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Applied Translational Medicine

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

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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…

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Why Outsource?

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

  Internal resources versus project requirements

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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

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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

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The Relationship: part 2

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

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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…

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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

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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

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General Lessons Learned

Manufacturing Scale-up

Cost-of-Goods

Case Study

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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)

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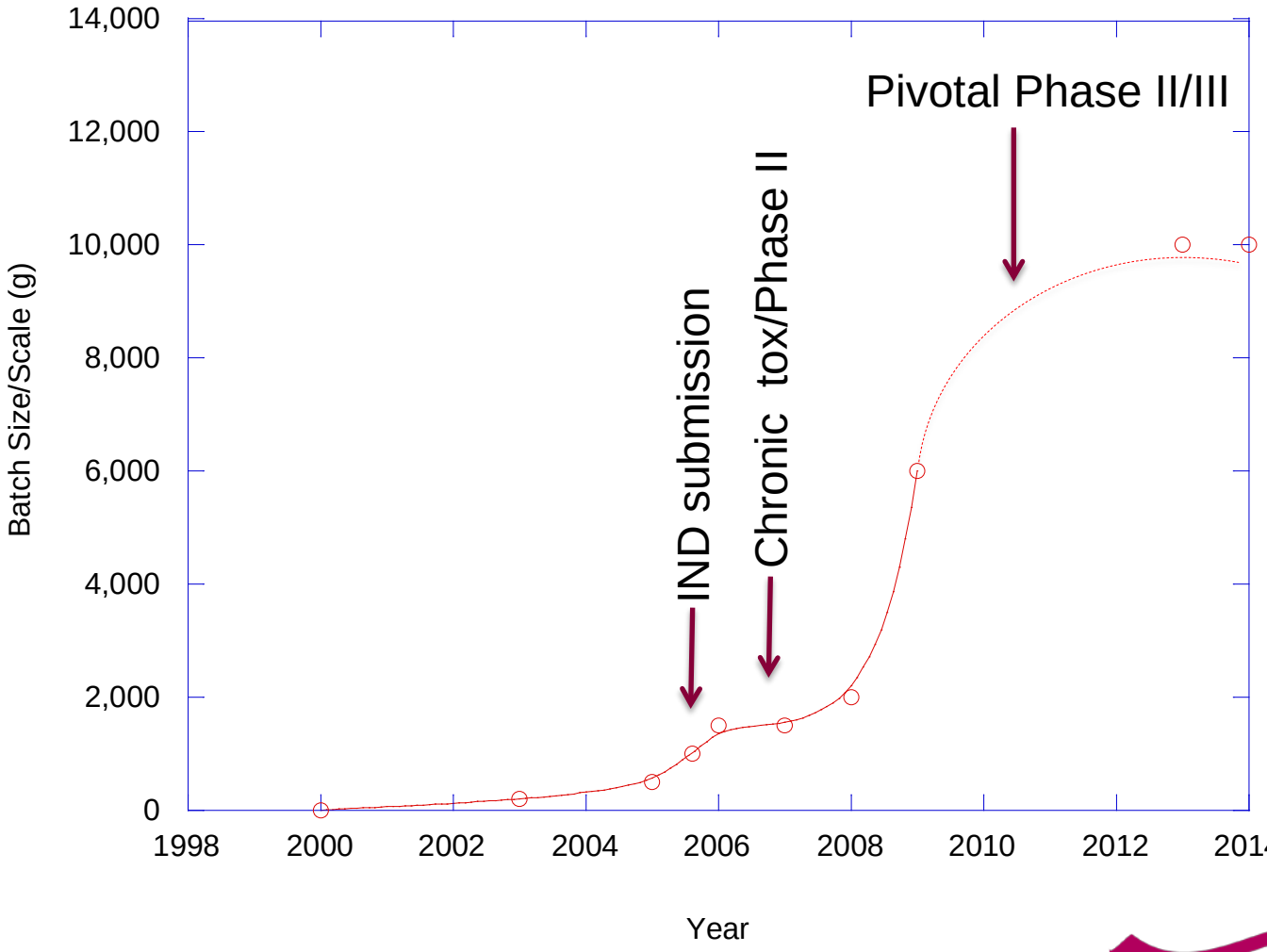
Solid-phase Scale-up



