Considerations in Submitting Abbreviated New Drug Application of Generic Peptide Drug Products

TIDES USA 2021

Workshop #5: FDA Guidance on ANDA Submission for Peptides

September 20, 2021

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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

Outline

- Introduction: ANDA* pathway and active pharmaceutical ingredient (API) sameness
- Regulatory considerations on generic synthetic peptides
- GDUFA** programs for complex drug products including peptides

*ANDA: Abbreviated New Drug Application
**GDUFA: Generic Drug User Fee Amendments

Regulatory Pathways of Drug Applications

New Drug Application (NDA)*		Abbreviated NDA (ANDA)	
A drug product that may have a New Molecular Entity (NME), new formulation, and/or new indication and includes information/investigations to demonstrate its safety and effectiveness		Must ***reference a listed drug***, contain information to establish ***therapeutic equivalence***, and may not be submitted if studies are necessary to establish safety or effectiveness	
Labeling Pharm/Tox Chemistry Manufacturing	Controls Microbiology Inspection Testing	*Labeling*** Pharm/Tox Chemistry Manufacturing	Controls Microbiology Inspection Testing
Animal Studies Clinical Studies (safety and efficacy) Bioavailability		Bioequivalence	

* Commonly referred to as the name-brand, innovator, or reference listed drug (RLD) product.
**ANDA labeling is the same as the labeling for the listed drug (with limited exceptions)

Generic Drugs and API Sameness

A generic drug is a 'copy' of the name-brand product, the reference listed drug (RLD). A generic must demonstrate it is therapeutically equivalent* to the RLD.

- **Pharmaceutical equivalent**
- Bioequivalent
- Can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling
- Adequately labeled
- Manufactured in compliance with cGMP regulations

*For definition, see 21 CFR 314.3(b)

cGMP: current Good Manufacturing Practice

Generic Drugs and API Sameness

To be Pharmaceutical Equivalent* (PE), a drug product:

- **Contains identical amounts of the same API as the RLD**
- Uses same dosage form (e.g., solution) and route of administration (e.g., injection)
- Meets the same compendial standards for strength, quality, purity, and identity including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates

<u>API sameness is a requirement for generic drugs</u>

* For definition, see 21 CFR 314.3(b)

Active Ingredient Sameness

- Active ingredient defined in 21 CFR 314.3(b)
- ANDA required to contain information to show that the active ingredient is the same as the RLD
  - Section 505(j)(2)(A)(ii) of the Federal Food, Drug, and Cosmetic Act
  - 21 CFR 314.94(a)(5)

Generic Drugs and Bioequivalence

Bioequivalence* (BE) is defined as:

- The absence of a significant difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action when administered at the same molar dose under similar experimental conditions
  - Most peptide drugs are parenteral solutions for injection, BE may be considered self-evident and can be waived per 21 CFR 320.22(b)(1)**

*For definition, see 21 CFR 314.3(b)

**Generic product should contain same active ingredient and inactive ingredients and in the same concentration as the reference product

Peptide Drugs

- Peptide: Any alpha amino acid polymer with a defined sequence that is 40 amino acids or fewer in size*
- Broad interest in developing generic synthetic peptide drugs
  - Technical development
    - Solid phase peptide synthesis
    - High resolution, sensitive analytical techniques
  - Large commercial market in the United States
    - Liraglutide: $4.8 billions USD in 2018#
    - Teriparatide: $1.0 billion USD in 2018#
  - Evolving regulatory considerations

*FDA Guidance for Industry: *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)*, December 2018, pp 13-14; Definition of the Term "Biological Product" (85 FR 10057, February 21, 2020) Polypeptide chains with more than 40 amino acids are designated as a protein and should be submitted as a Biologics License Application (BLA)

Source: IQVIA, National Sales Perspectives™. Extracted September 2019.

