Scientific and Regulatory Considerations for Synthetic Peptides Referencing Peptide Drug Products of rDNA Origin

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Promises about Generic Drugs

FDA approved generic drugs are **Therapeutically Equivalent** to the **Reference Listed Drugs (RLD)**

- They can be freely substituted for the RLD (brand product)
- Generic and RLD have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

Therapeutic Equivalence = Pharmaceutical Equivalence + Bioequivalence

Outline: Considerations for Generic Synthetic Peptide Drugs Referencing RLD of rDNA Origin

- Introduction: Recent Peptide Guidance
- Regulatory considerations on peptide-related impurities
  - Case study: teriparatide impurity profile
  - Immunogenicity risk assessment
- Other consideration: device comparability

ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Xiaohui Jiang at 240-402-7964.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578365.pdf

Scope of the Guidance

- Peptides (≤ 40 amino acids) are regulated as drug products
- Synthetic peptide drug products referencing RLDs of rDNA origin
- Five peptide products: glucagon, liraglutide, nesiratide, teriparatide, and teduglutide

Pharmaceutical Equivalence: Active Ingredient

- Physiochemical properties
- Primary sequence
- Secondary structure
- Oligomer and higher order structures
- Biological activities (*in vitro* or *in vivo*)

Impurities in Peptide Drug Products

- Residual chemicals
  - FDA and ICH guidelines
- Peptide-related impurities
  - Degradation related
    - Should be same between RLD and generic
  - Process related
    - Synthetic process related: deletion, insertion, etc.
- Host-cell related impurities
  - Applicable to products of rDNA origin only

Peptide-related Impurities

- For specified impurities common to proposed generic and RLD
  - Level in proposed generic ≤ RLD
- For any new impurities in the proposed generic
  - > 0.5% is not acceptable
  - Impurities at 0.1%- 0.5% identified, characterized and justified for not affecting the safety and efficacy

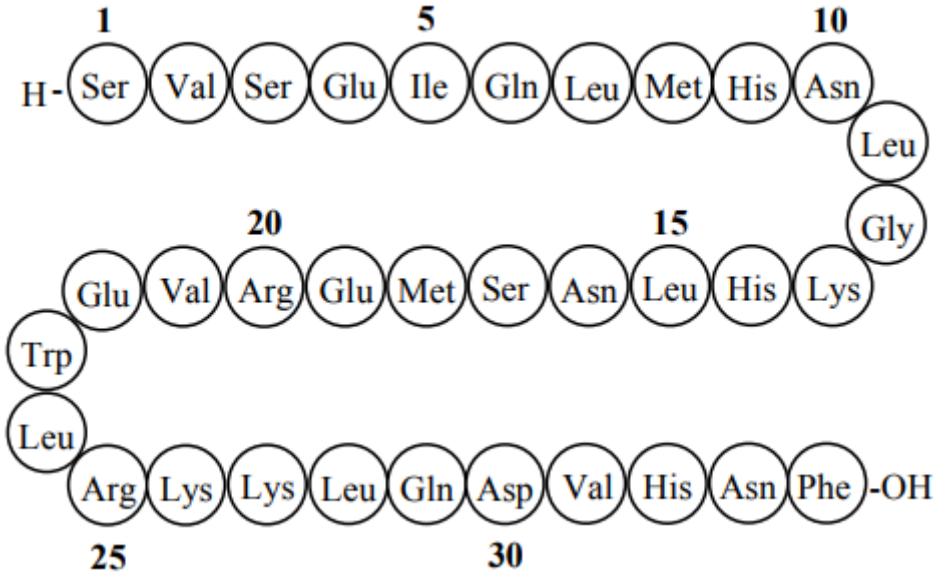
Need to know RLD's impurity profile range

Immunogenicity Risk Assessment

Case Study: Teriparatide

RLD Information

NDA: 021318
Name: FORTEO®
Holder: Eli Lilly
Indication: Treatment of osteoporosis
Process: Recombinant (rDNA) expressed in E. Coli.
Chemistry: 1-34 fragment of human parathyroid hormone (1-84)



