Lab Science to Support Generic Complex Drug Product Assessment

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Learning Objectives

- Describe the role of the Office of Testing and Research (OTR) in generic complex drug science
- Explain the benefits of using LC-HRMS techniques for quality assessments of peptide therapeutics
- Discuss some challenges in the characterization of inhalation drug products

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence in their *next* dose of medicine.

OTR Laboratory Capability

Division of Complex Drug Analysis

Division of Pharmaceutical Analysis

Division of Product Quality and Research

St. Louis

White Oak

OTR Laboratory Capability

Division of Complex Drug Analysis

Division of Pharmaceutical Analysis

Division of Product Quality and Research

Mass Spectrometry

NMR

High Performance Liquid Chromatography

Gas Chromatography

Particle Sizing

SEM

Dissolution

OTR Core Functions

OTR Key Areas of Focus

Priority 1:

Advanced Manufacturing

Priority 2:

Drug Quality Standards and Linkage to *In Vivo* Performance

Priority 3:

Advanced Characterization of Complex Drug Substances

Priority 4:

Physicochemical Characterization of Complex Drug Products

Priority 5:

Post-Market Product Quality and Public Health Issues

A.C. Fisher, S.L. Lee, D.P. Harris, L. Buhse, S. Kozlowski, L. Yu, M. Kopcha, J. Woodcock. Advancing pharmaceutical quality: An overview of science and research in the U.S. FDA's Office of Pharmaceutical Quality. *Int. J. Pharm*. 2016.

OTR Key Areas of Focus

Priority 3:

Advanced Characterization of Complex Drug Substances

Objective: characterization and comparative analysis of complex drug substances

Objective: develop in vitro approaches for characterizing complex formulations

Priority 4:

Physicochemical Characterization of Complex Drug Products

A.C. Fisher, S.L. Lee, D.P. Harris, L. Buhse, S. Kozlowski, L. Yu, M. Kopcha, J. Woodcock. Advancing pharmaceutical quality: An overview of science and research in the U.S. FDA's Office of Pharmaceutical Quality. *Int. J. Pharm*. 2016.

Advanced Analytics for Characterizing Generic Peptide Drug Substances

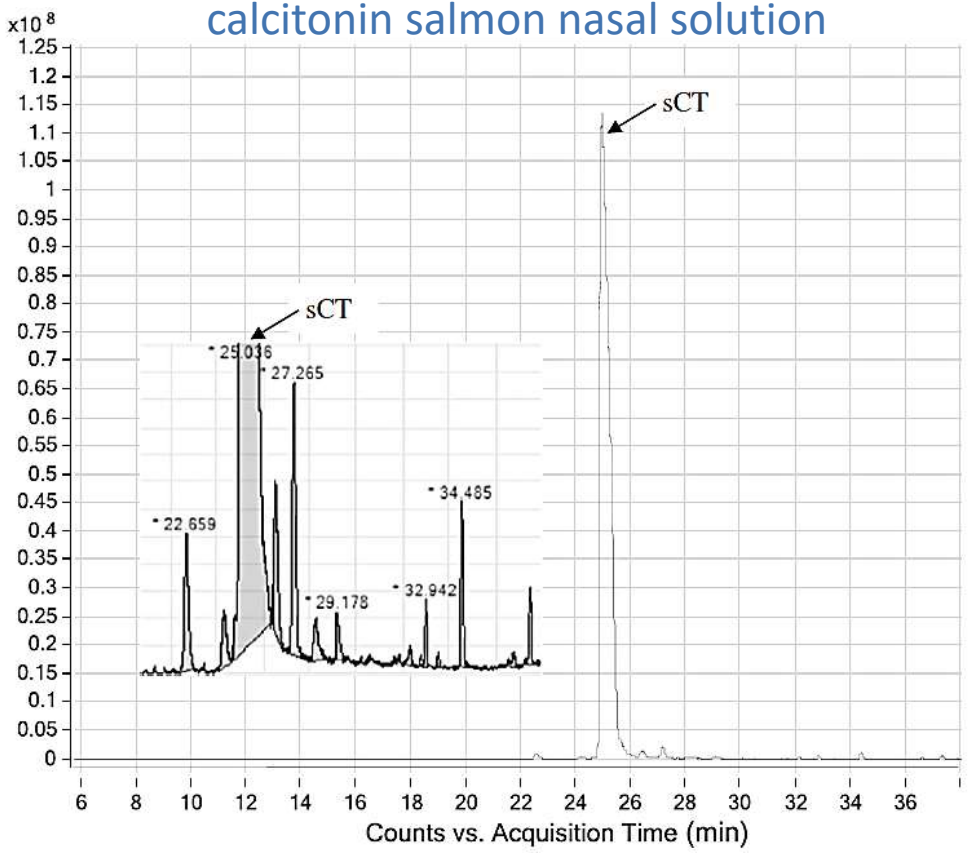
Therapeutic Peptide Drug Products

- Increasing numbers of peptide-related ANDAs
- Various production methods / impurities
- Inadequate QC methods submitted
- Advanced analytical techniques needed
  - LC-HRMS: advantages/challenges

ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin: https://www.fda.gov/files/drugs/published/ANDAs-for-Certain-Highly-Purified-Synthetic-Peptide-Drug-Products-That-Refer-to-Listed-Drugs-of-rDNA-Origin-Guidance-for-Industry.pdf

QC by LC-HRMS

- Validated method for three peptide drugs
- Many benefits over HPLC-UV
- Promising QC approach



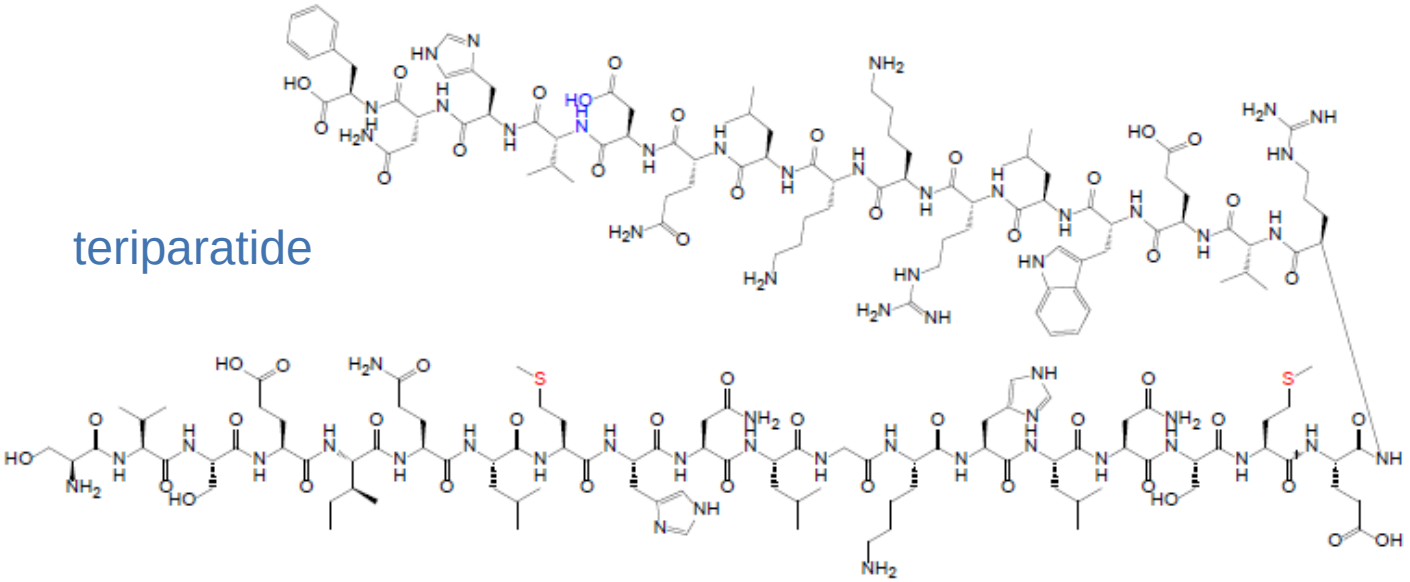
Z. Kui, I. Geerlof-Vidavsky, A. Gucinski, X. Jiang, M. Boyne. Liquid Chromatography-High Resolution Mass Spectrometry for Peptide Drug Quality Control. *The APPS Journal*, 2015.

Peptide Impurity Profile

- Teriparatide: compare RLD with synthetic version
- Data used to assess risk / immunogenicity
- Data to support regulatory decision-making

