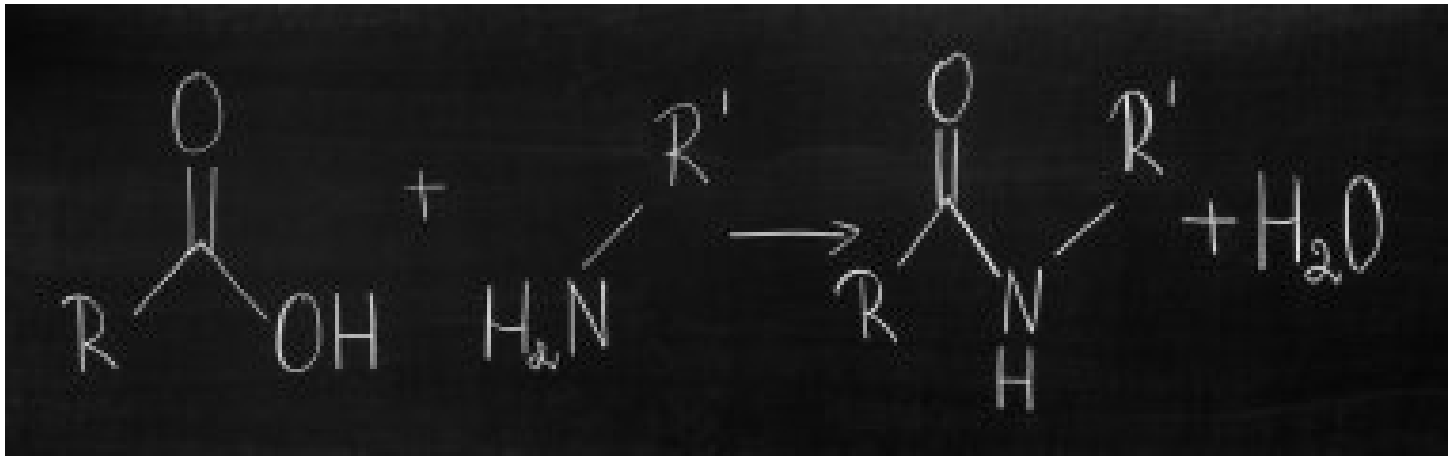

CMC Regulatory Considerations for Complex Generic Peptides

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Everyone deserves confidence in their *next* dose of medicine.

Pharmaceutical quality assures the availability, safety, and efficacy of *every* dose.

Disclaimer

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

What is a peptide? – FDA definition

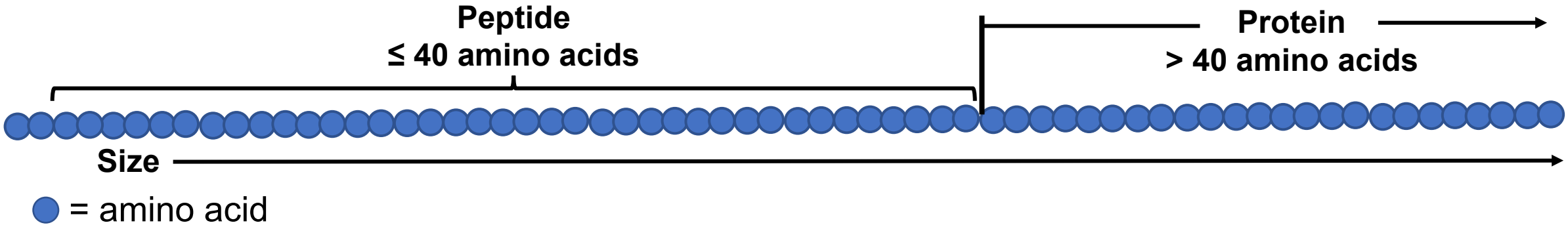
- FDA Final Rule "Definition of the Term 'Biological Product'" (85 FR 10057 March 23, 2020):

