Overview: Non-clinical Immunogenicity Assessment of Generic Peptide Products

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Disclaimer

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

Workshop Agenda:

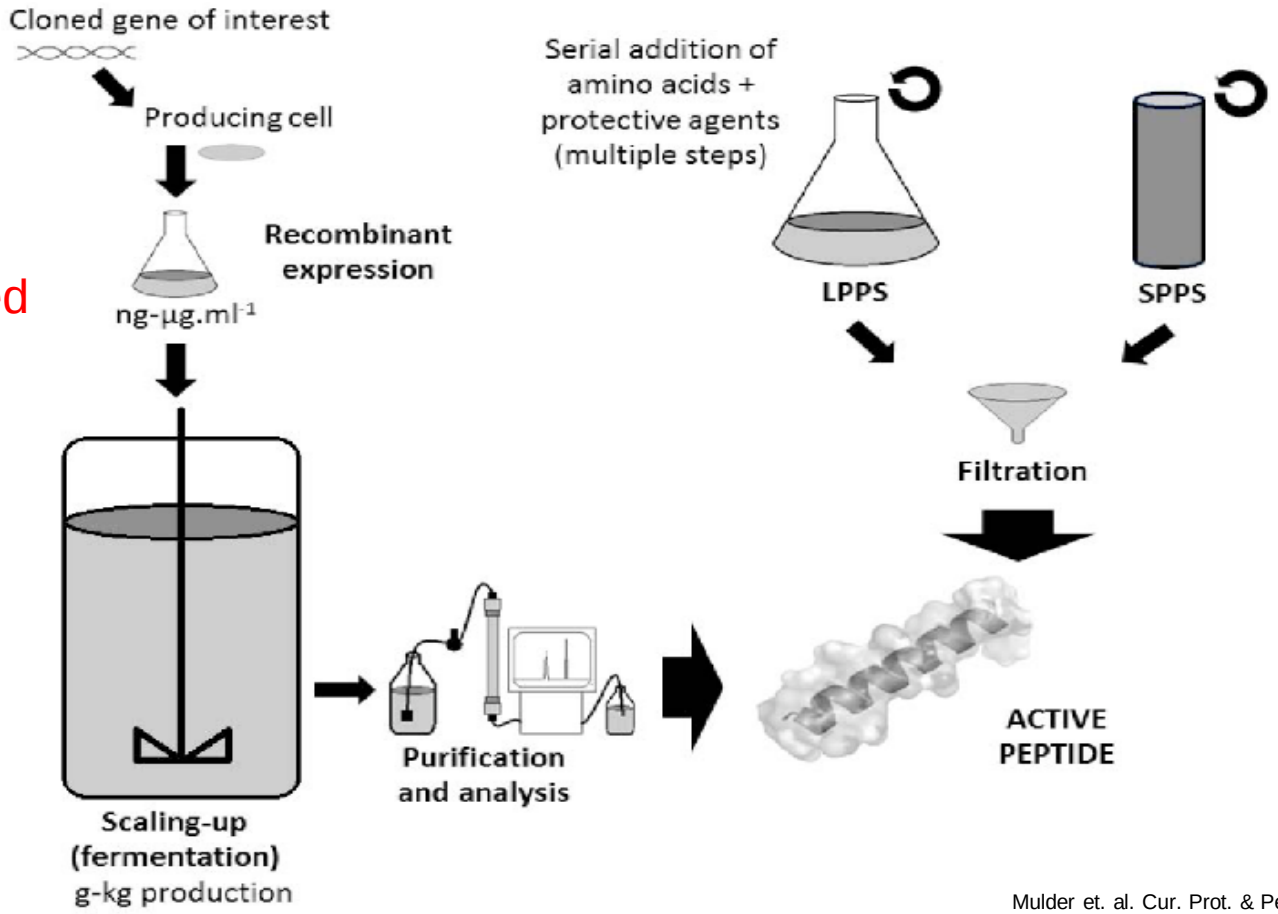
- Session 1: In silico methods to assess binding affinity to MHC: Method validation and MHC selection
- Session 2: In vitro assays to monitor innate immune activation and inflammation: technical challenges and best practices
- Session 3: Assays monitoring antigen-specific T cell activation: technical challenges and validations
- Session 4: Using non-clinical data to assess immunogenicity risk

