EuroPeptides 2014: Workshop
Considerations for Peptide Contract Manufacturing:
Case Study on Scale-up Considerations

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The views expressed in this presentation are mine and do not reflect those of my past, present or future employers…
Why Outsource?

- Access to expertise
- Access to capacity
- Compliance (GMP capabilities)
- Cost-effectiveness

Internal resources versus project requirements
What to Outsource?

- Peptide synthesis
  - Requires specialized equipment
    - Automated synthesizers
    - Reactors
    - HPLC purification
  - Specialized chemistry
    - TFA or HF cleavage
    - Hybrid synthesis

- Analytical characterization

- Regulatory oversight
When to Outsource?

- **Discovery support: Small scale**
  - Automated synthesizers
  - Lab bench scale
- **Preclinical support: Medium scale**
  - Solid-phase synthesis (specialized equipment)
  - Hybrid synthesis
- **Clinical support: Larg(er) scale**
  - Solid-phase/Hybrid
- **Commercial: Large scale**
  - Solid-phase/Hybrid
  - Solution-phase
The Relationship

- Managing expectations
  - Sponsor
    - Rapid turnaround
    - High quality
    - Lowest cost
  - Contract Manufacturer
    - Need to manage multiple projects
    - Flexible resource allocation
    - Constant flow of work
    - Profit
The Relationship: part 2

- Developing trust
  - Communication
  - No finger-pointing or playing the blame game
  - Root-cause investigation
  - Corrective action
  - Communication
  - Communication
  - Communication
  - Communication
Effective communication

- Critical in early-stage projects
- **Type of information**
  - Project updates
  - Issues (set expectations of when)
  - Process changes
- **Mechanisms**
  - Telephone
  - Email
  - Face-to-face
- Quality-Compliance agreement
- Supply agreement
On-site activities

- Site inspection (tour)
  - Does everything look clean, organized?
  - People?
- Review of SOPs (compliance)
- Meet the team
- Project manager, point-of-contact
- Review batch records
Agreements

- Initial stage (discovery, milligrams)
  - Quotes-purchase orders
  - Quantity and specifications

- GMP batches (clinical use)
  - Quality agreement
  - Development agreement
  - Supply agreement

- Note: IND/IMPD. Client/spiror responsible for human safety! Therefore, important to have oversight of manufacturing…
Quality agreements

Primary purpose

To delineate the responsibilities (or joint responsibilities) in the manufacture, testing and release of API for clinical human studies or commerce

Compliance

- cGMP
- SOPs
Elements of a quality agreement

- Responsibilities for review/approval
  - Manufacturing procedures
  - Master batch records
  - In-process, release and stability methods
  - Specifications

- Notifications-approval of changes in
  - Vendors
  - Deviations
  - Out-of-specifications
  - Non-routine findings
Additional agreements

- Process changes
  - How are they documented?
  - Client approval?
  - Impact on toxicology, clinical

- Specification changes
  - Experience with process
  - Feedback from regulatory agencies

- Validations
  - Analytical methods
  - Process
General Lessons Learned

Manufacturing Scale-up

Cost-of-Goods

Case Study
Projections

- PSP market (US)
  - Orphan indication
    (prevalence ~6.5 per 100,000)
  - 60 mg daily dose
  - Need ~150 kilograms (at launch)
  - ~500 kilograms per annum (at peak sales)
Solid-phase Scale-up

[Graph showing the increase in batch size/scale over years, with key milestones labeled: IND submission, Chronic tox/Phase II, Pivotal Phase II/III.]
Solid-Phase Manufacturing

- Existing solid-phase synthesis (10 kg batch size):
  - 3 x 3.3 kg synthesis, pool crude peptide, HPLC purify, batch lyophilization
  - “Sufficient” for product launch for orphan indication
- Would require 10-15 batches per year
- Within existing capacity of CMO at single site
- Challenge: to get to 500 kg/annum to support peak sales (3-4 years post-approval) as well as follow-on product approval in other indications (like AD)
Need to rapidly bridge to additional solid-phase capacity (second supplier) or explore liquid-phase synthesis
Cost: Solid-Phase Synthesis

Cost at gram scale synthesis

Target commercial scale: 0.15-0.2
Cost-Scale Considerations

- **Solid-Phase**
  - 0.15-0.2 relative cost

- **Solution-Phase**
  - Cost of initial development
  - Impurity profile
  - 0.035-0.05 relative cost
  - Dramatic reduction in cost (3- to 6-fold)
Davunetide: Solution-Phase Strategy

Condensation Segments and Building Blocks:

| Boc-Asn-OH | Fmoc-Val-Ser(ψpro)-OH | H-Gln-OtBu |
| H-Ala-Pro-OH | Z-Ile-Pro-OH |
Solution-Phase Considerations

- Minimize Racemization/Epimerization Impurities by
  - Synthesize dipeptide building blocks from Boc-, Z- or Fmoc-protected single amino acids
  - Isolate and purify resulting condensation segments
  - Segment condensation only with di- and tripeptides containing proline or pseudoproline at the C-terminus
Synthetic Scheme I