Peptide Drug Products

Proprietary name	Active ingredient	Amino acid length and origin	Generic?
FORTEO	teriparatide	34, rDNA	N
BONSITY	teriparatide	34, rDNA	N
VICTOZA/SAXENDA	Liraglutide	31 (not counting Glu-20), rDNA	N
NATRECOR	Nesiritide	32, rDNA	N
GATTEX	Teduglutide	33, rDNA	N
GLUCAGON	Glucagon	29, rDNA	Y
GVOKE	Glucagon	29, synthetic	N
BAQSIMI	Glucagon	29, synthetic	N
GLUCAGEN	Glucagon hydrochloride	29, rDNA	N
GLUCAGON	Glucagon hydrochloride	29, synthetic	N
ZEGALOGUE	Dasiglucagon hydrochloride	29, synthetic	N
OZEMPIC/WEGOVY/RYBELSUS	Semaglutide	31, rDNA	N
FORTICAL	Calcitonin Salmon	32, rDNA	N
MIACALCIN	Calcitonin Salmon	32, synthetic	Y
BYETTA	Exenatide	39, synthetic	N

Synthetic Peptides – Regulatory Considerations

- NO ICH* guidelines on peptide quality
- FDA guidance for industry: *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*
  - Draft guidance published in Oct 2017
  - Final guidance published in May 2021
- First generic synthetic glucagon referencing glucagon of rDNA origin was approved in Dec 2020

*ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

FDA Synthetic Peptide Guidance: Scope

- Only for synthetic peptide referencing an approved peptide drug product of rDNA origin
- Guidance only covers five peptide drug products: glucagon, liraglutide, nesiritide, teriparatide and teduglutide
  - Recommendations and principles may be applicable to semaglutide
- Guidance is not intended to be used for a synthetic peptide referencing a synthetic peptide drug product even though some of the principles in the guidance may be considered

FDA Synthetic Peptide Guidance: Focus

- API sameness evaluation
- Impurity profile assessment
  - peptide-related impurities
  - threshold for peptide-related impurities
  - immunogenicity assessment

Characterization of Synthetic Peptides

- Primary sequence, amino acid composition
- Optical rotation, other physicochemical properties
- Secondary structure
- Oligomer/Aggregation states
- Biological activities (by in vitro or animal studies)
- Impurities (peptide-related impurities and other impurities)

Use orthogonal analytical methods

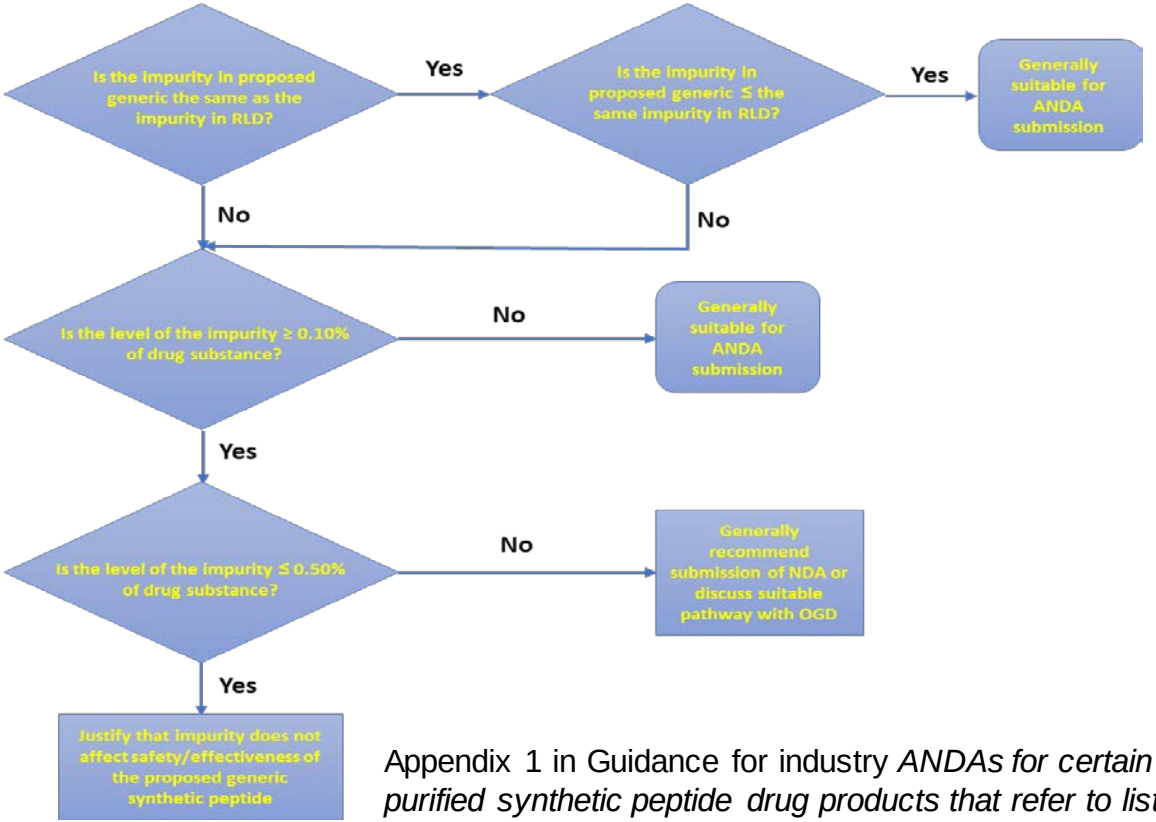
Peptide Impurities: Comparative Evaluation

