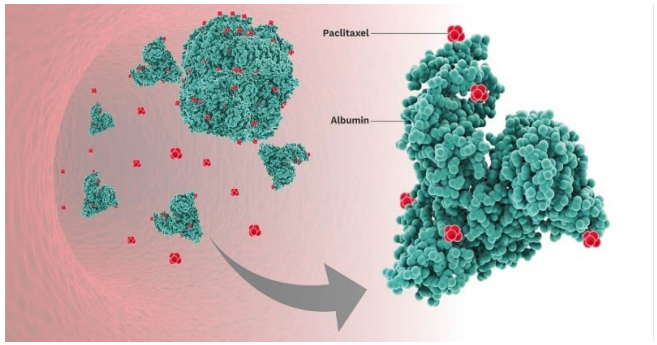
“Cracking the Code”

Regulatory Challenges in the Era of Complex Generics



2025 GRx + Biosims

Complex Generics

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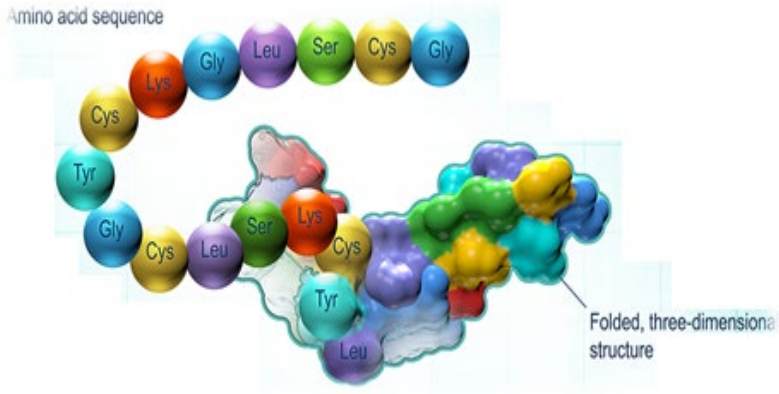
27 October, 2025



Disclaimer

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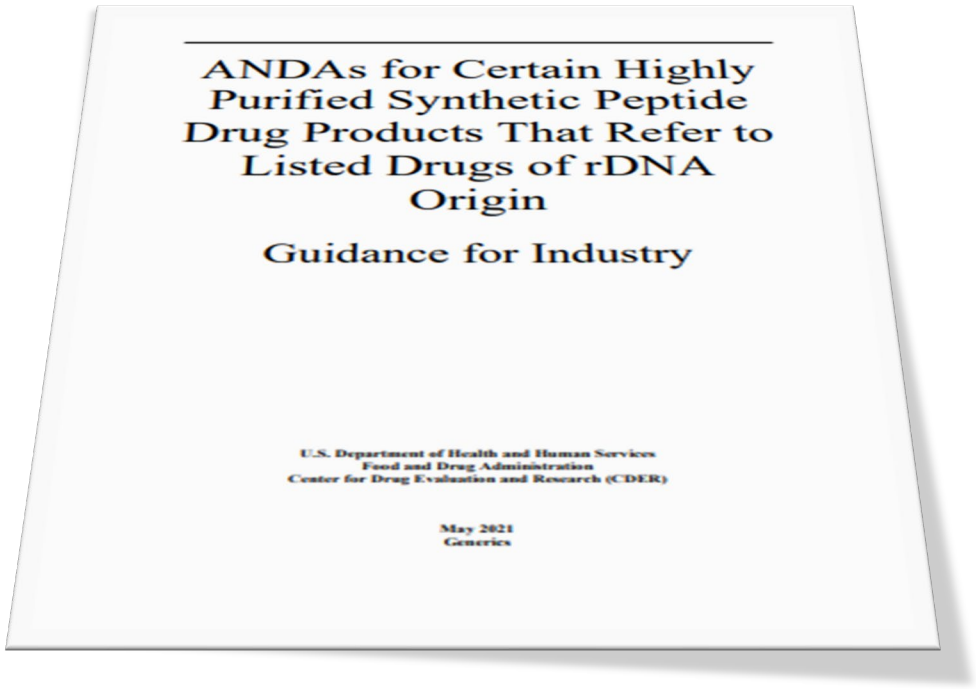
Agenda

