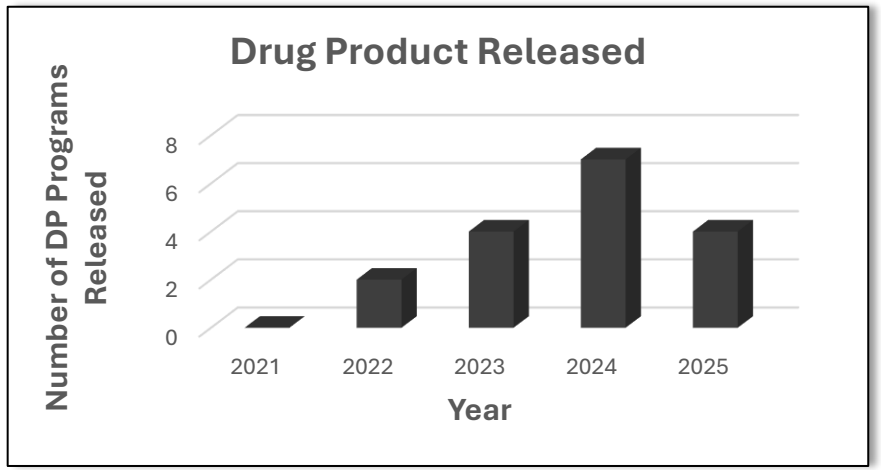
Once all specifications are met and documentation are reviewed for product release, the packaged drug product are sent to a third-party logistics storage facility and ultimately to the pharmacy of the institution treating the patient.

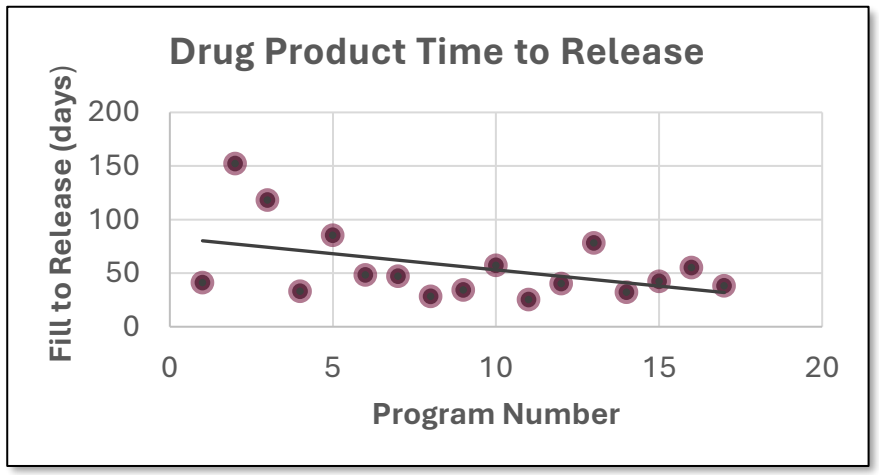
In parallel, the manufactured batch undergoes routine testing to ensure the product is stable and meets all specifications annually.