To ensure impurities in the proposed generic peptide drug will not alter the safety (including the immunogenicity) and efficacy compared to the RLD product

- In common peptide impurities: level in generic synthetic peptide is not higher than the level found in the RLD
- New peptide impurities: to identify and characterize if above certain threshold (no more than 0.5% of the API)
- To assess immunogenicity risk with in silico, in vitro methods
  - Individual new peptide impurity: in silico T-cell epitopes, other in vitro assays
  - Generic peptide product: innate immune system

Recommended Evaluation of Peptide-related Impurities

To evaluate <u>each</u> impurity in proposed generic drug



Appendix 1 in Guidance for industry *ANDAs for certain highly purified synthetic peptide drug products that refer to listed drugs of rDNA origin* (May 2021)

Facilitating Generic Drug Development and Approval: GDUFA Programs

- The Generic Drug User Fee Amendments (GDUFA); FDA engages external stakeholders (e.g., industry, academia, and research organizations) to advances public health by contributing to the development of safe and effective generic drugs. This includes:
  - Generic drug research program that funds necessary research (via grants and contracts): https://www.fda.gov/drugs/generic-drugs/science-research
    - **2020 Research priority A.1.** Improve advanced analytics for characterization of chemical compositions, molecular structures, and distributions in complex active ingredients
    - **2020 Research priority A.3.** Establish predictive in silico, in vitro, and animal models to evaluate immunogenicity risk of formulation or impurity differences in generic products
  - Controlled Correspondence (CC)
  - Product-Specific Guidances (PSGs)
  - Pre-ANDA Meetings on complex products

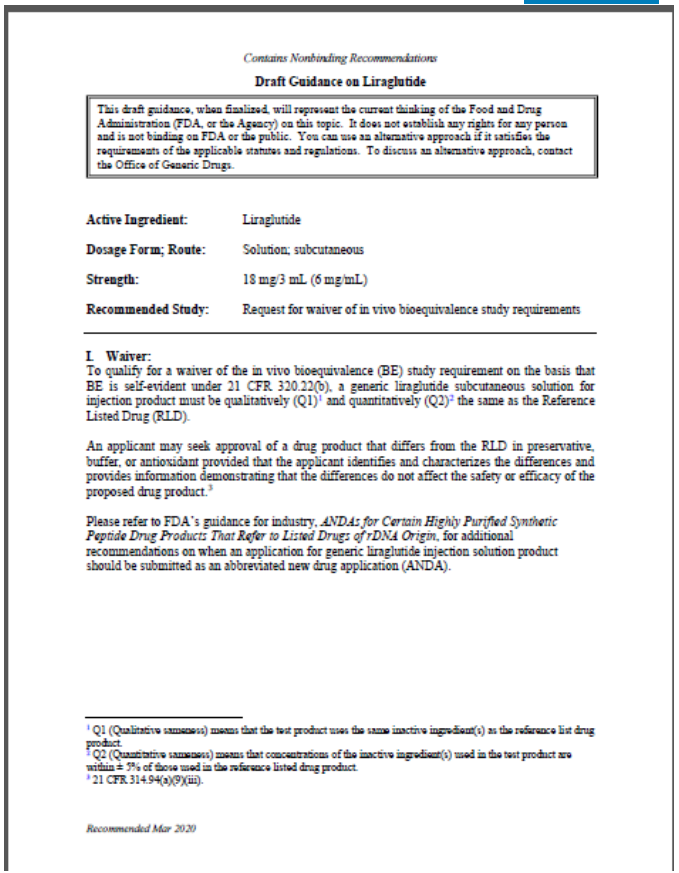
Controlled Correspondence

- Controlled correspondence (CC)* is appropriate for a specific and targeted inquiry about generic drug development
- CC can have one or a small set of closely related questions. For a peptide injectable product, appropriate questions for a CC include:
  - Formulation assessment: qualitative (Q1) and quantitative (Q2) sameness
  - Proposed buffer change
- FDA will usually respond to standard CC in 60 days and complex CC in 120 days

