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Overview: Non-clinical Immunogenicity Assessment of Generic Peptide Products

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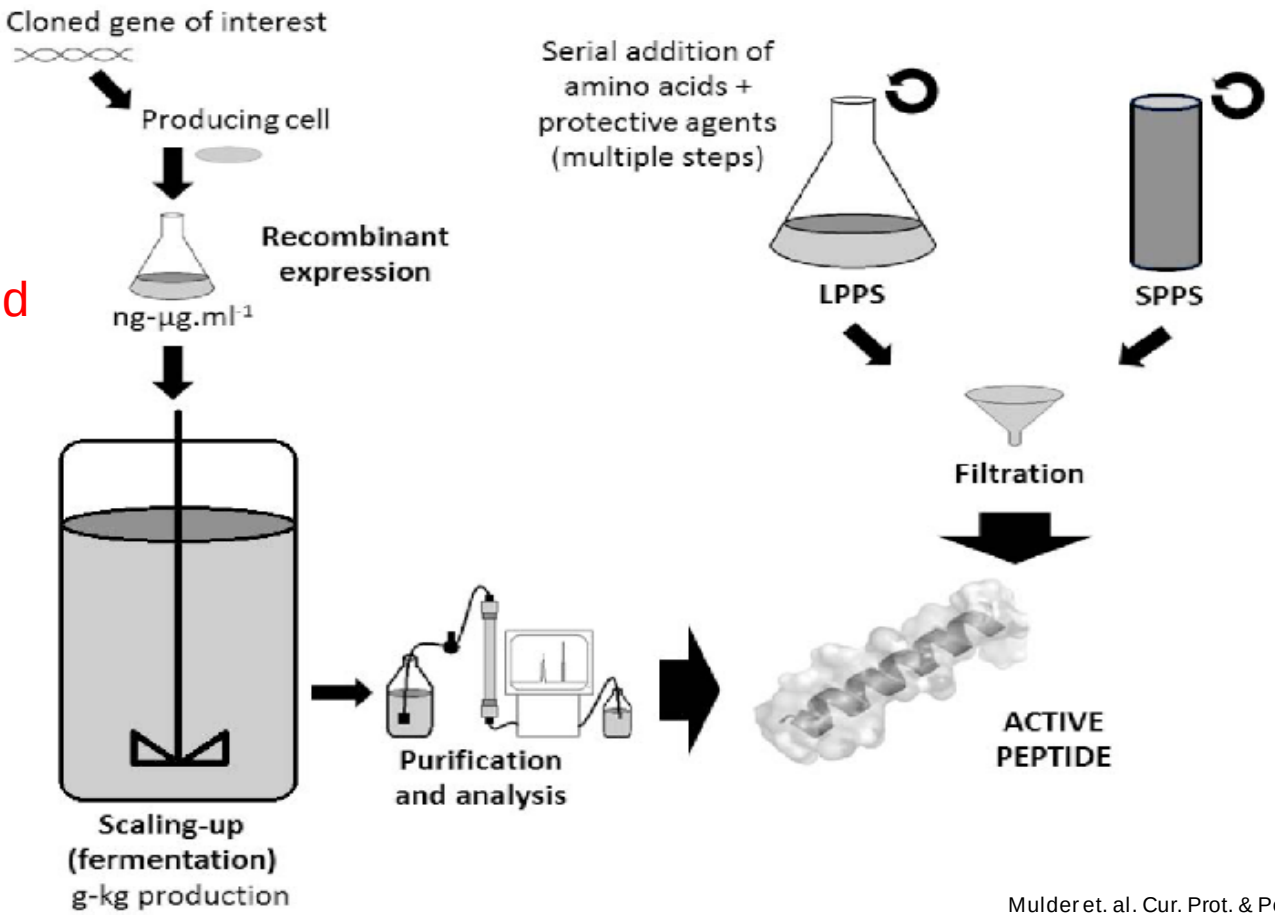
This presentation reflects the views of the author and should not be construed to represent FDA's official views or policies.