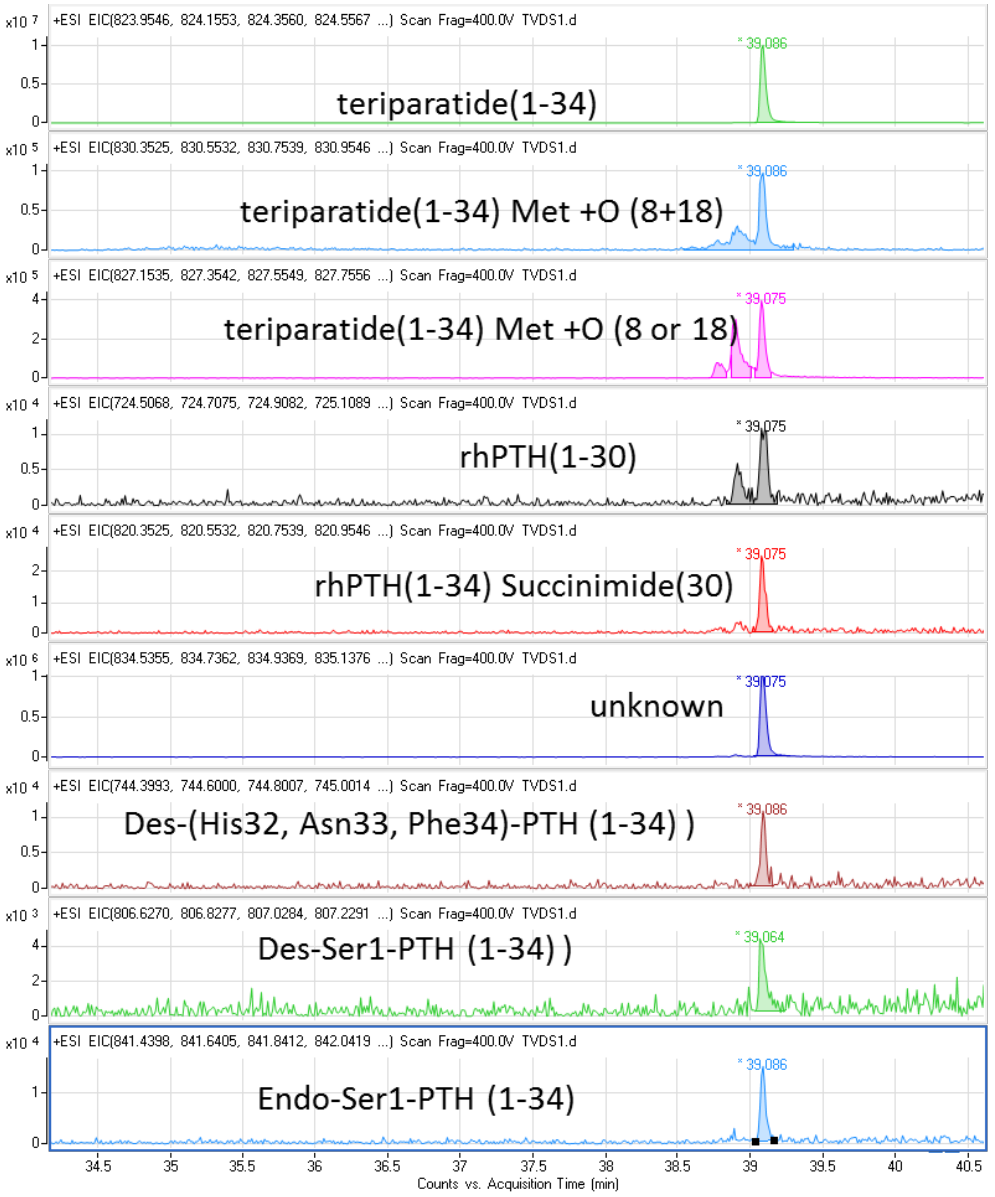
UPLC-HRMS Analysis of Impurity Profiles

Purpose: Evaluate impurity profiles of FORTEO® using UPLC-HRMS

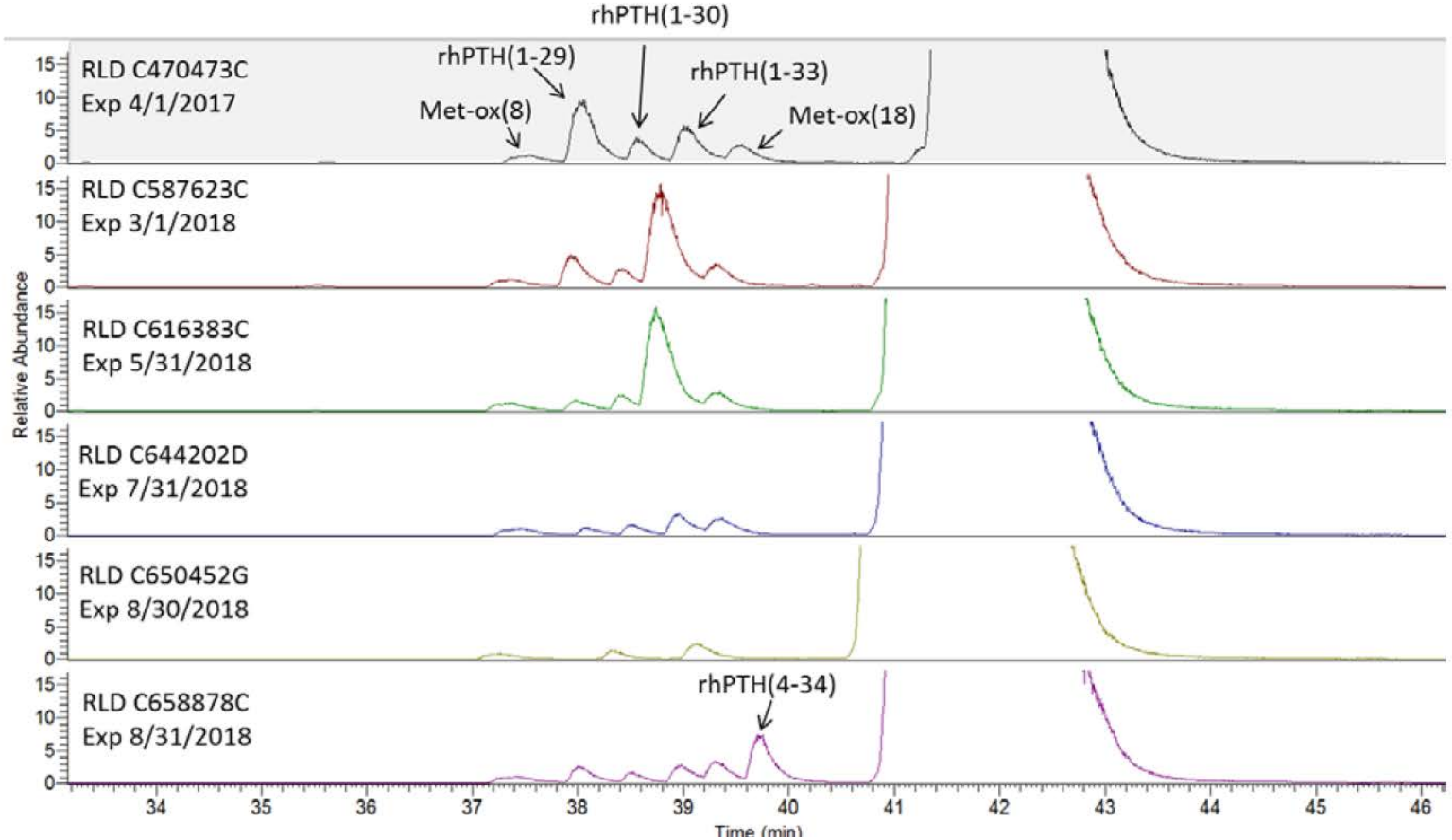
1. Quantitation of impurities by UPLC-HRMS and establish LOQ for individual peptide impurities
2. Establish peptide-related impurity profiles in the RLD