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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

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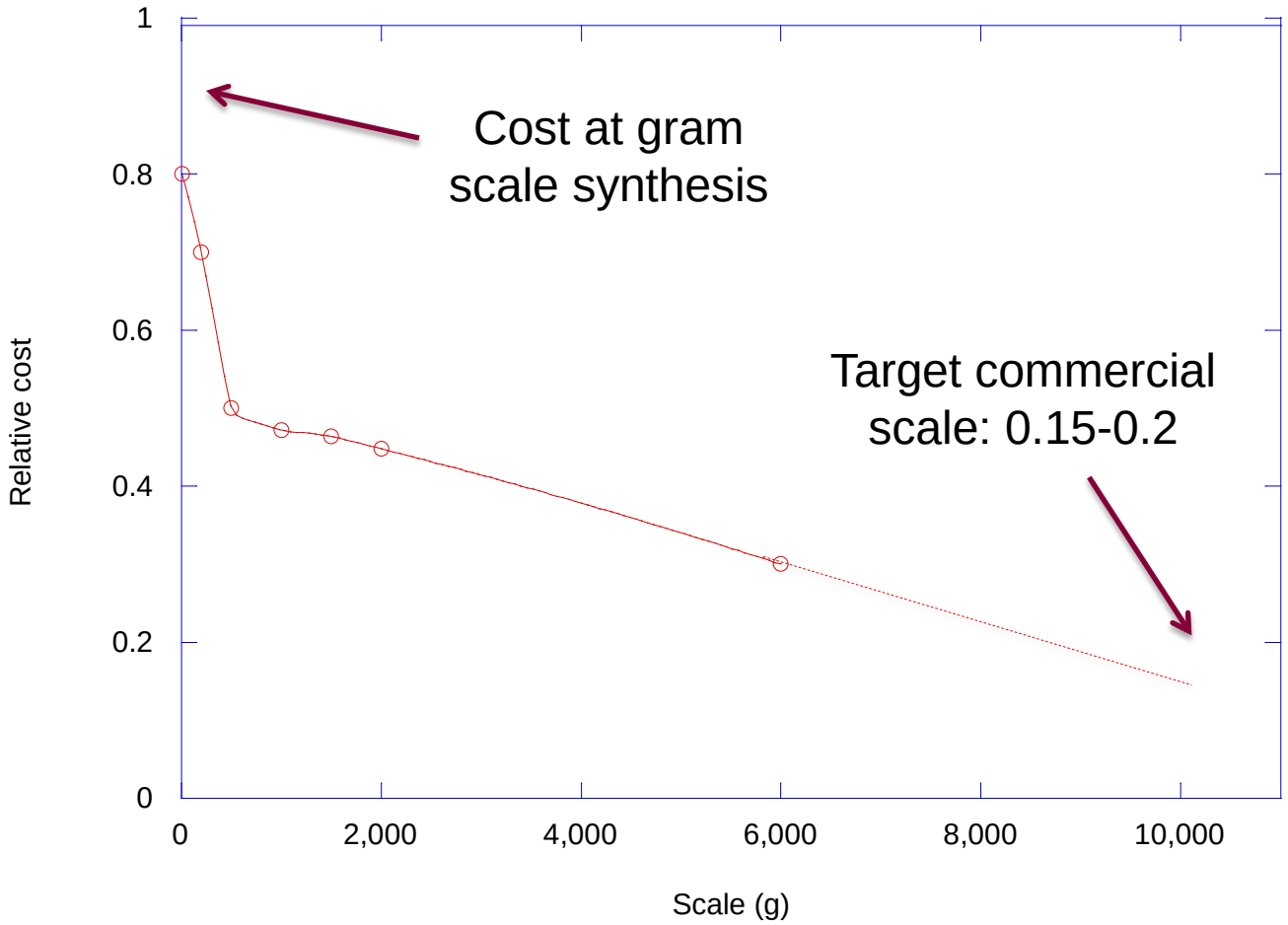
Cost: Solid-Phase Synthesis