Immunogenicity Risk Needs to be Assessed Because It May Impact Safety and Efficacy

- Developing antibodies can affect the pharmacokinetics (PK) by enhancing or delaying clearance
  - Neutralizing antibodies can diminish efficacy
- Anti-drug antibodies can cross-react to endogenous non-redundant proteins, and may cause deficiency syndrome
- Hypersensitivity responses can lead to
  - Cytokine Release Syndrome – rapid release of proinflammatory cytokines
  - Anaphylaxis – serious, acute allergic reactions

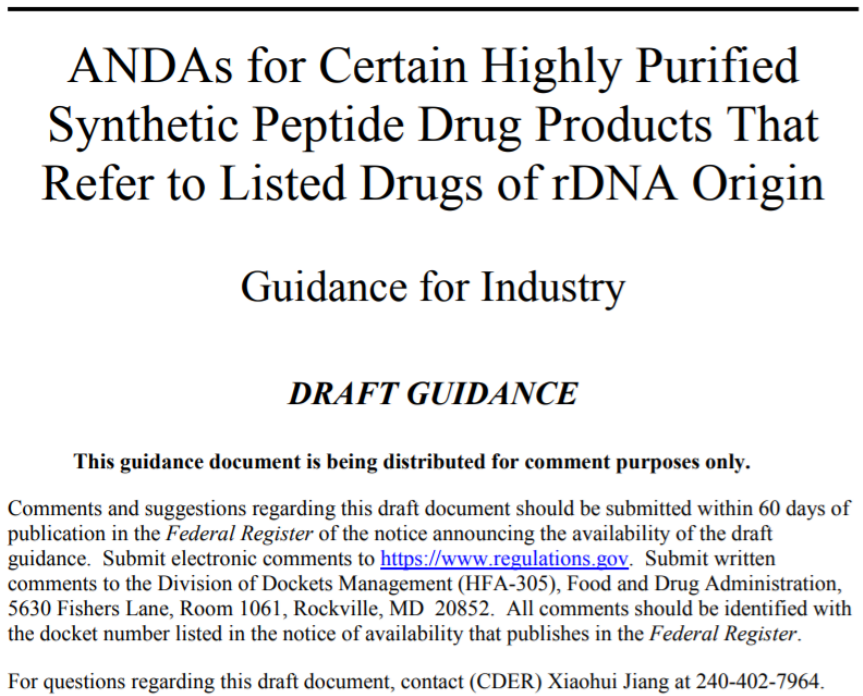
Peptide Made through Recombinant and Synthetic Processes

Differences in process-related impurities



Mulder et. al. Cur. Prot. & Pep. Sci., 2013

FDA Outlined Current Thinking and a Pathway in following Guidance for **Glucagon, Liraglutide, Nesiritide, Teriparatide, and Teduglutide**



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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

Peptide-related Impurities

- For specified impurities common to proposed generic and reference listed drug (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, including comparative immunogenicity risk tests

Scientific rationale for the guidance:

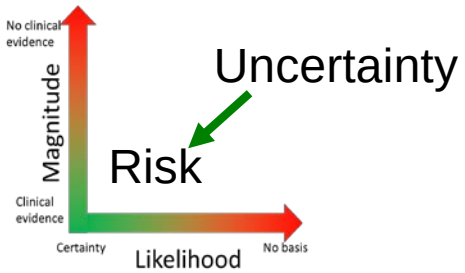
Immunogenicity Risk = Probability X Consequences