*"the term **protein** would mean any alpha amino acid polymer with a specific, defined sequence that is **greater than 40 amino acids in size**…"*

- FDA draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* (Revision 3):

*"FDA considers any alpha amino acid polymer with a specific, defined sequence that has **40 or fewer amino acids to be a peptide**…"*

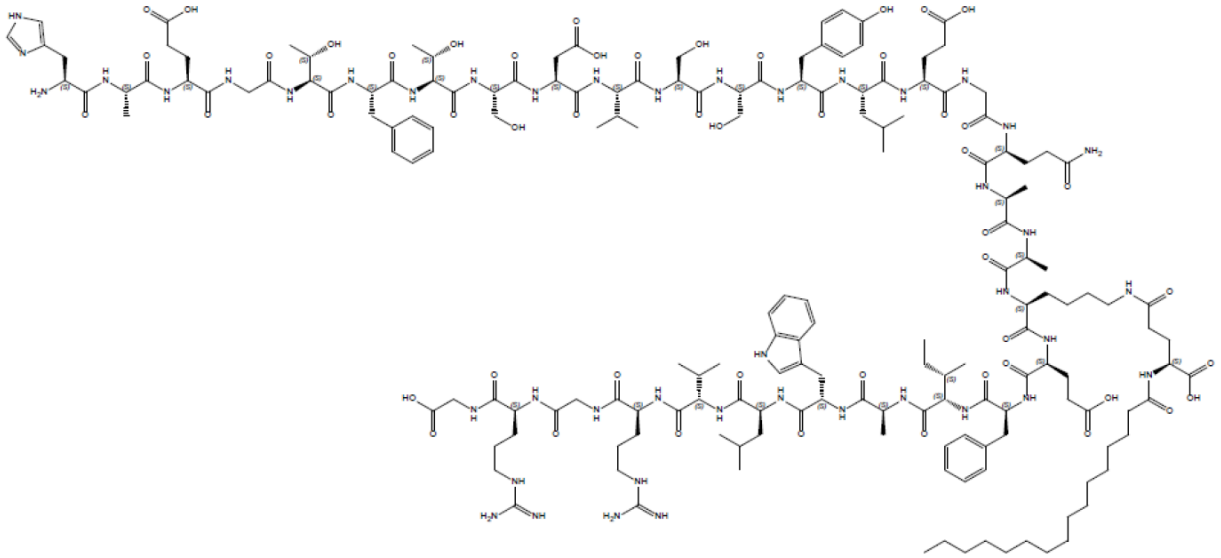
Peptide: any polymer composed of 40 or fewer amino acids



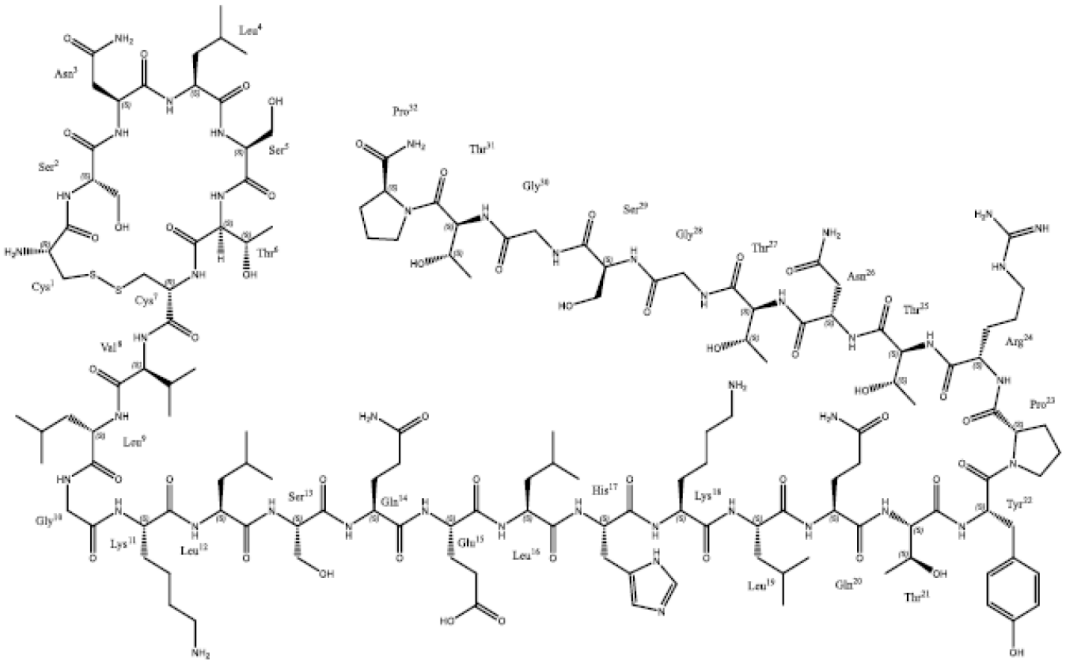
Regulatory implications: peptide versus protein classification determines regulatory pathway (NDA/ANDA vs. BLA/biosimilars) and review responsibilities/jurisdiction