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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)

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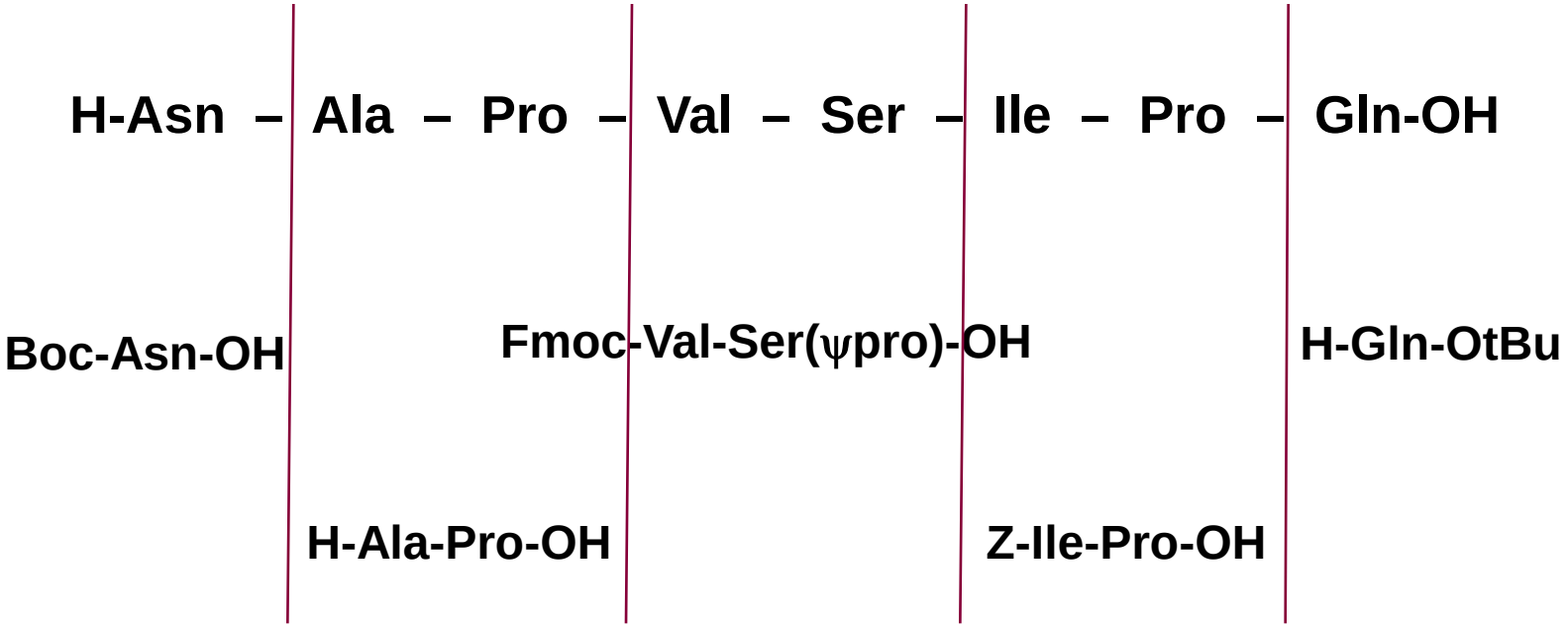
Davunetide: Solution-Phase Strategy

Condensation Segments and Building Blocks:



