An Engineer’s Perspective on Oligonucleotide Manufacturing and Applications from the Peptide Field

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www.cordenpharma.com
Overview

➤ The peptide field has experienced significant growth in demand over the past 20 years.

➤ This growth has fueled the need for peptide process & equipment innovation.

➤ Positive indications suggest that oligonucleotides are on the cusp of the same type of growth and need for creative thinking.

➤ There are many applications from the peptide field that can be applied to oligo manufacturing!
Outline

- Growth & innovation drivers in the peptide field
- Raw Material Challenges
- Peptide & Oligo Unit Operations
  - Scale-Up Considerations
  - Innovation Opportunities
Drivers for Peptide Growth

Increasing peptide demand in the late 1990’s

- Peptide drug substance requirements were typically < 10 kg/y
- Difficult and expensive to synthesize
- Fewer than 10 approved synthesized peptide therapeutics grew to more than 40 within 10 years
Drivers for Peptide Innovation

The T-20 Example

- New type of HIV therapeutic
- Unprecedented scale

Kgs forecast early 2000s to 6 Tons in < 5 years

- Poor isolation properties
- Supply chain challenges
Raw Material Challenges

**Increased Supply Chain Complexity**

- As T-20 demand increased so did the raw material challenges
- Supplier availability, expertise, & large scale capacity
- Supplier relationship management was key
- Quality concerns → understand purity profiles and effects
- Heavy solvent usage meant manufacturing infrastructure required, recycling considerations
- For comparison without solvent recycling,
  - ~500 L ACN per 1 kg peptide
  - ~2300 L ACN per 1 kg oligo
Typical Process Unit Operations

Peptides

Synthesis → Purification → Concentration → Isolation & Drying

Oligonucleotides

Experts taking care.
Peptide Synthesis Scale-Up

T-20 Example

- Demand required new equipment, approach
- Existing 10 m² ANFD retrofitted for SPPS
- Commercial SPPS went from 22 L to 10,000 L
- Economies of scale make sense since synthesis is lengthy

20 Days/Synthesis
22 L

20 Days/Synthesis
10,000 L
Oligonucleotide Synthesis Scale-Up

- Synthesizers commercially available
- Efficient plug flow reactor design
- Readily scale-able $\to$ $\mu$mol to mol batches
- Quick synthesis, $\sim$1 day
- Auxiliary equipment properly sized
- Changeover is key
Effect of Synthesis Changeover Time

20-mer Builds – 20 d peptide & 20 h oligo

- Assume 100% capacity at a 6 h changeover for 1 year

- 25% Loss of peptide capacity
- 85% Loss of oligonucleotide capacity

Synthesis 1
Synthesis 2

7d Changeover
Increasing Capacity Requires Infrastructure

*Large-capacity solvent storage, handling and recovery is required for higher production volumes*

- ✓ Reagent make-up equipment
- ✓ Column packing & unpacking methods
- ✓ Cleaning strategy
- ✓ Proper change-over management
Purification Scale-Up

Peptides – T-20 Example

- Throughput required 100 cm column, largest one made at the time!
- 6 T/y meant >2 kg/injection
- Plus supporting equipment & infrastructure – buffers, fractions, waste handling, and loads of ACN
- Chromatography scales well, 1 cm → 100 cm
- Developed UPLC fraction method for quick analysis

Oligonucleotides

- Largely similar to peptides
- Balance column size, resin cost and plant time
Choosing Purification Column

Balance production time & resin cost

- 5 cm
- 15 cm
- 100 cm
- 20 cm
- 45 cm
- 8 cm
- 60 cm
- 30 cm
- 80 cm

Graph:
- Purifying 20 kg Oligo
  - Manufacturing Time
  - Resin Cost

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Experts taking care.
Peptide Isolation & Drying

T-20 Process Innovation

- Peptides typically utilized lyophilization or spray drying
- T-20 volumes required a new way to isolate and dry
- Precipitation process was developed, after much work!
- Isolation could be decoupled from drying – expensive equipment

### Solid-Liquid Separation
- Centrifuge
- Filter Press
- ANFD & depth filtration
- Nutsche Bag Filters

### Drying
- Conical Dryer
- ANFD
- Lyophilizer
- Spray Dryer
Peptide Precipitation Benefits

Larger particle sizes

- Less air oxidation pathways (i.e. degradation)
- Less hygroscopic
- Ease of handling – operational and IH considerations

Increased Throughput

- Precipitation scale-up
- Isolation in the 100’s kg, if needed
Oligonucleotide Isolation & Drying

Currently Lyophilization

- Go-to equipment for oligos
- Capacity is highly dependent on concentration
- Emphasis on concentration methodologies
- New approach to downstream processing demonstrated – talk on Thursday, May 10th

Thursday, May 10, 12:20

Oligonucleotide Downstream Optimization for Large Scale Manufacturing
Amanda Lewis, Senior Chemist, Oligonucleotide Division, Corden Pharma

IEX Purification → UF/DF → Precipitation & Reconstitute → Lyophilize at high conc. > 10x Capacity Increase
Oligonucleotide Innovation – Where could we go?
References

Corden Pharma Colorado

- Richard Dauer
- Robert Topping
- Brad Dehoff
- Kurt Vagle

Publications

THANK YOU!

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