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

Peptide Made through Recombinant and Synthetic Processes

Differences in process-related impurities

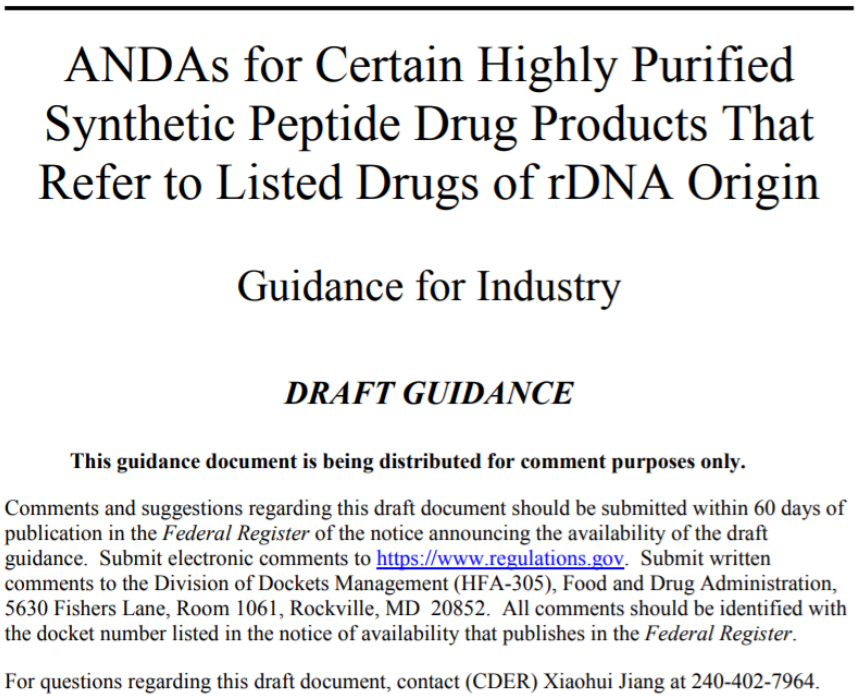


Mulder et. al. Cur. Prot. & Pep. Sci., 2013

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

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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

The underlying guidance rationale:

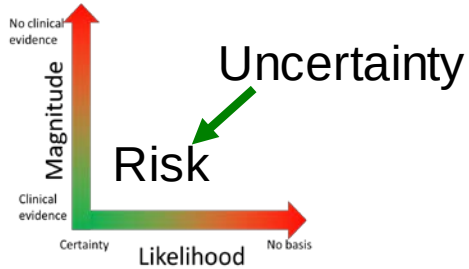
Immunogenicity Risk = Probability X Consequences