Talk focus: Chemically synthesized peptides

- Peptides can be **produced through chemical synthesis,** fermentation, or recombinant DNA technology. This talk will focus on chemically synthesized peptides.
- Peptides with no greater than 40 amino acids (AAs) having **complex higher-order structure and/or potential immunogenicity concerns** are considered as complex APIs (e.g., liraglutide, calcitonin).



Liraglutide



Calcitonin salmon

Sameness to RLD

- To achieve pharmaceutical equivalency, ANDAs *must* contain information to show that the active ingredient of the proposed generic drug product is the “same as” that of the RLD.
- For complex generic peptide drug products, sameness is usually directly related to API sameness as most formulations are generally simple.
- The sameness can generally be established through physicochemical characterization and biological evaluation.
- Although compendial standards may be available, comparative testing of complex generic peptide with RLD is recommended.
- ANDA applicants are encouraged to apply orthogonal analytical methods (high resolution mass spectrometry, liquid chromatography, high-resolution multi-dimensional NMR) to characterize the following properties and other properties, as appropriate:
  - Primary sequence and physicochemical properties
  - Secondary structure
  - Oligomer/aggregation states
  - Biological activities (in vitro or animal studies)

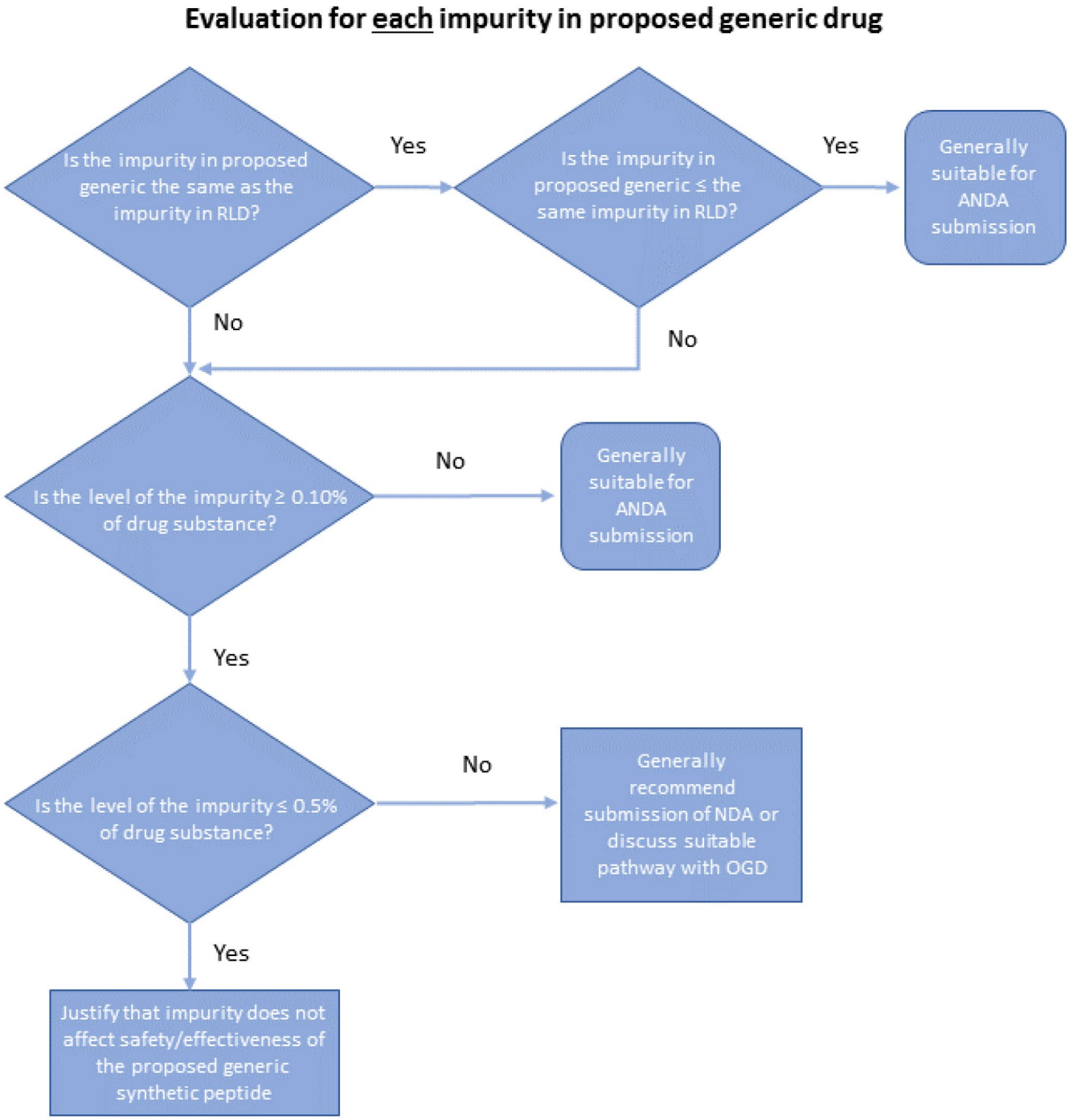
Generic synthetic peptides with RLDs of rDNA origin

- Five approved peptides of rDNA origin: glucagon, liraglutide, nesiritide, teriparatide, and teduglutide.
- A determination of whether an application for the synthetic peptide should be submitted as an ANDA depends largely on its impurity profile as compared to the impurity profile for the peptide of rDNA origin.