21

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

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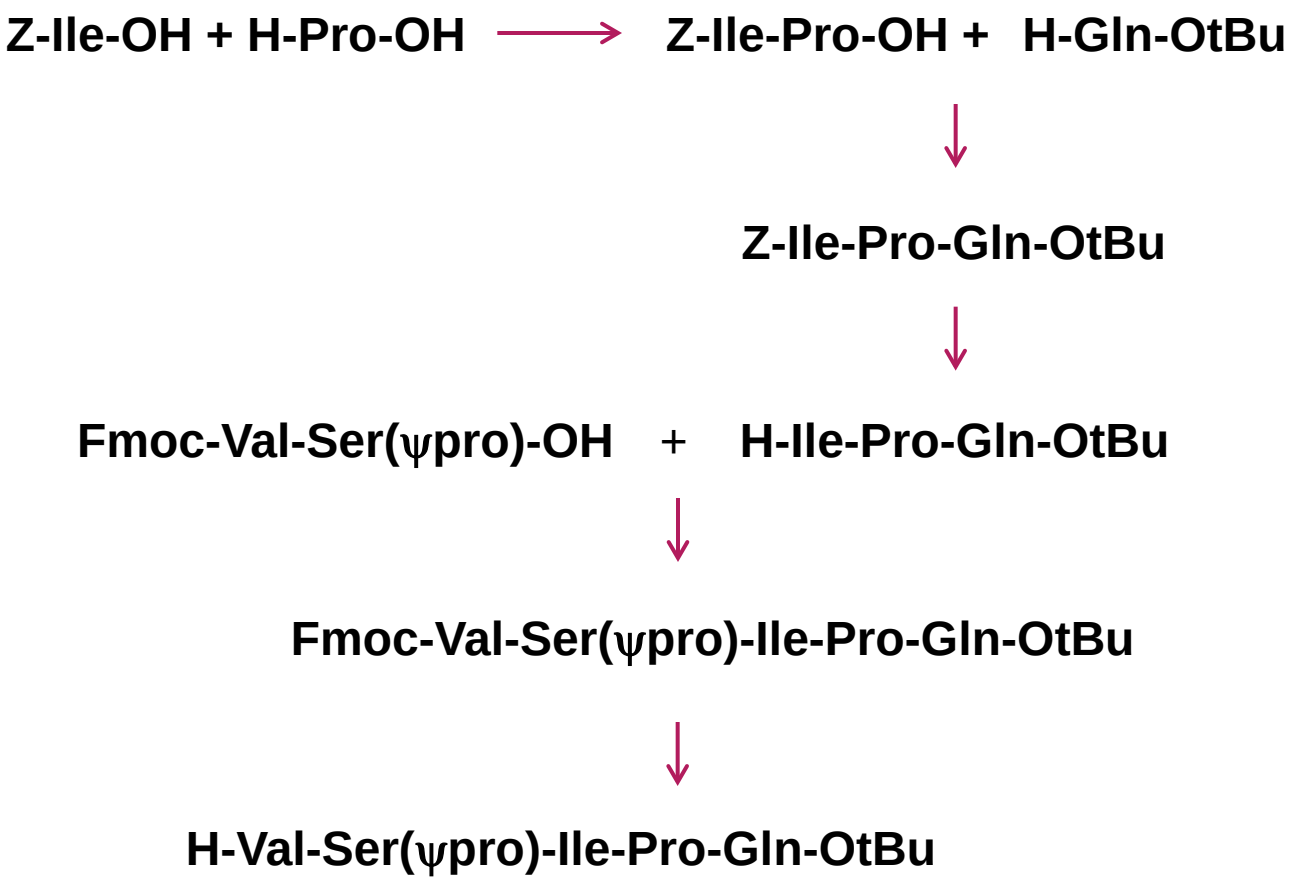
22

Synthetic Scheme I



23

Synthetic Scheme II

Z-Ala-Pro-OH + **H-Val-Ser(ψpro)-Ile-Pro-Gln-OtBu** (From Scheme I)