* Guidance for Industry *Controlled Correspondence Related to Generic Drug Development* https://www.fda.gov/media/109232/download

Product-Specific Guidances

- Started in 2007, PSGs provide clear and direct advice to ANDA applicants.
  - PSGs are posted on a quarterly basis*
  - As of June 2021, there are 1,896 posted PSGs
  - FDA will post a PSG for New Chemical Entity (NCE) NDAs (non-complex) 2 years prior to the earliest lawful ANDA filing date
  - FDA will post a PSG for complex products as soon as scientific recommendations are available
  - Represent the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs



Contains Nonbinding Recommendations

Draft Guidance on Liraglutide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient:	Liraglutide
Dosage Form; Route:	Solution; subcutaneous
Strength:	18 mg/3 mL (6 mg/mL)
Recommended Study:	Request for waiver of in vivo bioequivalence study requirements

I. Waiver:
To qualify for a waiver of the in vivo bioequivalence (BE) study requirement on the basis that BE is self-evident under 21 CFR 320.22(b), a generic liraglutide subcutaneous solution for injection product must be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD).

An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[3]

Please refer to FDA's guidance for industry, *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*, for additional recommendations on when an application for generic liraglutide injection solution product should be submitted as an abbreviated new drug application (ANDA).

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference list drug product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the reference listed drug product.
[3] 21 CFR 314.94(a)(9)(iii).

Recommended Mar 2020

* https://www.accessdata.fda.gov/scripts/cder/psg/

The Pre-ANDA Program

The Pre-ANDA Program was established by GDUFA II* to:

- clarify regulatory expectations for prospective applicants early in product development
- assist applicants to develop more complete submissions
- promote a more efficient and effective ANDA assessment process
- reduce the number of review cycles required to obtain ANDA approval, particularly for Complex Products

*GDUFA II started Oct. 1, 2017 and is a 5-year agreement (FY18-22)

Complex Products

COMPLEX…	Example	Example Products
Active ingredients	Peptides, complex mixtures, polymeric compounds, natural source products	Glucagon
Formulations	Liposomes, colloids	Doxorubicin HCl liposome injection
Routes of Delivery	Locally acting drugs such as dermatological products and complex ophthalmological products and otic dosage form formulated as suspensions, emulsions or gels	Acyclovir cream
Dosage Forms	Transdermal systems, extended release injectables	Paliperidone palmitate extended-release suspension
Drug-Device Combinations	Auto injectors, metered dose inhalers	Epinephrine auto injector
Other products	Complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement	Abuse deterrent opioid formulations

Meeting Types

Pre-ANDA meetings accelerate access to generics of complex products through early engagement with the FDA. Guidance for Industry: *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*[*]

- Pre-ANDA product development meeting (PDEV)
  - Early engagement in product development program
- Pre-Submission meeting (PSUB)
  - Ready to or close to submitting ANDA application
- Mid-review-cycle meeting (MRCM)
  - After ANDA has been submitted; Only for ANDA applicants who have had prior PDEVs or PSUBs

* https://www.fda.gov/media/107626/download

Meeting vs Controlled Correspondence

- Controlled correspondence
  - Has single or a small group of closely related questions
  - Seeks information on a specific elements of generic drug development
  - FDA can provide written feedback
- Pre-ANDA Meeting
  - Best for multidisciplinary questions or proposals where a substantive discussion may be warranted
- Response timelines:
  - Standard CC within 60 days; Complex CC within 120 days
  - Meeting: usually within 120 days of being granted

Summary

- Regulatory considerations on generic synthetic peptide drug development include recommendations on API sameness demonstration, impurity characterization, and immunogenicity risk assessment

- Office of Generic Drugs considers peptides to be complex drug products that will benefit from GDUFA research and pre-ANDA interactions between FDA and external stakeholders

- Generic applicants are encouraged to take advantage of CC and Pre-ANDA meeting programs to seek Agency's feedback on generic synthetic peptide drug development

Acknowledgement

- Rob Lionberger
- Lei Zhang
- Kris Andre
- Markham Luke
- Darby Kozak
- Yan Wang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