- Differences in impurities, particularly peptide-related impurities, may affect the safety or effectiveness of a peptide drug product as compared to the RLD.
  - Some of the principles of this guidance may apply to other generic synthetic peptide products (e.g., comparative characterization of higher-order structure, oligomer/aggregation states, biological activity, peptide-related impurity profile)
  - Which aspects to apply also depends on immunogenicity risk assessment

Impurity profile

- Peptide-related impurities: insertion/deletion/modification to AA sequences, and residues of the peptide
- Host cell-related impurities: only in rDNA-origin peptides
- Other (non-peptide-related) impurities: residual solvents, reagents, metals, etc

- Identify all peptide-related impurities found at 0.10% or greater
- Existing peptide-related impurity NMT level found in the RLD
- New peptide-related impurity should be NMT 0.5% (a new peptide-related impurity level higher than 0.5% could raise immunogenicity concerns, and may not be adequately addressed through ANDA)



Impurity profile – cont'd

For each new impurity, applicant needs to provide:

- Full identification and characterization of the new impurity
- Justification data showing the new impurity does not modify physicochemical properties, biological activity, or immunogenicity risk
  - Does not contain sequences that have an increased affinity for major histocompatibility complex (MHC), known as T-cell epitopes.
  - Does not increase the aggregation propensity or the nature of the aggregates formed, especially under stress conditions
  - Does not contain impurities or contaminants that produce a greater or distinct stimulation of innate immune activity as compared to the RLD