RLD Impurity Profiling

- LC-MS can identify, separate and quantify co-eluting impurities
- LOD = 0.02%
  LOQ = 0.05%
- Potential issues with quantitation using MS
  - In-source modifications
  - Signal suppression
  - Linearity



Impurity Profiles from Six Lots of RLD



- RLD has lot-to-lot variations in impurity profiles
- Impurity variations may be due to differences in process and/or shelf-life

Summary: Impurity Profiling of Teriparatide using UPLC-HRMS

- UPLC-MS analysis is capable of detecting and quantifying peptide impurities below 0.1%
- UPLC-MS method needs to be validated
  - Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics (July, 2015)
    https://www.fda.gov/downloads/drugs/guidances/ucm386366.pdf
- Orthogonal methods and experiments can be used to verify the results
- Impurity profiles from multiple lots of the RLD, throughout the product shelf life, should be evaluated

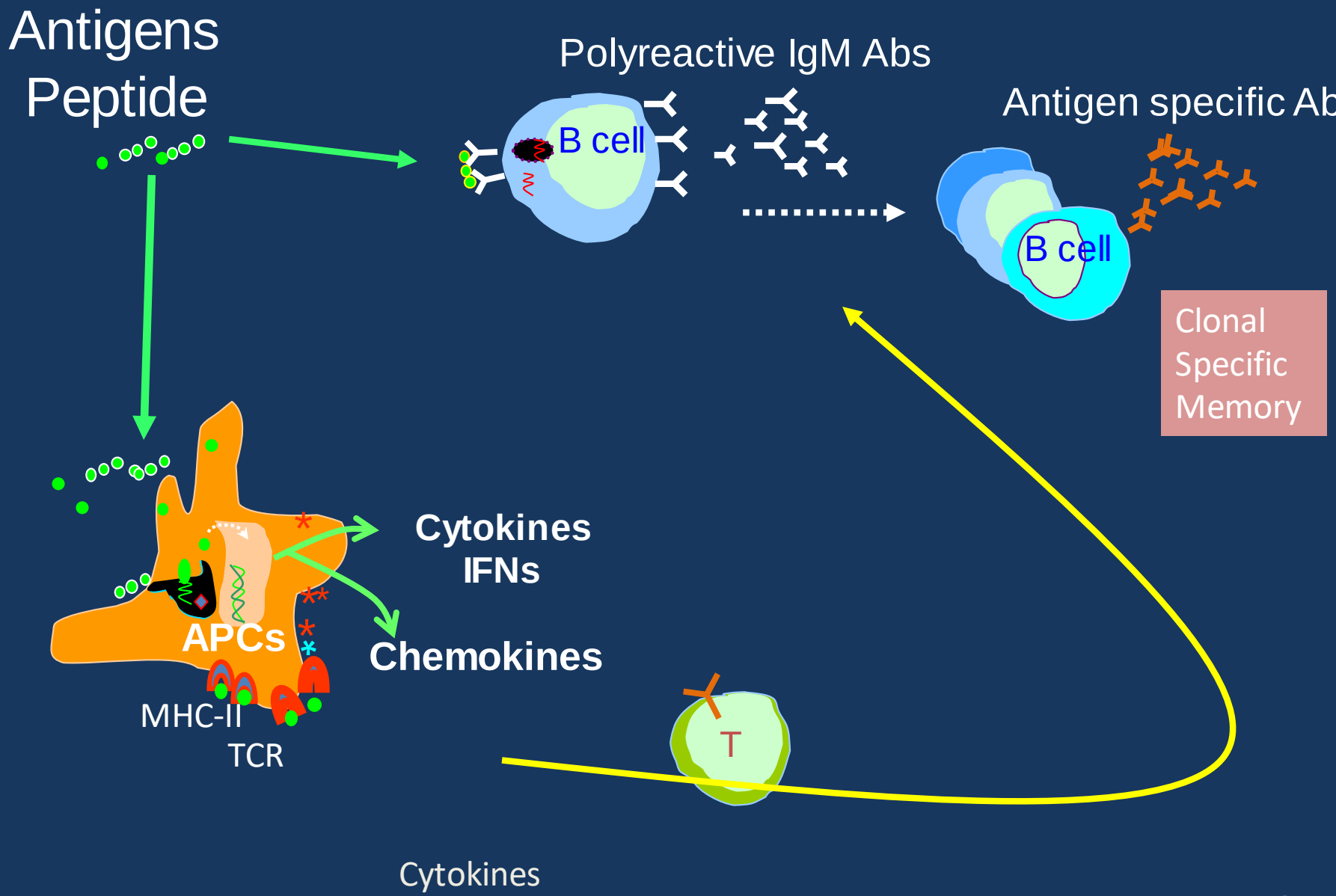
Immunogenicity May Impact Product Safety and Efficacy: Examples