↓

Z-Ala-Pro-Val-Ser(ψpro)-Ile-Pro-Gln-OtBu

↓

Boc-Asn-OH + **H-Ala-Pro-Val-Ser(ψpro)-Ile-Pro-Gln-OtBu**

↓

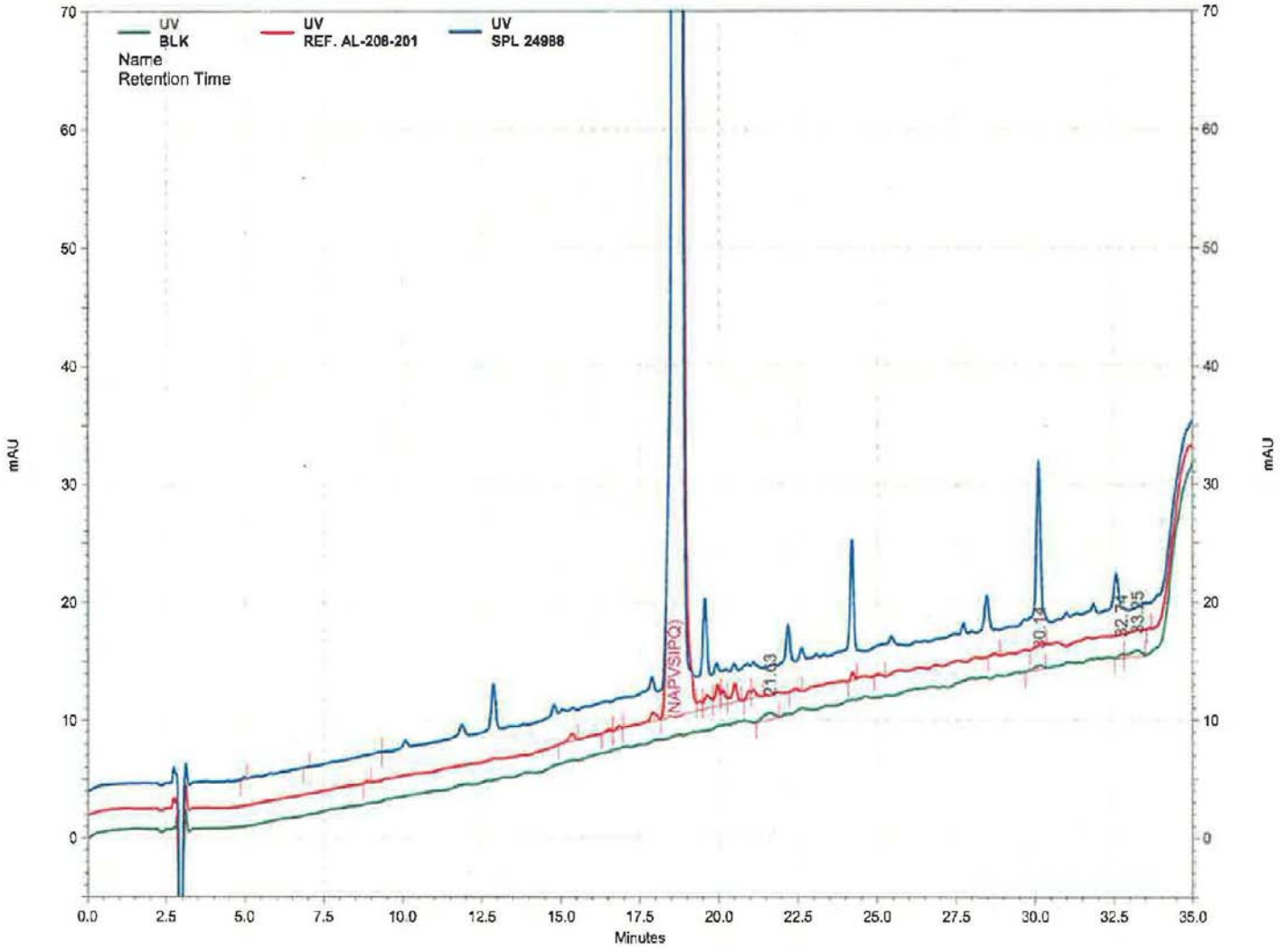
Boc-Asn-Ala-Pro-Val-Ser(ψpro)-Ile-Pro-Gln-OtBu

↓

H-Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln-OH

24

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)

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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

