The Fundamentals of Oligonucleotide Manufacturing

OLIGONUCLEOTIDE SYNTHESIS MARKET OUTLOOK



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>300 candidates in clinical trials

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THE GOLD STANDARD: SOLID PHASE SYNTHESIS

Goal: Achieve scalable and consistent oligonucleotide synthesis

Strategy: Solid-support flow-through synthesis columns for midto large-scale processes



Considerations:

- Synthesis column must be able to accommodate back-and-forth swings in volume resulting from solvent interactions
- Key driver of yield is uniform column flow distribution of amidite and reagents across all bead surfaces of the solid support



CLEAVAGE & DEPROTECTION

Goal: Cleavage of the crude oligo from the solid support, and removal of the protecting groups

Strategy: Amine wash at elevated temperatures between 30-60°C depending on the molecule and the process (RNA requires additional cleavage step) typically conducted manually in a stand-alone vessel

Considerations:

 Fully automated software-controlled systems to manage both cleavage and deprotection validated for mid- to large-scale GMP manufacturing are available

PURIFICATION: SYSTEMS

Goal: Separate full-length target oligos from undesired shortmers and longmers

Strategy: Reversed phase (RP) or ion exchange (IEX) chromatography



Considerations:

- Consistent and precise gradients for effective impurity removal and high recovery
- Hygienic design
- Safety-rated for flammable solvent-based RP purification
- Automation capabilities with intuitive UI









PURIFICATION: COLUMNS

Dynamic axial compression (DAC) column system



Mid-sized oligonucleotides favor the small beads with small pore sizes for resolution and throughput

Considerations:

- Columns for oligos must withstand backpressures of 10-50 bar, depending on bed height, temperature, eluent conditions, and flow rate
- Use a reproducible platform system for packing versus manual processes
- Qualify the packing with one or more column performance tests



OCELOT SYSTEM CONTROL

https://fluidmgmt.ak-bio.com/

All automated systems from Asahi Kasei Bioprocess are powered by OCELOT™ System Control — easyto-use, universally compatible software.