Key Metrics

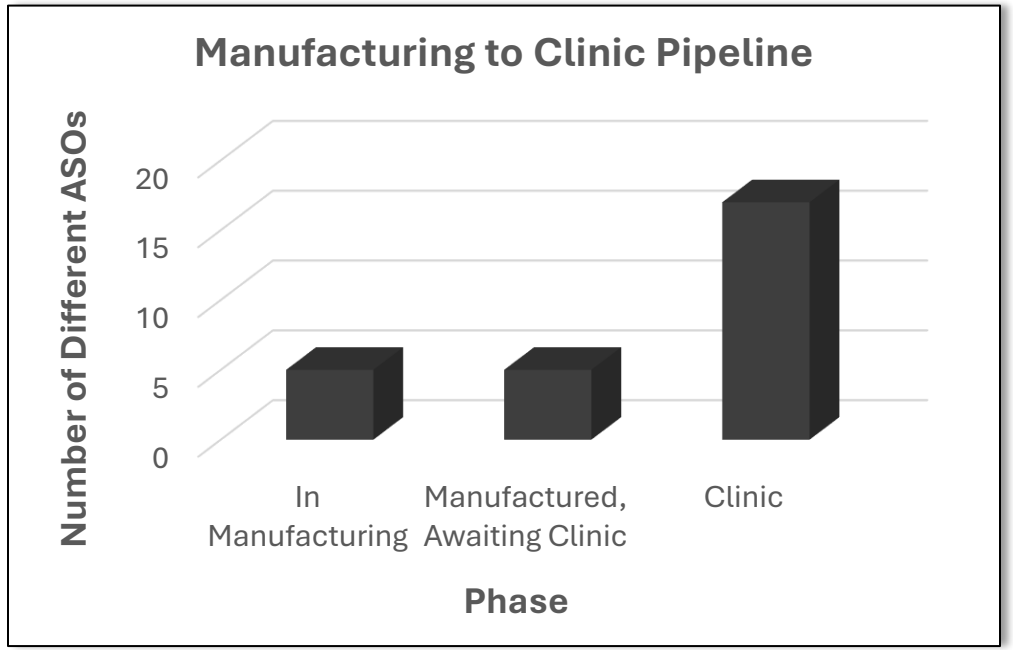
- Number of approved CDMOs have grown from 0 in 2020 to 5 in 2025
- Number of new drug products manufactured has increase year over year
- The platform approach has:
  - Allow for more efficient and consistent manufacturing time
  - Reduced manufacturing defects further allowing for more timely release

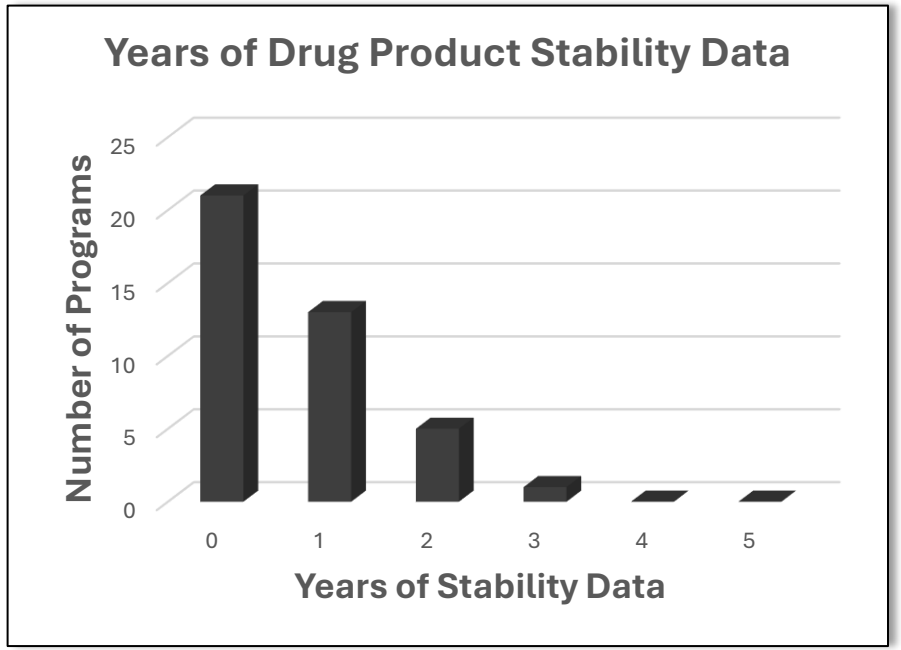




Key Metrics

•As the number of completed programs grows, so does the quantity of data available to further support our understanding of the robustness of ASOs





We would like to thank all of our CDMOs, partners, and the whole n-Lorem team, who are making this work possible

Thank you

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