- Population ✓
- Treatment ✓
- Product

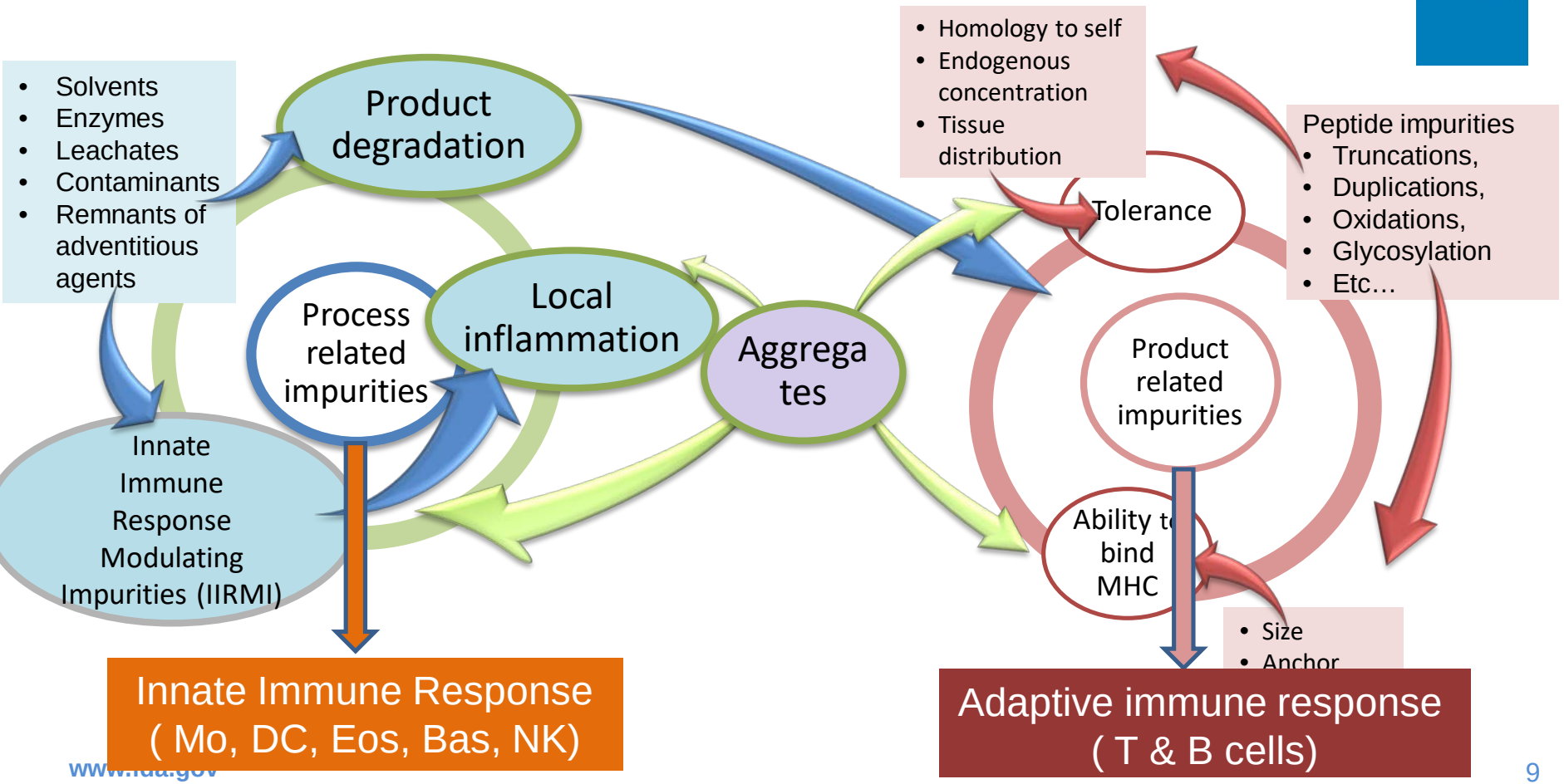
- Safety ✓
- Efficacy ✓

If API is same, then the only residual uncertainty are the impurities

- Product-related impurities
- Process-related impurities
- Aggregates



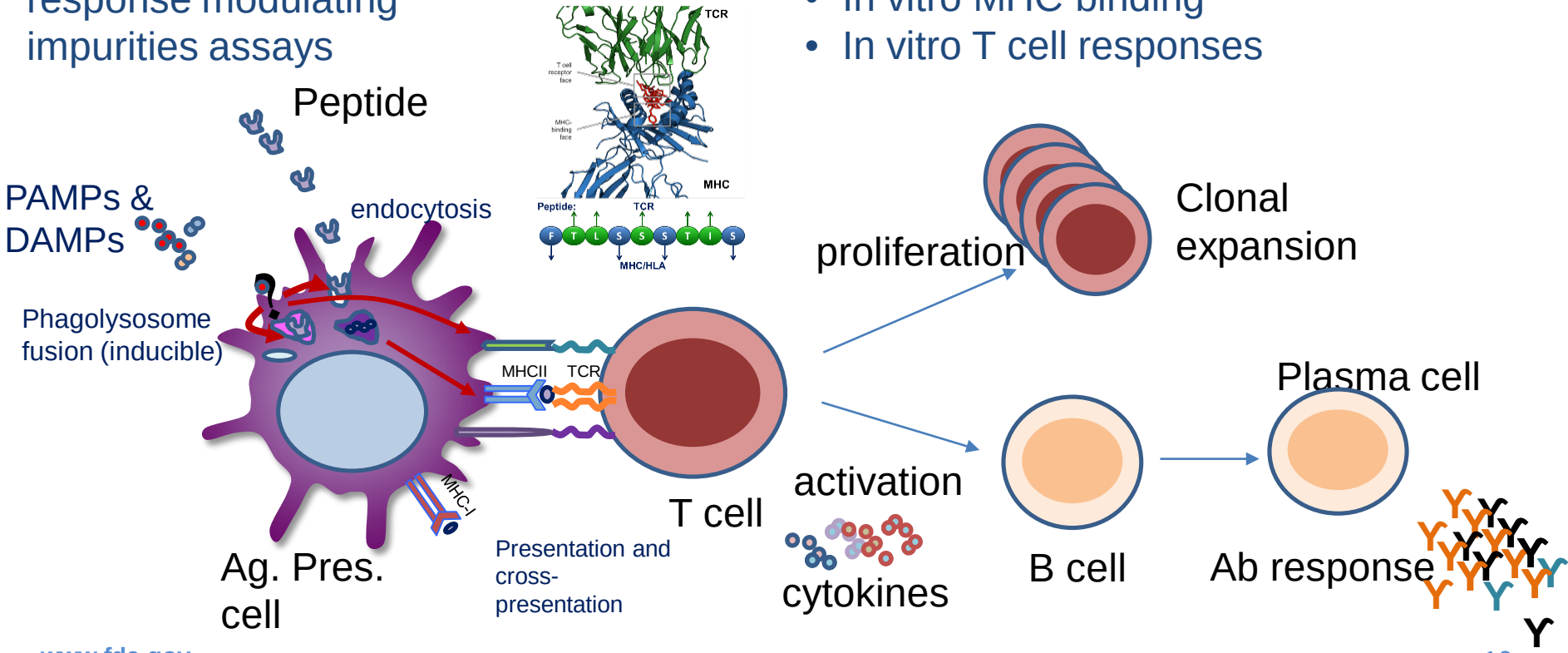
Product and Process Related Impurities:



Immune response: risk assessment tools

- Innate immune response modulating impurities assays

- In silico 1ry sequence
- In vitro MHC binding
- In vitro T cell responses



Criteria: No Increased Risk relative to the RLD

- Assessing the risk of product and process related impurities is not sufficient to determine the immunogenicity risk, but can support, as part of a totality of evidence approach, a risk assessment of “relative” immunogenicity risk as compared to the product that was used in clinical trials.

- However, establishing “no increased risk” requires well-validated assays with demonstrated capability of detecting impurities that impact on immunogenicity risk.

Objective of the Workshop

- Discuss regulatory concerns and considerations regarding the use of non-clinical assays for immunogenicity assessment of generic peptides
- Foster communication regarding technical challenges with validating or performing assays to assess immunogenicity risk and help establish best practices.
- Explore future research directions that the facilitate the performance of sensitive and reproducible assays to assess the immunogenicity risk of impurities in generic peptide products