- Developing antibodies
  - Affect the PK by enhancing clearance or delay clearance
  - Neutralizing antibodies can diminish efficacy
  - Anti-drug antibodies (ADA) can cross-react to endogenous non-redundant proteins, and may cause deficiency syndrome

- Hypersensitivity responses
  - Cytokine Release Syndrome – Rapid release of proinflammatory cytokines
  - Anaphylaxis – serious, acute allergic reactions

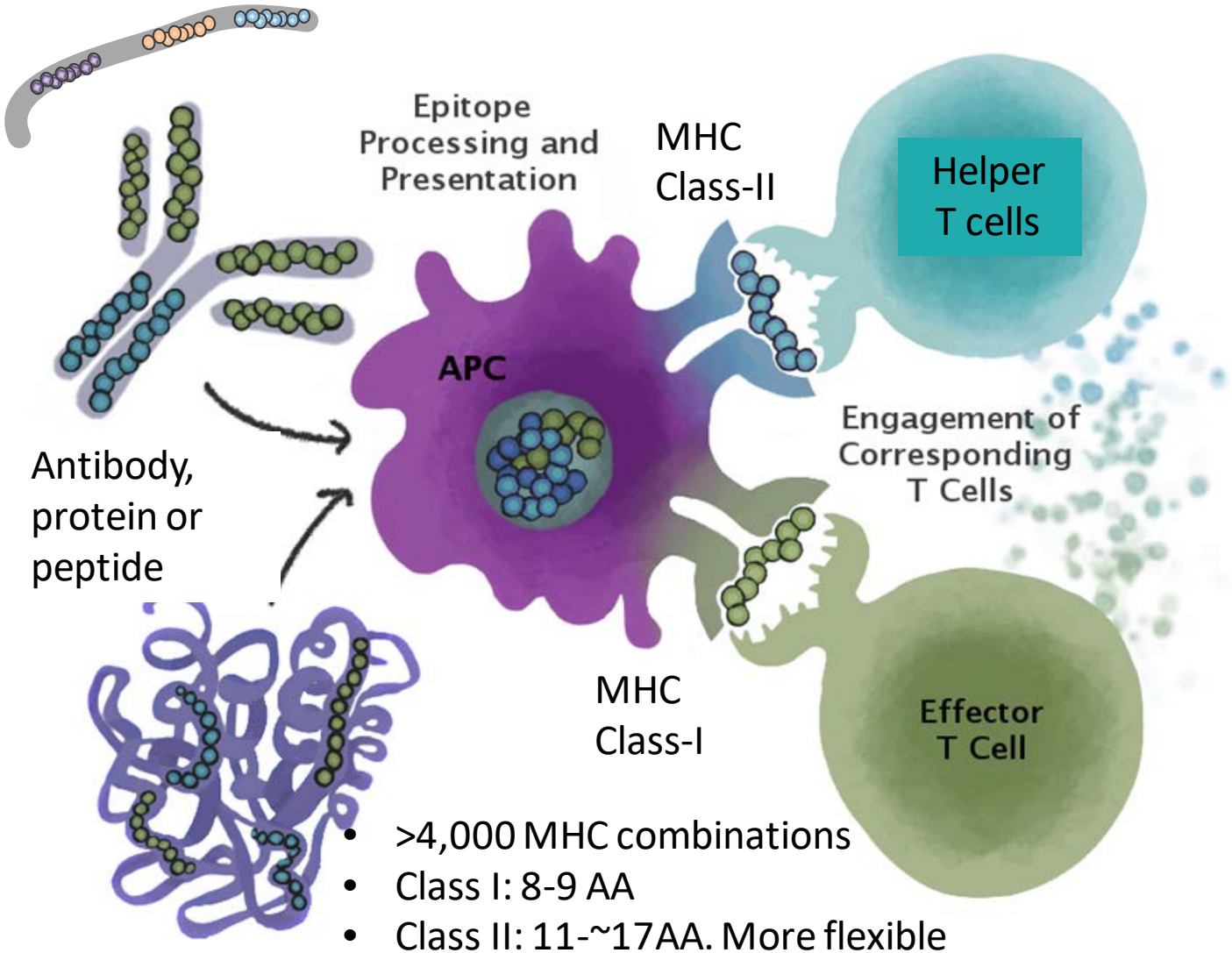
Refer to Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products (Aug 2014)
https://www.fda.gov/downloads/drugs/guidances/ucm338856.pdf

