TIDES 2013: Course 2

Considerations for Peptide Contract Manufacturing:
Lessons Learned on Outsource Management

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Disclaimer

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: Larger 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
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/sponsor 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
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

edqm

Edition 2010

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http://www.edqm.eu/
Published but withdrawn in 2004
Withdrawn FDA Guidance

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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

Peptid 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?