Peptide Impurities

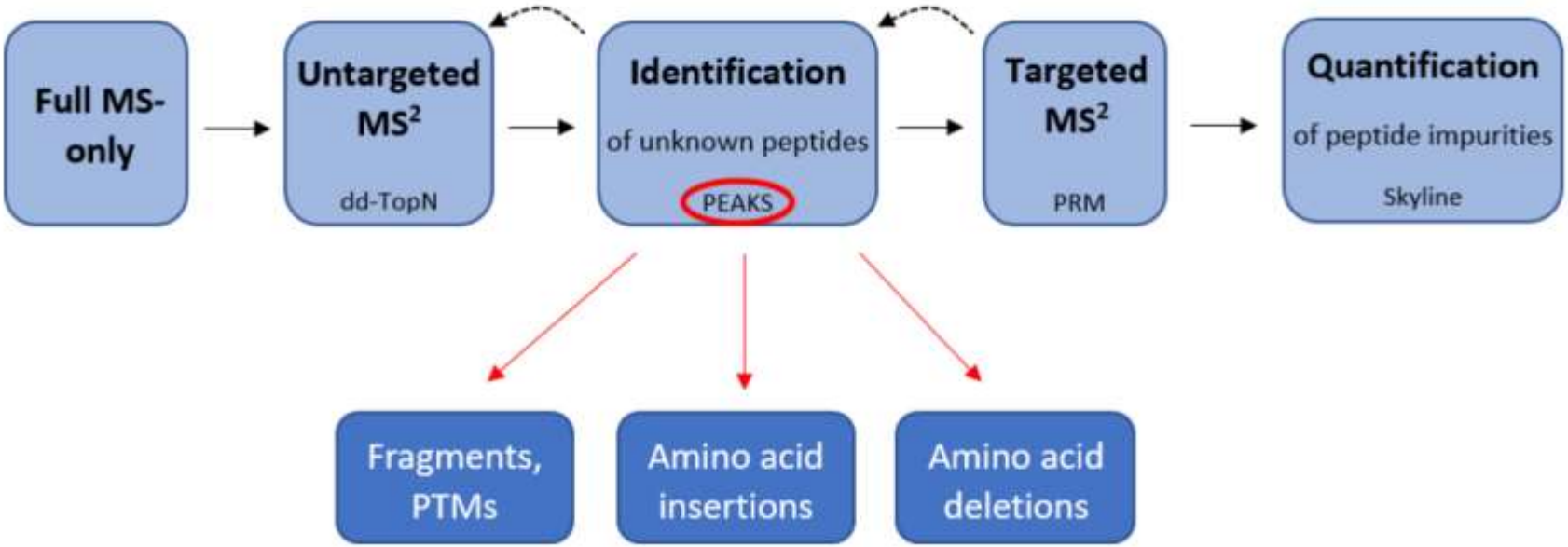
teriparatide



AA deletion
AA insertion
truncation
deamidation
oxidation
host cell
cell media

ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin: https://www.fda.gov/files/drugs/published/ANDAs-for-Certain-Highly-Purified-Synthetic-Peptide-Drug-Products-That-Refer-to-Listed-Drugs-of-rDNA-Origin-Guidance-for-Industry.pdf

Peptide Impurity Workflow



Challenges in Characterization of Inhalation Drug Products

Orally Inhaled and Nasal Drug Products

- Drug-device combination products
- Weight of evidence approach is challenging
- Bio-relevant mouth-throat models
- Alternative particle sizing methods

Draft Guidance on Beclomethasone Dipropionate:
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Beclomethasone%20dipropionate%20Inhalation%20Aerosol%20Metered%20NDA%20207921%20PSG%20Page%20RC%20May%202019.pdf

Bio-Relevant Mouth-Throat Models

USP

Alberta Idealised Throat (AIT)

