Development & Manufacturing of Peptides & Oligonucleotides

CPHI Japan, Tokyo
18th April 2018

www.cordenpharma.com
CordenPharma Overview

Your Full-Service CDMO Partner

- Full-Service CDMO Organized under 5 Technology Platforms
- € 365 Million Total Sales (2016)
- 11 Manufacturing Facilities in Europe / US (9 GMP Plants, 2 R&D Labs)
- 1,670 Employees
CordenPharma covers the full GMP supply chain of pharmaceutical custom manufacturing (raw materials and non-GMP pharmaceutical intermediates partially sourced from WeylChem).

API manufacturing accounts for c.62% of net sales and usually has a shorter ramp-up phase than respective Drug Product projects.

CordenPharma focuses on all stages of a drug lifecycle with competitive advantages in clinical development and commercial production.
CordenPharma - Value Proposition

- Serving Global Pharma & Biotech Customers
- Organized under 5 Distinctive Technology Platforms
- Broad Range of Expertise:
  - API’s: Small Molecules, Peptides, Oligonucleotides, Lipids, Carbohydrates, Highly Potent, Cytotoxics, Conjugates
  - Drug Products: Oral, Liquids, Injectables, Highly Potents, Anti-infectives / Antibiotics
- Global Coverage Allowing for Flexibility
- Your Full-Service Provider from Clinical Development to Full-Scale Commercial Supply of APIs & Drug Products
## Compliance

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Peptides, Oligonucleotides, Lipids & Carbohydrates Platform

www.cordenpharma.com
Platform Unique Positioning

Fully Integrated Supply API and Drug Product: Short Time to Market

- One Partner: Straightforward Communication and Project Management
- Efficient Exchange between API and Drug Product Teams
- Shorten Timelines
Peptides Capabilities

- Solid-Phase Peptide Synthesis
- Solution-Phase Peptide Synthesis
- HPLC Purification Capabilities
- Small to Large Scale
- Highly Potent Peptides (OEL 1 ng/m³)
- Conjugations
- Synthetic Vaccines
Peptide Overview

A Broad Range of Technical Capabilities from **Process Design** and **Scale-Up** to **Commercial Manufacturing** – g-scale to 100’s of kg production under full cGMP conditions

- Complex Peptides & Peptidomimetics
- Proprietary Process Technologies for cost-effective manufacturing
- Peptide Conjugations (PEGs, Proteins, Lipids, Carbohydrates)
- Cyclic Peptides & Peptides with multiple Disulfide Bridges
- Short Peptides (up to 12 residues), often without HPLC purification
- Arginine-rich Peptides
- Long Sequences (>30-AA) at 100’s kg
- CMC Section: Process & Analytical Services (stability, test methods, validations, etc)
- Filings: DMF Filing (e.g. USA, EU, Japan), IND, NDA, ANDA, IMPD
Solid-Phase Peptide Synthesis at any Scale

Solid-Phase Synthesis:

- Full range of synthesizer covering any scale at any stage of development
- Batch automation
- Large-volume solvent and waste-handling logistics
- Precipitation / isolation of fragments and final APIs
- Enfuvirtide fragment scale up to 920 kg
Solution-Phase Peptide Synthesis

State-of-the-art Manufacturing Infrastructure:

- Corrosion-resistant Vessels (Hastelloy)
  - 2000 – 12,000 L pilot / commercial scale
- Wide range of reactor sizes
  - 20 L to 18,000 L vessels
- Precipitation, Isolation & Drying
  - Heinkel 600 & 800 centrifuges
  - AP 300 & 600 BHS Autopress
  - 20 L to 3 m³ filter / dryers
  - 50 L to 3000 L conical screw dryers
Peptide Purification Capabilities

- Full range of HPLC, LPLC Scale
  - Orthogonal chromatography capability
  - Continuous acetonitrile recovery
  - Diagnosis & control of gel formation

- Precipitation, Isolation & Drying
  - AP 300 BHS Autopress
  - PSL filter / dryer
  - Lyophilization
Peptides, Oligonucleotides, Lipids & Carbohydrates Platform

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Peptides, Oligonucleotides, Lipids & Carbohydrates Platform

Your Expert Partner for Bio-Organic APIs

Areas of Indication
- APIs covering a wide range of therapeutic indications
- Vaccines
- Adjuvants
- Drug Delivery Systems
- Drug Targeting: Conjugations
Lipids > Targeting & Delivery Strategies

Natural Lipid

Bioconjugate Chem. 2012, 23, 1091–1104

Nanomicelles

Journal of Controlled Release 258 (2017) 1–9
Carbohydrates / Peptides
Targeting & Delivery Strategies