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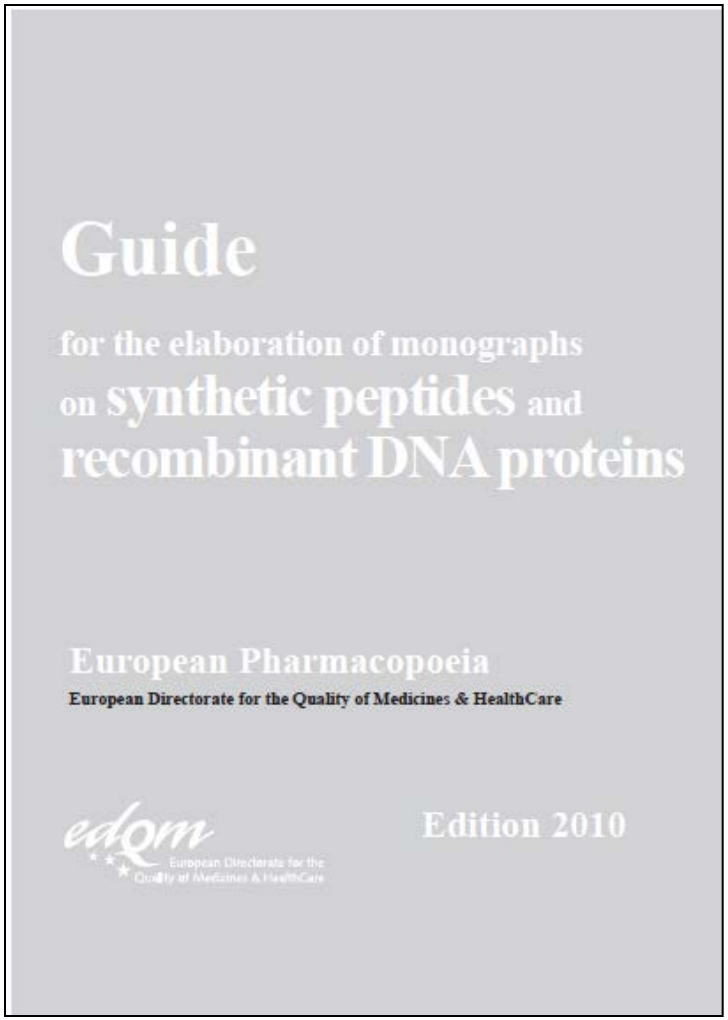

http://www.edqm.eu/

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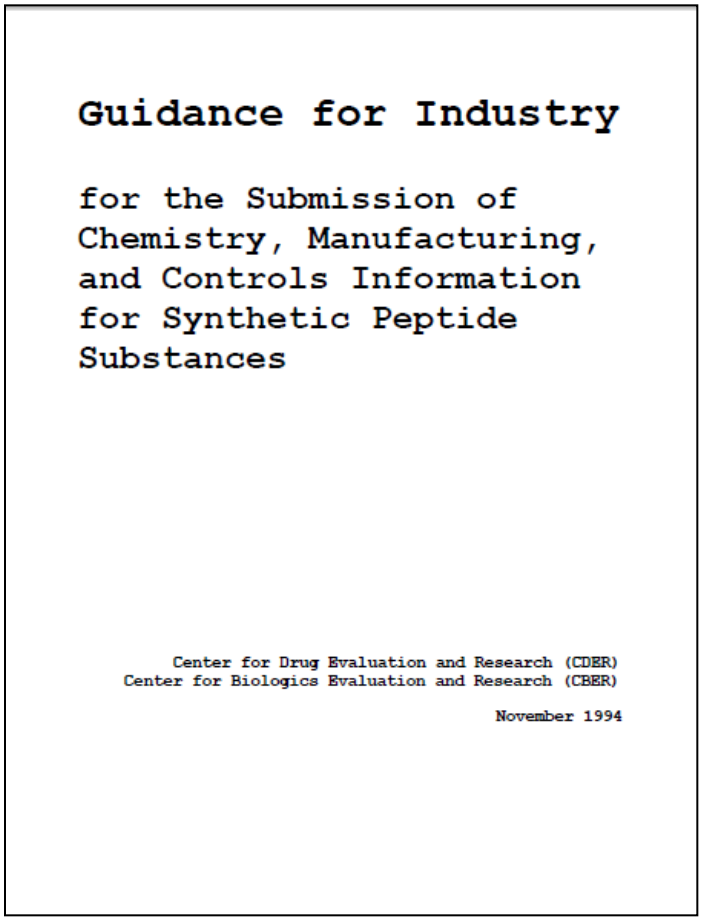