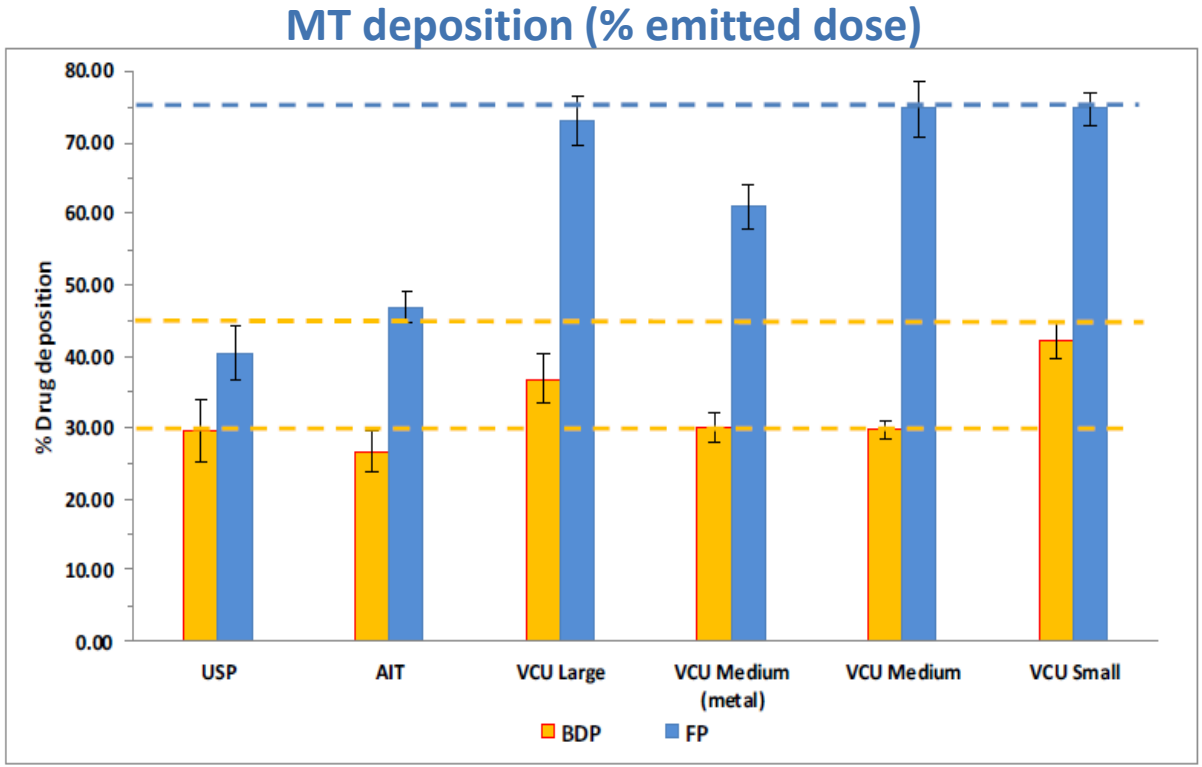
Commercial product

Virginia Commonwealth University (VCU) models

3D printed

Reference:
www.rddonline.com/resources/tools/models.php

Bio-Relevant Mouth-Throat Models



A. Kaviratna, G. Tian, X. Liu, R. Delvadia, S. Lee, C. Guo, Evaluation of Bio-Relevant Mouth-Throat Models for Characterization of Metered Dose Inhalers, *AAPS PharmSciTech*, 2019.

Alternative Particle Sizing Method: MDRS

Morphology-Directed Raman Spectroscopy

- Nasal spray suspensions
- Component-specific
- Non-destructive

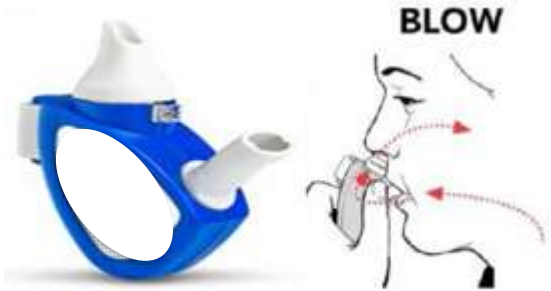
Research to guide development, optimization, and validation of MDRS methods as alternate to comparative clinical endpoint BE studies

1. Q. Liu, M. Absar, B. Saluja, C. Guo, B. Chowdhury, R. Lionberger, D. Conner, B. Li, Scientific Considerations for the Review and Approval of First Generic Mometasone Furoate Nasal Suspension Spray in the United States from the Bioequivalence Perspective, *The APPS Journal*, 2019.
2. B. Thomas, M. Absar, R. Devadia, D. Conti, K. Witzmann, C. Guo, Analytical Method Development for Characterizing Ingredient-Specific Particle Size Distributions of Nasal Spray Suspension Products, *J. Pharm. Sci.*, accepted.

New Devices and Laser Diffraction

Soft Mist Inhaler

Breath Actuated
Nasal Powder



Laser Diffraction
rapid PSD measurements
versatile sampling methods

Summary

- Generic drug research is an integral part of OTR's work
- OTR's laboratory-based research programs
  - Provide data to support guidance development
  - Facilitate evaluation of generic drug applications
  - Allow for risk-based assessments of new drugs

Challenge Question #1

Advantages of LC-HRMS for characterization of peptides include:

A. Qualitative and quantitative data in a single experiment, no need for a UV chromophore, and no specialized training required for QC lab staff

B. Qualitative and quantitative data in a single experiment, can resolve co-eluting analytes, and no specialized training required for QC lab staff

C. Qualitative and quantitative data in a single experiment, can resolve co-eluting analytes, and no need for a UV chromophore

D. No need for a UV chromophore, no specialized training required for QC lab staff, and can resolve co-eluting analytes

Challenge Question #2

A particle sizing technique that can also differentiate between chemical components is:

A. Morphology-directed Raman spectroscopy

B. Laser diffraction

C. Bio-relevant mouth-throat models and cascade impactor analysis

D. Dynamic light scattering

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Questions?

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