Nucleic acid

Micelle

i.e. GalNac

Carbohydrate Targeting Agent

CPP

CPP-Conjugates

RNA-Conjugates

Mifamurtide API, osteosarcoma therapy

Experts taking care.
Oligonucleotide Value Proposition - Summary

Building on Decades of Peptide Expertise

- **Integrated Supply Chain**
  - Cationic lipids and carbohydrates for Oligo drug delivery (e.g. LNP and GALNAc chemistry)
  - Drug product – liquid vials, pre-filled syringes, lyophilized product

- **Technology Synergies**
  - Conjugation
  - Solid phase and solution phase peptide synthesis
  - MPLC and HPLC, RP & IEX
  - Precipitation, Isolation and lyophilization

- **Manufacturing Scale & Expertise**
  - Gram scale to >> 100 kg batch scale for peptide APIs
  - Experience developing and scaling up peptide APIs for over 40 years

- **Quality & Regulatory**
  - Quality system built for life cycle management from clinical through post process validation
  - Excellent regulatory agency and customer inspection history
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- **OligoPilot 100**: 2-9 mmol scale (5 - 35g per run)
- **OligoPilot 400**: 4-60 mmol scale (15-120g of Oligo after DSP) per run
- **OligoProcess**: 100-4000 mmol scale (400g-16kg of Oligo after DSP) per run

* Additional OligoPilot 100 in 2018 for small scale GMP production
** Rolling out our first GMP Oligo Process in Q2 2018
Custom DNA / RNA - API Manufacturing Services

- Sugar modifications, i.e. 2’-OH, 2’-F, 2’-OMe,…

- Backbone modifications (sulfurization,…)

- Base modifications

- SiRNA duplex

- 3’ and 5’ modifications
  - GalNac
  - Amino linker
  - Cholesterol
  - PEG
  - Peptide
  - Lipids
Analytical Equipment Requirements
(Pilot & Process Scale)

- Analytical instrumentation for raw material, process and final control includes (minimal & non-comprehensive list):
  - HPLC (SEC, Ion exchange & Ion pairing)
  - LC-MS (ESI, Ion Trap)
  - NMR (PAT for phosphoramidite coupling)
  - Micro calorimeter, DSC
  - UV-VIS (temperature controlled)
  - Q-tof
  - Sequencing
  - nnn
Experience & Expertise Q/A

- Several non-GMP & GMP projects started so far
- Relation with Ionis
- Growing oligo team with specific expertise
- PhD MS expert with oligo experience
- Experienced in transferring methods from Waters to Agilent
## Oligonucleotide - API Manufacturing Equipment

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<th>Type</th>
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<td>Oligo Synthesis</td>
<td><strong>2 x AKTA 100</strong>&lt;br&gt;<strong>OP 400</strong>&lt;br&gt;&lt;br&gt;<strong>Oligo Process</strong></td>
<td>Qualified&lt;br&gt;Qualified&lt;br&gt;Qualified Q2 2018</td>
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<td>Cleavage / Deprotection</td>
<td>100L – 8,000L Hastelloy Reactors</td>
<td>Qualified</td>
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<td>Chromatography</td>
<td><strong>L/MPLC (cm)</strong>&lt;br&gt;12&lt;br&gt;18&lt;br&gt;30&lt;br&gt;45&lt;br&gt;50&lt;br&gt;60&lt;br&gt;80</td>
<td><strong>HPLC (cm)</strong>&lt;br&gt;5&lt;br&gt;8&lt;br&gt;15 (3)&lt;br&gt;45&lt;br&gt;80&lt;br&gt;100</td>
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<td>UF</td>
<td>6 m²&lt;br&gt;30 m²</td>
<td>Qualified&lt;br&gt;Planning</td>
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<td>Lyophilization</td>
<td>36L&lt;br&gt;90L+</td>
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<td>Solvent Recycling</td>
<td>Batch Distillation&lt;br&gt;Continuous Distillation</td>
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**Bold** = to be placed in service
CordenPharma Colorado

- Location: Boulder, Colorado USA
- Acquisition: September 2011
- Employees: 250

- Integrated Resource for the Development & Manufacture of Advanced Intermediates and APIs for Global Pharmaceutical and Biotechnology Industries
- Development & Manufacture of Complex Synthetic Peptides, Oligonucleotides and Conjugates
- Development & Manufacturing of Highly Potent, Cytotoxic & Non-Cytotoxic APIs
- Excellent Track Record in Development from Early Stage to Launch
- SafeBridge® IV Certified

Core Competencies
- Leader in Development & Manufacture of Synthetic Peptides
- Process Analytical Technology & Track Record in Regulatory Filing
- Development & Scale-up of Highly Potent & Oncology APIs
THANK YOU

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