Immune Responses



Courtesy of Dr. Daniela Verthelyi

Cognate Activation of T-cells



- >4,000 MHC combinations
- Class I: 8-9 AA
- Class II: 11-~17AA. More flexible
- T cells w/high affinity for self are deleted / anergic

Courtesy of Dr. Daniela Verthelyi

Evaluating the Risk of Immunogenicity in the Proposed Peptide Products

- T-cell activation through MHC binding by peptide-related impurities
  - *In silico* studies MHC binding, *in vitro* binding and functional assays of specific impurities

- Innate immune activity comparison between proposed generic and RLD products
  - *In vitro* cell-based assays
  - Animal models

MHC = Major Histocompatibility Complex

In silico MHC Binding Prediction

Evaluate the likelihood of MHC binding and the presence of T-cells epitopes by high-throughput screening of partial and complete sequences of peptide-related impurities

- Different *in silico* tools predict binding to MHC and identify potentially immunogenic regions

- Evaluate the immunogenic potential of T-cell epitope clusters for
  - individuals of different MHCs
  - Potential cross-reactivity with non-redundant proteins/peptides

Adopted from slides by Dr. Daniela Verthelyi

However…

- Population differences

  The genes encoding the MHC class I and class II are highly polymorphic among the population (~4000 combinations of HLA class II α and β subunits).

- MHC-II is harder to predict

  MHC-II molecule is open at both ends allowing binding of peptides extending out of the groove.

- B-cell epitopes are hard to predict

  Epitope is not necessarily linear

Adopted from slides by Dr. Daniela Verthelyi

Evaluate the Innate Immune Activity

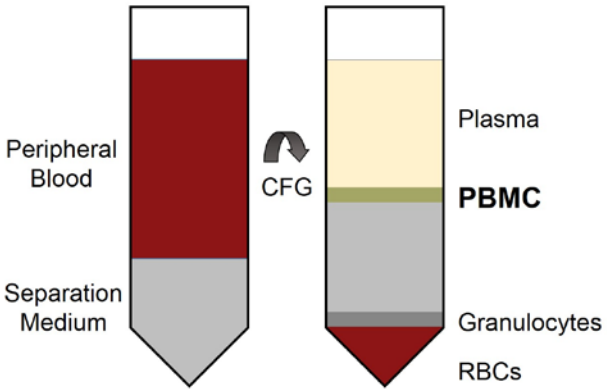
Examples of *in vitro* and *in vivo* Studies*

- *In vitro* cell-based assays
  - Peripheral Blood Mononuclear Cell (PBMC) Assay
  - Cell lines (HEK293-TLR, macrophage, monocytes)
- *In vivo* animal based
  - Immune-humanized mice