Guidance for Industry

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

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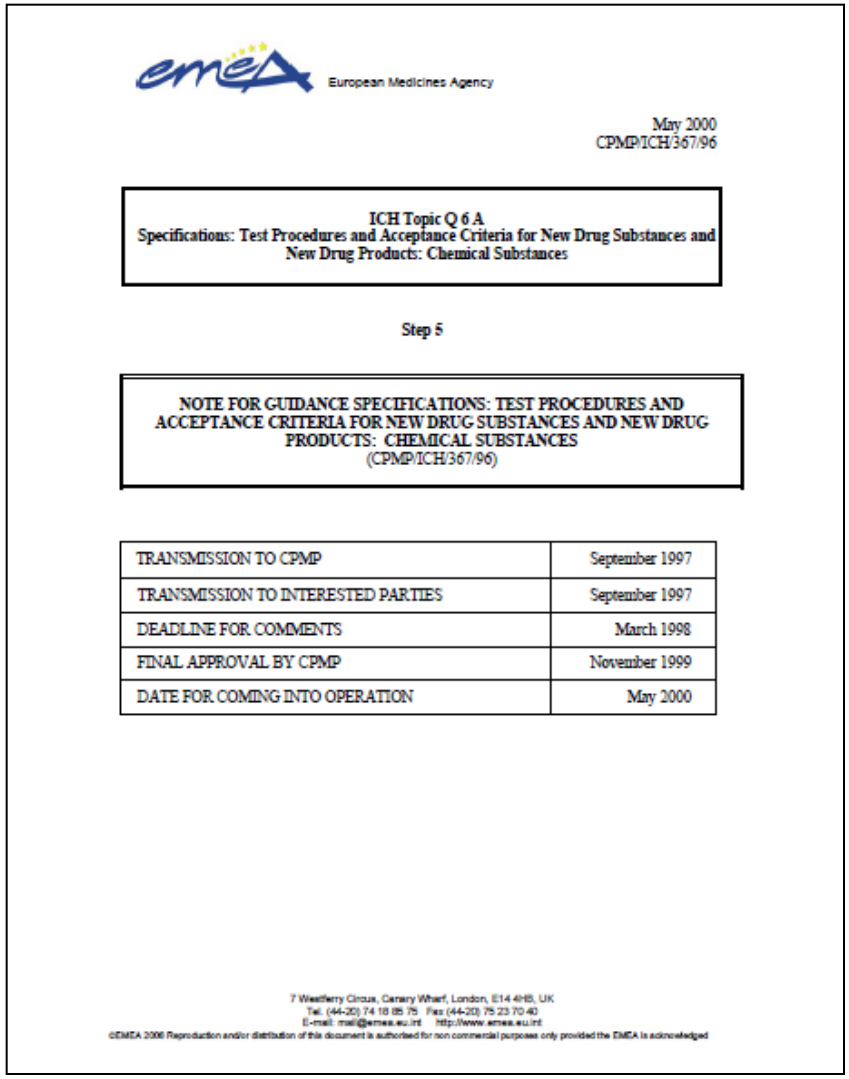
Withdrawn FDA Guidance

TABLE OF CONTENTS



European Medicines Agency

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

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E-mail: mail@emea.eu.int http://www.emea.eu.int

Not peptide specific,
but useful guidance

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

Review

Journal of PeptideScience

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Quality specifications for peptide drugs: a regulatory-pharmaceutical approach

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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; quality 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

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Questions?