

TIDES 2013: Course 2

Considerations for Peptide Contract Manufacturing:

Lessons Learned on Outsource Management

Bruce H Morimoto, PhD Exec Director, Applied Translational Medicine, Celerion bruce.morimoto@celerion.com

May 12, 2013





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

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...







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



Edition 2010

4.	SYNT	HETIC PEPTIDES9
	4.1.	DEFINITION9
	4.2.	CHARACTERS
	4.3.	IDENTIFICATION
	4.	3.1. General considerations
	4.4.	Tests
	4.	4.1. Related peptides
	4.	4.2. Optical rotation and absorbance11
	4.	4.3. Acetic acid, loss on drying, water content
	4.	4.4. Tests for bacterial endotoxins/pyrogens11
	4.5.	Assay

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



Withdrawn FDA Guidance

TABLE OF CONTENTS

I.	INTR	ODUC	TION	1
II.	DESC	CRIPTI	ON AND CHARACTERIZATION	2
	Α.	Desc	ription	2
	В.	Chara	acterization/Proof of Structure	2
III.	SYNT	THESIS	S/METHOD OF MANUFACTURE	4
	Α.	Starti	ng Materials	4
		1.	Amino Acids and Derivatives	4
		2.	Resins Used for Peptide Synthesis	4
		3.	Chemical Reagents and Solvents	5
	Β.	Flow	Chart of Synthesis	5
		1.	Solution-Phase Synthesis	5
		2.	Solid-Phase Synthesis	5
	C.	Detai	led Description of Synthesis	5
		1.	Solution-Phase Synthesis	5
		2.	Solid-Phase Synthesis	6
		3.	Modification of the Completed Peptide	7
	D.	Purifi	cation of the Peptide	7
		1.	Purification Strategy	7
		2.	Description of the Purification Process	7
		3.	Drying of Purified Drug Substance	8
IV.	PRO	CESS	CONTROLS	8

i

	Α.	React	tion Completion	3
		1.	Solution-Phase Synthesis	3
		2.	Solid Phase Synthesis	3
		3.	Disulfide Linkage 8	3
	В.	Intern	nediate Specifications and Tests)
	C.	Colun	nn Performance 9)
	D.	Remo	oval of Solvents and Reagents)
V.	REFE	RENC	E STANDARD S)
VI.	SPEC	FICA	TIONS/ANALYTICAL METHODS 11	
VII.	CON	FAINE	R-CLOSURE SYSTEM 11	
VIII.	STAB	ILITY		2

ii



May 2000 CPMP/ICH/367/96

ICH Topic Q 6 A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

Step 5

NOTE FOR GUIDANCE SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES (CPMP/ICH/367/96)

TRANSMISSION TO CPMP	September 1997
TRANSMISSION TO INTERESTED PARTIES	September 1997
DEADLINE FOR COMMENTS	March 1998
FINAL APPROVAL BY CPMP	November 1999
DATE FOR COMING INTO OPERATION	May 2000

Not peptide specific, but useful guidance

http://www.ema.europa.eu/

7 Weatherry Circus, Cararry Wharf, London, E14 4HB, UK Tel. (44-20) 74 18 85 75 Fix: (44-20) 75 23 70 40 E-mail: mail@emes.eu.int CEMEA 2006 Reproduction and/or distribution of this document is authorized for no commercial purposes only provided the EMEA is acknowledged

Review

PeptideScience

Received: 12 May 2009

Revised: 24 June 2009

Accepted: 25 June 2009

Published online in Wiley Interscience: 11 September 2009

Journal of

(www.interscience.com) DOI 10.1002/psc.1167

Quality specifications for peptide drugs: a regulatory-pharmaceutical approach

Valentijn Vergote,^a Christian Burvenich,^b Christophe Van de Wiele^c and Bart De Spiegeleer^{a*}

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 Pharmacopeia), 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; guality attributes; acceptance criteria; regulatory affairs; ICH guidelines; Ph. Eur. and USP pharmacopoeial monographs; related substances thresholds

Journal of Peptide Science (2009) Vol 15(11), p 697-710



QUESTIONS?