- **Synthetic Peptides**
  - Guidance
  - Case Studies (4)
  - Rethinking Peptide Guidance - Scientific and Regulatory Rationale
- **Nano Suspensions:** Bioequivalence Vs. *In vitro*
- **Differentiated framework:** DMF holder Vs. ANDA Applicant
- **Shaping Tomorrow:** Regulatory Pathways for Complex Generics
- **Acknowledgement**

FDA Guidance- Synthetic Peptides

1. ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin, **May 2021**



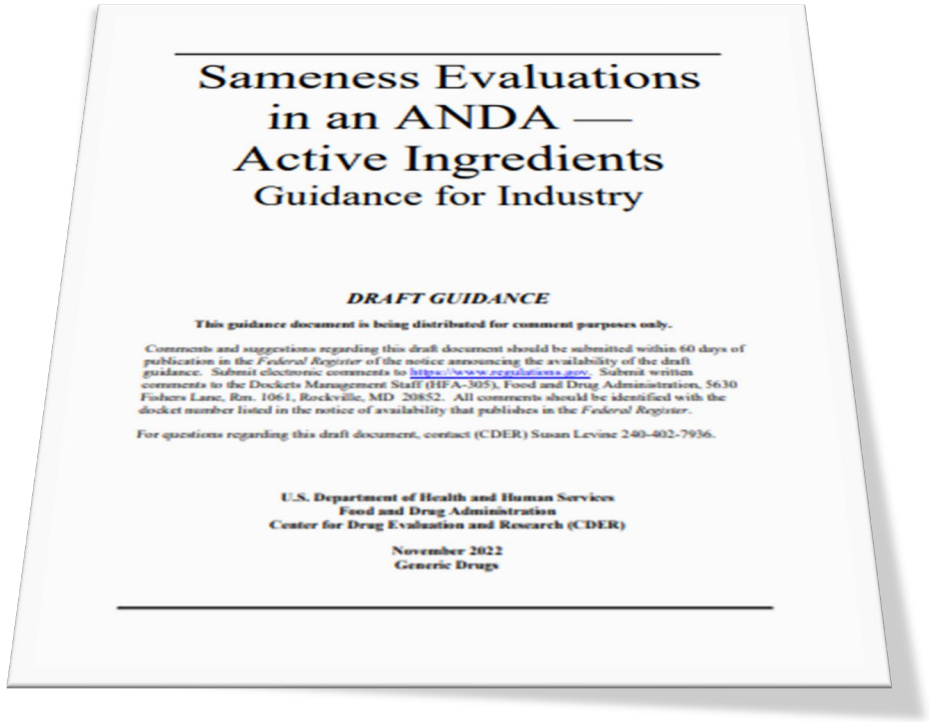
ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2021
Generics

2. Sameness Evaluations in an ANDA — Active Ingredients **November 2022**



Sameness Evaluations in an ANDA — Active Ingredients

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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 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*.

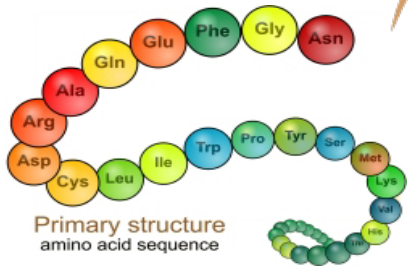
For questions regarding this draft document, contact (CDER) Susan Levine 240-402-7936.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2022
Generic Drugs

Complex Peptides- Case Study 1

API Characterization: Aligning Global Expectations



Points to consider

- API characterization (i.e., Primary sequence, physicochemical, Impurities, HOS, Biological activity, etc.) is performed by the DMF holder and submitted in the DMF. However, it's an expectation that an ANDA applicant should one-time characterize the API.
  Note: As part of API sameness, ANDA Applicant is demonstrating comparability in terms of HOS, Aggregation, Impurity profiling, and Biological activity.
- Regulatory standards are not fully harmonized with other international agencies, such as the EMA, creating challenges in the global development of complex peptide products.