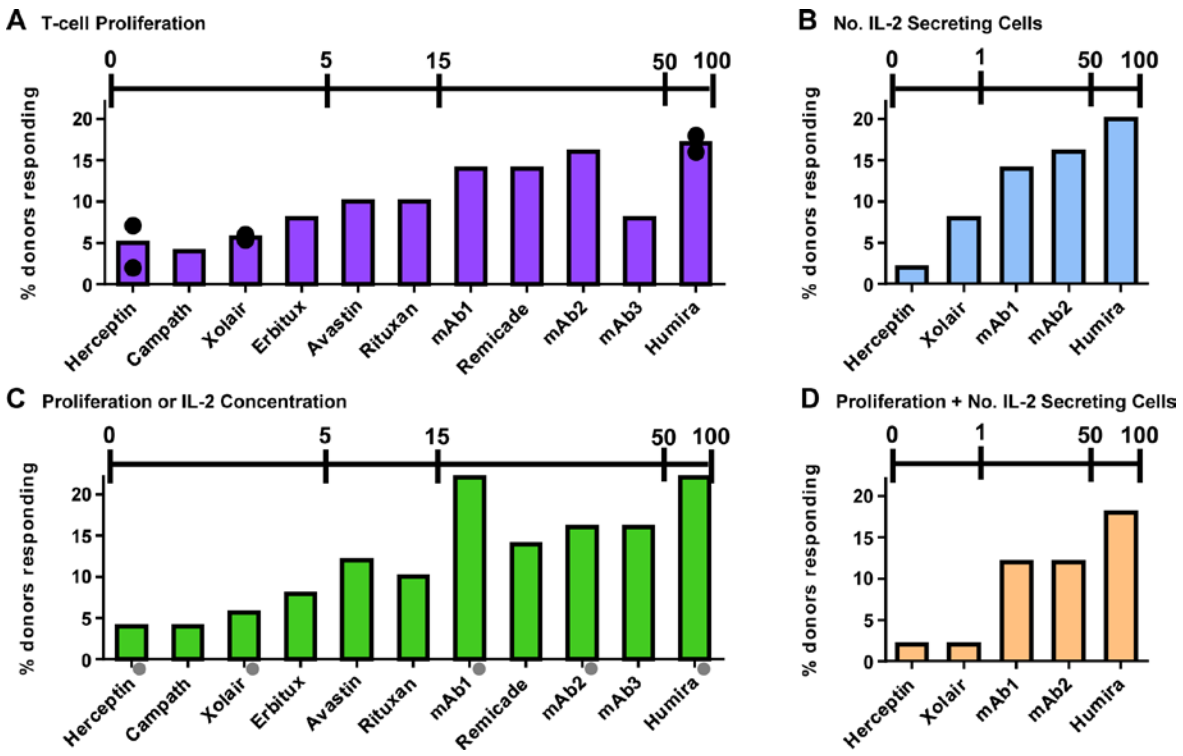
*The Agency may recommend additional *in-vitro* and/or *in-vivo* studies, as appropriate

PBMC Assay

PBMC cells are extracted from donated human blood, hence it may be considered to have some clinical relevance.



Studies have shown the capability of predicting clinical immunogenicity by monitoring T-cell proliferation and cytokine releases



*Joubert *et al*. PLoS, 2016

Cell Line (HEK-293, Macrophages/ Monocytes) Assays

Cell-based assays can be used to support the immunogenicity risk assessment of particular impurity and/or drug product, particularly when comparing potential risk.

HEK-BLUE and macrophage cell lines transfected with Toll-Like Receptors (TLRs) allow for recognition of TLR ligands with sensitivity that is similar to human PBMCs.

Table 2. Limit of detection for PPR ligands by monocyte/macrophage cell lines and PBMC.