Z-Ile-OH + H-Pro-OH → Z-Ile-Pro-OH + H-Gln-OtBu

↓

Z-Ile-Pro-Gln-OtBu

↓

Fmoc-Val-Ser(ψpro)-OH + H-Ile-Pro-Gln-OtBu

↓

Fmoc-Val-Ser(ψpro)-Ile-Pro-Gln-OtBu

↓

H-Val-Ser(ψpro)-Ile-Pro-Gln-OtBu
Synthetic Scheme II

\[ \text{Z-Ala-Pro-OH} \quad + \quad \text{H-Val-Ser(} \psi \text{pro}) \text{-Ile-Pro-Gln-OtBu} \quad (\text{From Scheme I}) \]

\[ \quad \downarrow \]

\[ \text{Z-Ala-Pro-Val-Ser(} \psi \text{pro}) \text{-Ile-Pro-Gln-OtBu} \]

\[ \quad \downarrow \]

\[ \text{Boc-Asn-OH} \quad + \quad \text{H-Ala-Pro-Val-Ser(} \psi \text{pro}) \text{-Ile-Pro-Gln-OtBu} \]

\[ \quad \downarrow \]

\[ \text{Boc-Asn-Ala-Pro-Val-Ser(} \psi \text{pro}) \text{-Ile-Pro-Gln-OtBu} \]

\[ \quad \downarrow \]

\[ \text{H-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-OH} \]
HPLC analysis: Purity profile
Solution-Phase Conclusions

- Yield better than anticipated
- Revised relative-cost: 0.01-0.02
- Process still needs optimization
Lessons Learned

- Important to integrate manufacturing plans into
  - Sales and marketing
    - Target population change from AD to PSP
    - 1.2 mil patients versus 70,000
  - Clinical Development
    - Dose change from 5 mg to 60 mg
    - Significant increase (12-fold)
Final Thoughts

- It is all about the relationship!

- Communication is key

- Agreements help define and set expectations

- Contracts are to protect both sides when the relationship falls apart, so plan accordingly
Guide
for the elaboration of monographs
on synthetic peptides and recombinant DNA proteins

European Pharmacopoeia
European Directorate for the Quality of Medicines & HealthCare

Edition 2010

4. SYNTHETIC PEPTIDES ................................................................. 9
   4.1. DEFINITION ........................................................................... 9
   4.2. CHARACTERS ....................................................................... 9
   4.3. IDENTIFICATION ................................................................. 10
       4.3.1. General considerations .................................................... 10
   4.4. TESTS ..................................................................................... 10
       4.4.1. Related peptides ............................................................. 10
       4.4.2. Optical rotation and absorbance ..................................... 11
       4.4.3. Acetic acid, loss on drying, water content ....................... 11
       4.4.4. Tests for bacterial endotoxins/pyrogens ........................... 11
   4.5. ASSAY ................................................................................... 11

http://www.edqm.eu/
Guidance for Industry

for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances

Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
November 1994

Published but withdrawn in 2004
# TABLE OF CONTENTS

I. INTRODUCTION .................................................. 1

II. DESCRIPTION AND CHARACTERIZATION .................. 2
   A. Description ................................................. 2
   B. Characterization/Proof of Structure .................... 2

III. SYNTHESIS/METHOD OF MANUFACTURE ................. 4
   A. Starting Materials ........................................ 4
      1. Amino Acids and Derivatives ....................... 4
      2. Resins Used for Peptide Synthesis .............. 4
      3. Chemical Reagents and Solvents ............... 5
   B. Flow Chart of Synthesis .................................. 5
      1. Solution-Phase Synthesis ......................... 5
      2. Solid-Phase Synthesis ............................. 5
   C. Detailed Description of Synthesis .................... 5
      1. Solution-Phase Synthesis ......................... 5
      2. Solid-Phase Synthesis ............................. 6
      3. Modification of the Completed Peptide ....... 7
   D. Purification of the Peptide ............................ 7
      1. Purification Strategy ............................... 7
      2. Description of the Purification Process ....... 7
      3. Drying of Purified Drug Substance ............ 8

IV. PROCESS CONTROLS ........................................... 8

V. REFERENCE STANDARD ........................................ 8

VI. SPECIFICATIONS/ANALYTICAL METHODS ................. 11

VII. CONTAINER-CLOSURE SYSTEM ............................. 11

VIII. STABILITY .................................................. 12
Not peptide specific, but useful guidance

http://www.ema.europa.eu/
Quality specifications for peptide drugs: a regulatory-pharmaceutical approach

Valentijn Vergote, Christian Burvenich, Christophe Van de Wiele and Bart De Spiegeleer

Peptide drugs, as all types of pharmaceuticals, require adequate specifications (i.e. quality attributes, procedures and acceptance criteria) as part of their quality assurance to ensure the safety and efficacy of drug substances (i.e. active pharmaceutical ingredients) and drug products (i.e. finished pharmaceutical dosage forms). Compendial monographs are updated regularly to keep up with the most recent advances in peptide synthesis (e.g. reduced by-products) and analytical technology. Nevertheless, currently applied pharmacopoeial peptide specifications are barely harmonized yet (e.g. large differences between the European Pharmacopoeia and the United States Pharmacopoeia), increasing the manufacturers’ burden of performing analytical procedures in different ways, using different acceptance criteria. Additionally, the peptide monographs are not always consistent within a single pharmacopoeia. In this review, we highlight the main differences and similarities in compendial peptide specifications (including identification, purity and assay). Based on comparison, and together with additional information from peptide drug substance manufacturers and public evaluation reports on registration files of non-pharmacopoeial peptide drugs, a consistent monograph structure is proposed. Copyright © 2009 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: peptide drug substance; quality attributes; acceptance criteria; regulatory affairs; ICH guidelines; Ph. Eur. and USP pharmacopoeial monographs; related substances thresholds
Questions?