Characterization studies

Characteristic	Analytical method
Structure/Sequence confirmation	MS, amino acid analysis (AAA), NMR (1D, 2D), HPLC-HRMS/MS, peptide mapping
Enantiomeric purity	Chiral AAA, GC-MS
Counter ion identity/content	RP-HPLC, ion chromatography
Higher order structure	Circular dichroism (far-UV/near-UV), FT-IR, NMR (1D, 2D)
Oligomers/aggregates	Size-exclusion chromatography
Biological activity	Cell-based and other biological assays

Impurity thresholds

	ICH Q3A (MDD ≤ 2 g)	Certain Generic Peptides with RLD of rDNA origin
Reporting Threshold	0.05%	--
Identification Threshold	0.10% (or 1.0 mg/day)	0.10%
Qualification Threshold	0.15% (or 1.0 mg/day)	0.5%

- Thresholds generally established on a **case-by-case** basis

ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin Guidance for Industry (MAY 2021)

Common deficiency areas

API characterization/sameness

- Sensitive and high-resolution analytical methods (e.g. UHPLC-HRMS/MS) for sequencing and peak purity.
- 2D NMR (TOCSY, NOESY, HSQC, etc) are generally recommended in addition to 1D NMR.
- Higher order structure by CD and NMR.
- Oligomer/aggregation propensity and the nature of the aggregates should be investigated and similar to RLD.
- Peptide mapping comparison study may be requested in addition to MS/MS sequencing, in order to confirm the identity and to monitor the degradative patterns of complex peptides.