TLR ligand	RAW-BLUE	MM6	THP1	PBMC
Pam3CSK4	500pg/mL	500pg/mL	100pg/mL	1ng/mL
Poly I:C	<LLOD	<LLOD	1μg/mL	100ng/mL
Endotoxin	100pg/mL	10pg/mL	10pg/mL	1pg/mL
Flagellin	<LLOD	<LLOD	5μg/mL	5μg/mL
FSL-1	100pg/mL	100pg/mL	100pg/mL	100pg/mL
Imiquimod	100ng/mL	<LLOD	<LLOD	100ng/mL
CLO75	50ng/mL	<LLOD	<LLOD	100ng/mL
CpG	60ng/mL	<LLOD	<LIOD	100ng/mL
Zymosan	1μg/mL	10ng/mL	10ng/mL	1ng/mL
MDP	<LLOD	10μg/mL	<LLOD	10ng/ mL

doi:10.1371/journal.pone.0125078.t002

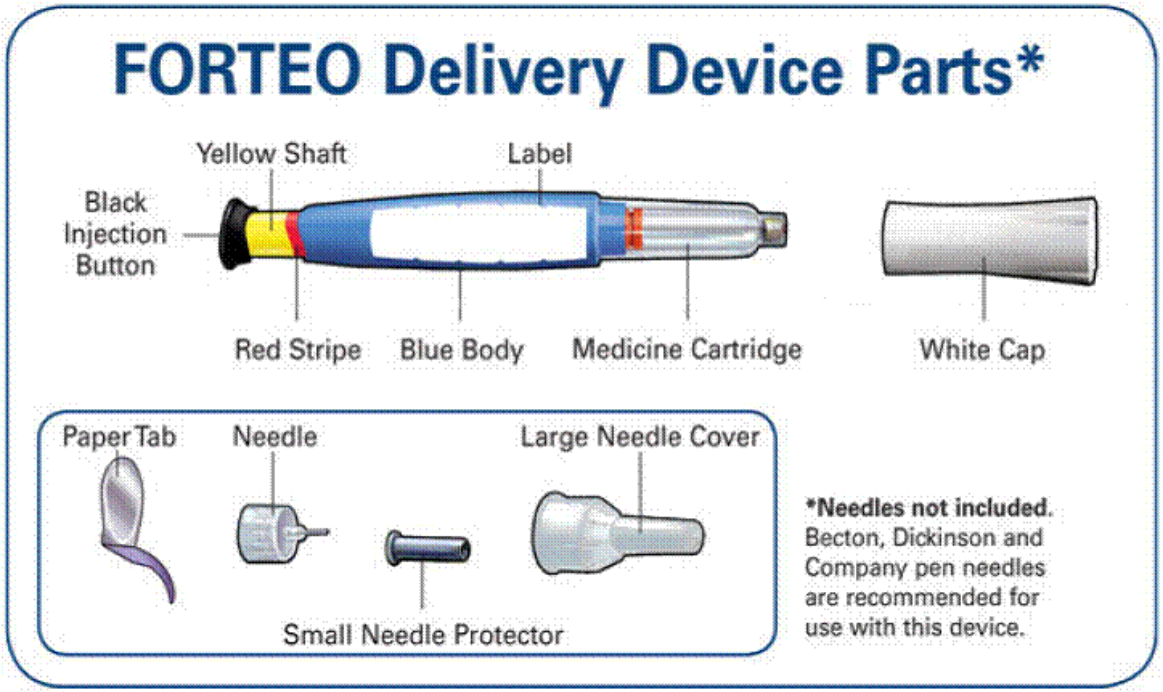
*Haile *et al.* PLoS ONE, 2015

Summary: Immunogenicity Risk of Peptide-related Impurities

The best approach is to develop highly purified drug products without differences in peptide-related impurities

If not possible….
Methods and studies are needed to evaluate the risk of triggering immune or inflammatory responses

Additional Area of Consideration: Drug–Device Combination Products



Comparability of Devices

- Applicants are encouraged to minimize differences in proposed generic product and RLD devices.
  - Device design and operating principle
  - User interface
- Comparative analyses may be needed to confirm that a proposed difference in device design and/or labeling instructions is still acceptable for substitution without the need for intervention by a health care provider and/or without additional training prior to use.

Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry

DRAFT GUIDANCE

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January 2017

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf

Conclusion: Considerations for Generic Peptide Drugs Referencing rDNA RLDs

Generic and RLD should have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

- Comparable API and product (including device[1])
- Comparable safety profiles[2]
  - Peptide-related impurities
  - Potential immunogenicity risks

1. Draft Guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA, Jan 2017
2. Draft Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin, Oct 2017

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