Way forward

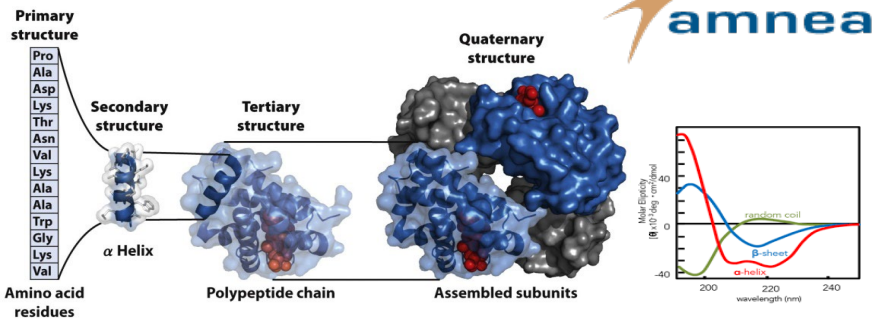
- If the DMF is scientifically assessed/ completeness assessment is done, FDA to consider waiving the generation of API characterization data by the ANDA Applicant to avoid duplication/ redundant work.
- Any additional data requirement can be requested from the DMF holder.

Key takeaway

- Waive off the generation of API characterization data at the ANDA Applicant's end.

Complex Peptides- Case Study 2

Drug Product (DP) Characterization- Near expiry



Points to consider

- Comparative DP Characterization (i.e., HOS, Aggregation and Impurity Profiling) needs to be repeated on near-expiry batches. Due to this, the first cycle approval for complex peptide is challenging.
- Clear path forward/ decision tree for characterization requirements for a small chain (as low as 4 AA), big chain (39AA) or cyclic peptide products is not laid out in the existing peptide guidance.

Way forward

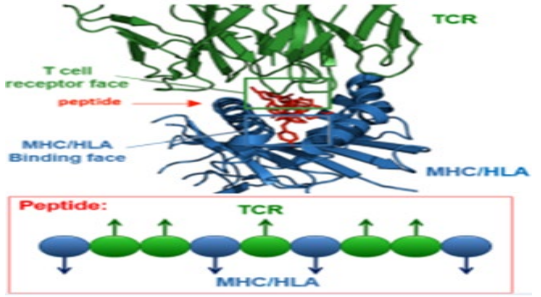
- FDA to consider the characterization data of scale-up/development batches (~12-18 months) as a representative of near-expiry samples, culminating in first-cycle approvals.
- Guidance revision to provide clarity on characterization aspects based on the cyclic or linear peptide, as well as peptide chain length.

Key takeaway

- ***Consider forgoing comparative DP Characterization on near-expiry submission batches.***

Complex Peptides- Case Study 3

Optimizing Immunogenicity Requirements



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Points to consider

- **Peptide-related impurities** (level higher than RLD but less than 0.5%): Case-by-case basis recommendations vary e.g., some cases it's only the Toxicity study OR immunogenicity OR both. Is it due to peptide chain length/size?
- **Non-peptide related impurities:** Current know-how? Risk assessment or a Safety study?
- Guidance doesn't provide a clear path forward/ decision tree for Peptide and non-Peptide related impurities; defining 'orthogonal approaches' and acceptable methodologies for **immunogenicity**.

Way forward

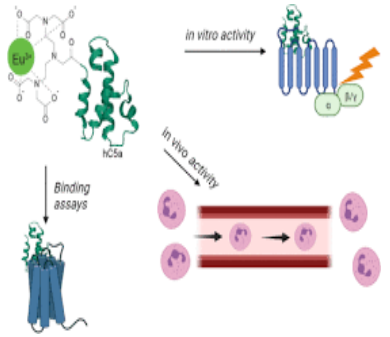
- Early clarity on scope and criteria (guidance document mechanism) enables efficient planning, ultimately timely submissions and approvals.
- Collaborative dialogue (either through Pre-Dev meetings/ CCs)
- Apply **predictive modelling/published literature/ FDA knowledge databases for other approved generics** to justify waiving the immunogenicity studies when safety is well established by other approved products. Eg. Justifying the impurity levels based on levels observed in an approved generic product to waive off the immunogenicity study.