Impurity profiling, identification, quantification

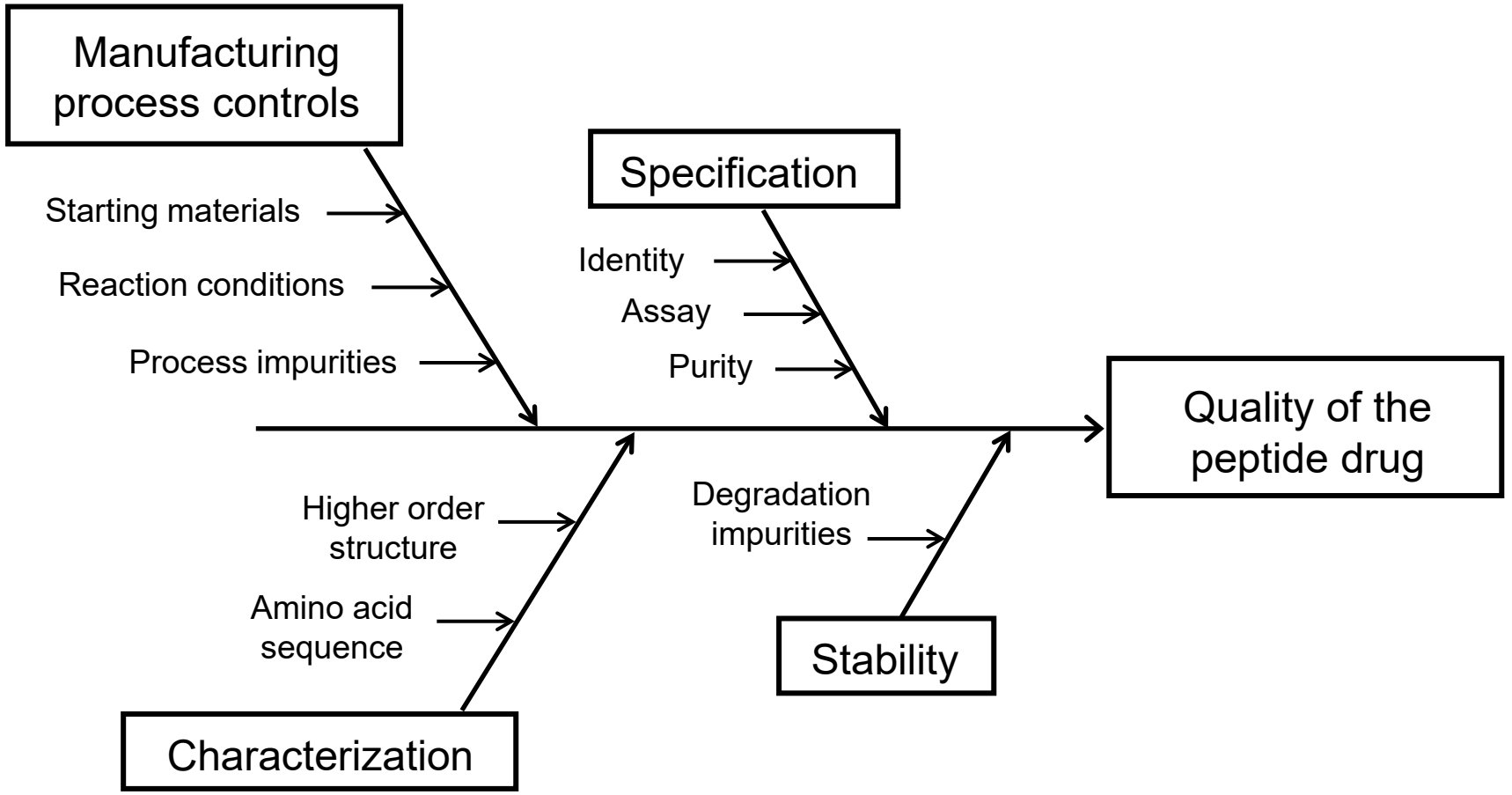
- NLT 3 batches of generic at release *vs* 3 batches at the end of shelf life *compared to* 3 batches of RLD prior to expiry (aging under label conditions).
- Provide impurity profile comparative study by sensitive and high-resolution analytical methods (e.g. UHPLC-HRMS/MS) to ensure peak purity, and to detect and characterize peptide-related impurities.
- D-isomers.
- Comparable innate immune response risk.

Reference: Liquid Chromatography-High Resolution Mass Spectrometry for Peptide Drug Quality Control by Zeng K et al., AAPS J. 2015, 17, 643-651

- Combination of LC chromatographic separation and selective HRMS detection.
- When LC co-elution happens, HRMS TIC (total ion chromatogram) may still achieve baseline separation.
- EIC (extracted ion chromatogram) may identify and distinguish the related peptides when co-elution happens.

Conclusions

- Provide a description of the composition, manufacture, characterization, and specifications of the drug substance and drug product to establish sameness to the RLD and support the ANDA submission.
- Ensure the identity, strength, quality, purity, and sameness of the drug substance and bioavailability of the resulting drug products.
- **Reach out to the Agency** early for inquiry about the generic drug development process.



Guidances in developing complex generic peptides

- Sameness Evaluations in an ANDA – Active Ingredients (November 2022)
- Product-Specific Guidances for Generic Drug Development
- ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin Guidance for Industry (MAY 2021)
- Guidance for industry Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA. (October 2022)
- Controlled Correspondence Related to Generic Drug Development Guidance for Industry (March 2024)
- USP/EP Monographs
- ICH Q1A-E (Stability)
- ICH Q2 Analytical Validation
- ICH Q3A-D (Organic impurities, residual solvents, elemental impurities)
- ICH Q7 Good Manufacturing Practice Guide for Active pharmaceutical ingredients
- ICH Q11 Development and Manufacture of Drug Substances
- ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
- USP <1502> Biotechnology-Derived Articles – Amino Acid Analysis
- USP <1503> Quality Attributes of Synthetic Peptide Drug Substances
- USP <1504> Quality Attributes of Starting Materials for the Chemical Synthesis of Therapeutic Peptides

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