- Population ✓
- Treatment ✓
- Product

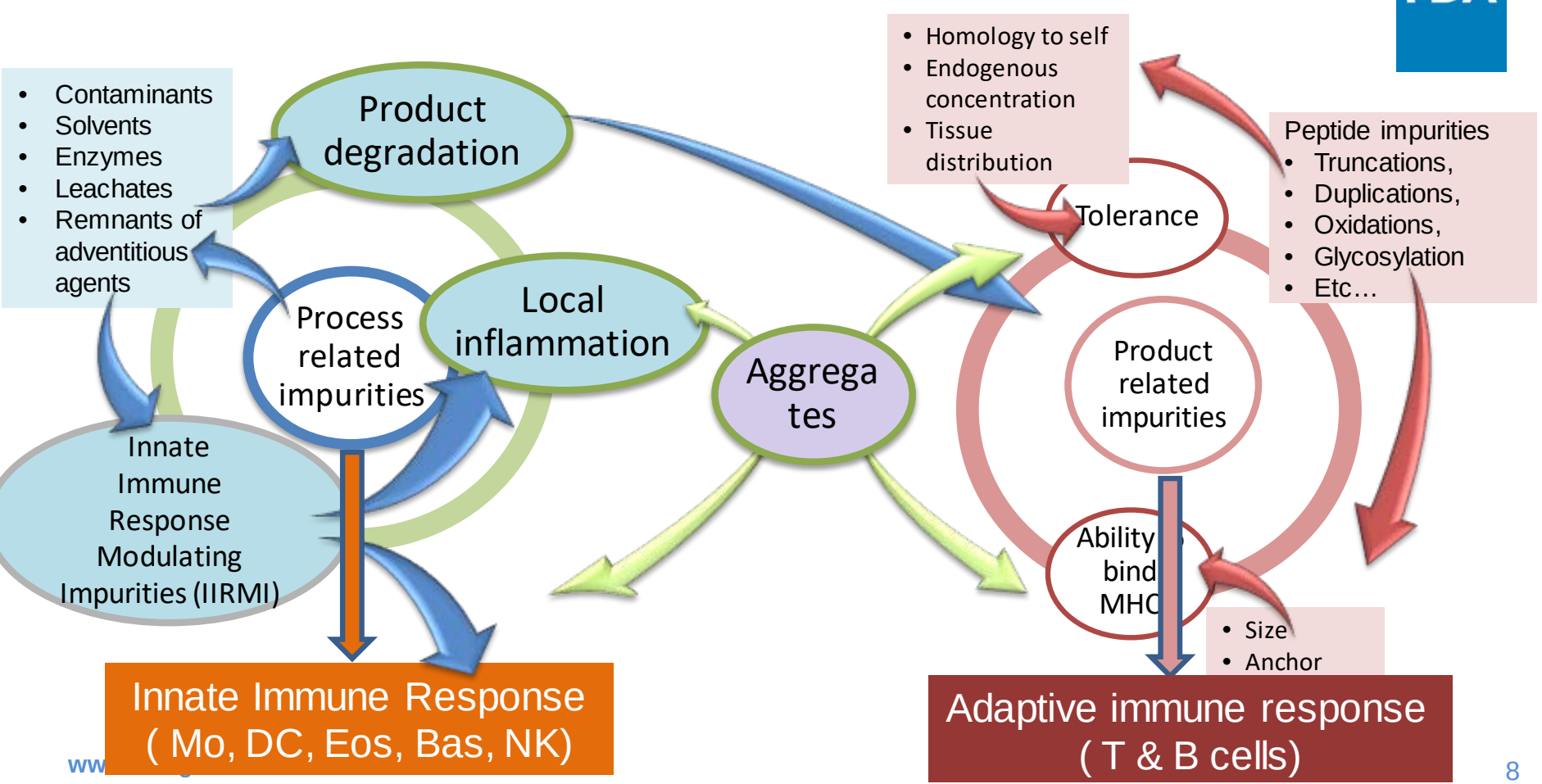
- Safety ✓
- Efficacy ✓

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

- Product-related impurities
- Process-related impurities



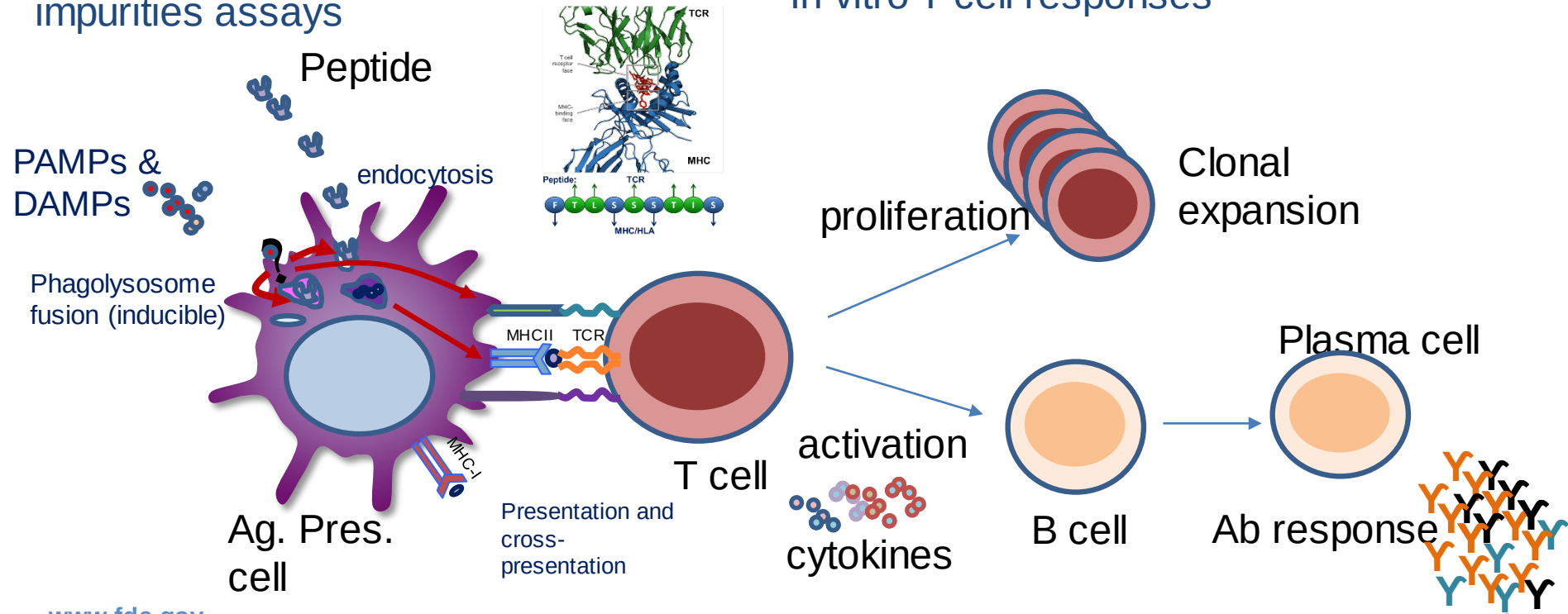
Product and Process Related Impurities:



Immune response: risk assessment tools

- Innate immune response modulating impurities assays

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



Regulatory Criteria: No Increased Risk

- Assessing the risk of product and process related impurities is not sufficient to determine the immunogenicity risk, but can support a risk assessment of “relative” immunogenicity risk as compared to the product that was used in clinical trials.
- Assessment of Product and Process-Related Impurities using orthogonal assays for Product and Process-related Impurities contributes to the totality of evidence used to assess the potential immunogenicity risk.
- 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 with using non-clinical assays for immunogenicity assessment
- Communicate some of the technical challenges with validating and performing non-clinical immunogenicity assays
- Explore future research directions for standardizing the non-clinical immunogenicity assays to be used in generic peptide products and establishing best practices.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Examples of Concerns and Questions with In silico and in Vitro Assays

- Are the assays used suitable to address the impurities?
- Assay development and validation
  - Duration of the assay, number of cells per well, concentration of the product used, suitability controls, cell viability, etc.
  - Validation of assay sensitivity
- Donor peripheral blood mononuclear cells (PBMC) population used?
  - HLA classes diversity: HLA DR, DQ, DP
  - Target population
  - Prior knowledge (e.g. in silico studies)
- How to correlate the results from in vitro assays to what is known regarding clinical immunogenicity?