Key takeaway

- *A standardized framework, informed by prior generic peptide approvals, to optimize regulatory strategies and achieve timely approvals.*

Complex Peptides- Case Study 4

Reassessing Bioassay Testing Requirements



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Points to consider

- Regulators require routine bioassay testing in API and DP.
- Regulatory standards are not fully harmonized with other international agencies, e.g., EMA, which accepts the one-time bioassay testing between DP and RLD.

Way forward

- **Extensive Analytical Evidence:** Comprehensive data, including bioassays, structure analysis, and aggregation studies, support product quality and safety. Based on this, routine bioassay testing can be avoided.

Key takeaway

- ***Waive-off Bioassay as a routine testing*** *based on the totality of analytical evidence and ensuring regulatory requirements remain scientifically justified.*

Rethinking Peptide Guidance

A Scientific and Regulatory Rationale

Harmonizing API characterization approach across agencies, facilitating smoother global development and approvals.

A **harmonized framework** that accounts for peptide chain length (including smaller peptides) for more predictable Drug Product characterization requirements.

A **flowchart or matrix** linking peptide attributes to immunogenicity expectations.

FDA to formalize a risk-based immunogenicity framework: **Low-risk peptides**: Minimal assessment; **High-risk peptides:** full immunogenicity risk evaluation.

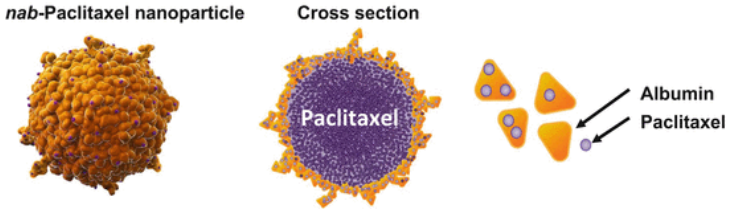
Include **examples from past approvals** to illustrate, giving a clear pathway.

Harmonizing **scientifically justified specifications** can reduce regulatory burden, improve global consistency, and accelerate approvals (e.g., impurity limits: EMA 1.0% vs. FDA 0.5%).

Nano-Suspensions

Example: Paclitaxel (nanoparticle albumin-bound)

USFDA Vs. EMA guidance – A Regulatory Contrast



Active Ingredient: Paclitaxel

Dosage Form; Route: For suspension; IV (infusion)

Recommended Studies: Two studies

1. Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
   Design: Single-dose, two-way crossover, in vivo
   Strength: 100 mg/vial (260 mg/m^2 dose administered in 30 minutes)
   Subjects: Breast cancer patients after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy
   Additional comments:

   a. Submission of a Bio Investigational New Drug Application (Bio-IND) is required prior to the conduct of a bioequivalence in vivo study for a cytotoxic drug product such as paclitaxel (see 21 CFR § 320.31).

Recommended Sep 2012; Revised Aug 2021

→ **USFDA recommends *in vivo* bioequivalence studies**

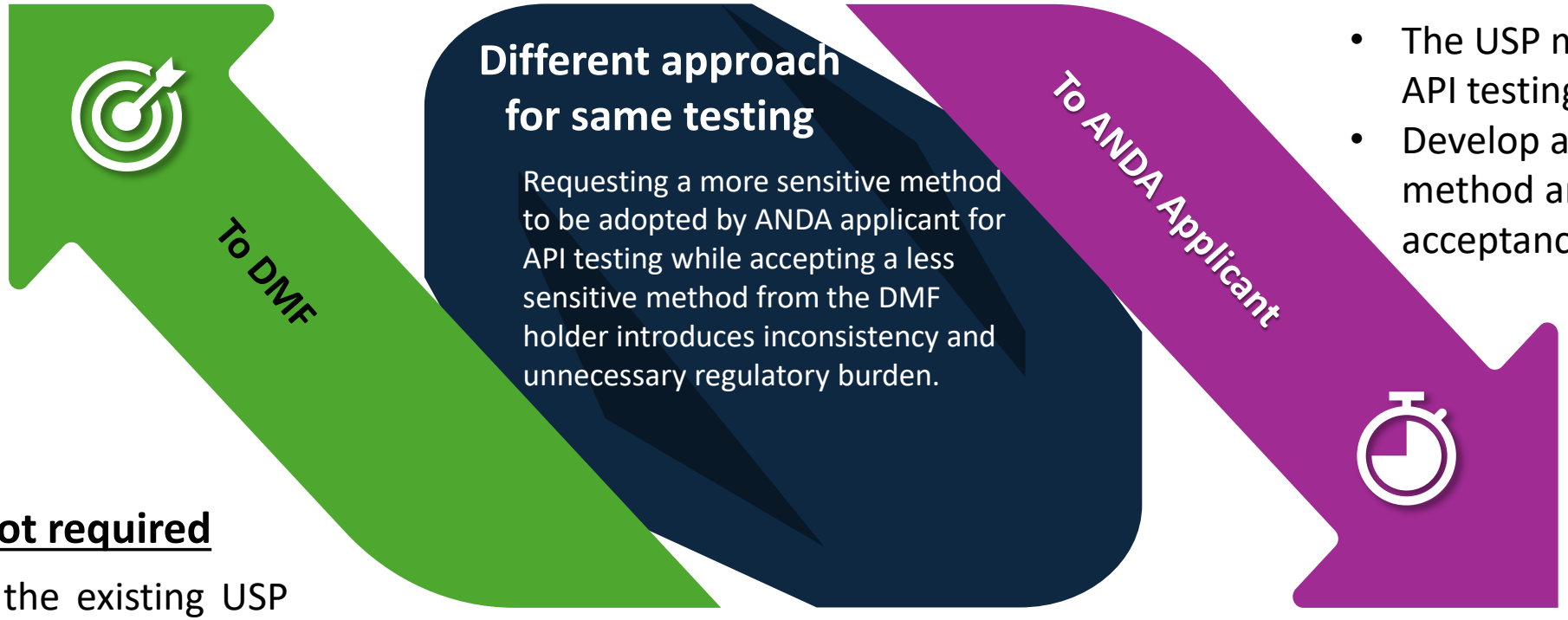
Can a harmonized approach be adopted that allows a biowaiver based on robust physicochemical evidence?

Requirements for bioequivalence demonstration (MWP)

Bioequivalence study design**	**Single dose:** 260 mg/m^2 Q3W in patients with breast cancer **Background:** In principle, suspensions for infusion are not waived from the *in vivo* demonstration of bioequivalence. However, in this case a waiver based on in vitro similarity might be applicable if certain conditions are met, taking into account that the suspension rapidly disassembles upon infusion in blood (see below).
	cross-over
	Other critical aspects:

→ **EMA provides a scientific pathway for a biowaiver**

Differentiated framework: DMF holder Vs. ANDA Applicant



Not required

Verify the existing USP method for LOQ

Develop a sensitive method

- The USP method X for API testing is insensitive.
- Develop a sensitive method and propose an acceptance criteria.

Thank you, FDA *- your collaborative initiatives, including PDEV meetings and post-CRL engagements, are extremely productive in transforming complex generics development and accelerating approvals.*

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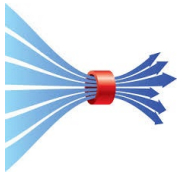
Shaping Tomorrow:

Regulatory Pathways for Complex Generics

Communicate. Clarify. Accelerate.

- Introduce clarification requests under the Pre-development meeting.
- Communicate PSG revisions in advance to prospective ANDA applicants.
- Proactive PSG revisions based on complex generic approvals to formalize clear recommendations on characterization techniques, orthogonal methods etc.

Global Rules, Local Wins - Harmonization with international regulatory bodies to facilitate global approvals.



Fixing the Review Bottleneck - Coordination within FDA divisions to meet mid-cycle timelines and avoid delays that result in Complete Response (CR) letters.

Transparency That Talks - Detailed feedback can help companies better understand regulatory requirements and adjust their development strategies accordingly.

Acknowledgment

- Dr. Srinivas Kone, PhD (Chief Scientific Officer, Generics)
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- Dr. Pavan Kumar Gangavarapu (VP, Global Regulatory Affairs)
- Niraj Patel (Manager, Scientific Regulatory Excellence)
- Dr. Nitin Dhekale, PhD (Assistant General Manager, AR&D)

Rise Lead Succeed

THANK YOU