Considerations for Abbreviated New Drug Application of Generic Peptide Drug Products

TIDES US 2020

Workshop #3: FDA Draft Guidance on ANDA Filings for Peptides

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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
- Pre-ANDA Program for Complex Drug Products

*ANDA: Abbreviated New Drug Application

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) Bio availability		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)

Approved Peptide Drug Products

Proprietary name	Active ingredient	Amino acid length and origin	Generic?
FORTEO	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	N
GVOKE	Glucagon	29, synthetic	N
GLUCAGEN	Glucagon hydrochloride	29, rDNA	N
GLUCAGON	Glucagon hydrochloride	29, synthetic	N
OZEMPIC/RYBELSUS	Semaglutide	31, rDNA	N
FORTICAL	Calcitonin Salmon	32, rDNA	N
MIACALCIN	Calcitonin Salmon	32, synthetic	Y
BYETTA	Exenatide	39, synthetic	N

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
- 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 same API as the RLD**
- Uses same dosage form (e.g., solution) and route of administration (e.g., injection)
- Is identical in strength or concentration
- Meets the same compendial standards for strength, quality, purity, and identity

API sameness is a requirement for generic drugs

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 of absorption compared to the reference drug when administered at the same molar dose of the therapeutic ingredient 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)

505(j)(8)(B) of FD&C Act; 21 CFR 320.22(b)

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

Generic Peptides

- API sameness evaluation
- Impurity profile assessment (including immunogenicity consideration)

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. Polypeptide chains with more than 40 amino acids are designated as a protein and should be submitted as a Therapeutic Biologics Application (BLA)

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

Synthetic Peptides – Regulatory Considerations

- NO ICH* guidelines on peptide quality
- Draft guidance for industry: *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin* (Oct 2017)
  - Guidance covers five peptide drugs: teriparatide, glucagon, nesiritide, liraglutide, and teduglutide
  - Recommendations and principles are applicable to semaglutide
  - The general characterization principles and strategies in this guidance may be considered when developing other synthetic generic peptide drugs

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

Characterization of 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

Calcitonin-Salmon Impurity Analysis

- Calcitonin-Salmon: a 32 amino acid peptide hormone for postmenopausal osteoporosis
- Several Calcitonin-Salmon nasal spray products have been approved (of rDNA and synthetic origin)
- FDA Lab applied a data-dependent acquisition (DDA) LC-MS-MS and data-independent acquisition (DIA) LC-MS^E approach to analyze peptide impurities in Calcitonin-Salmon nasal spray

Rapid Screening of Peptide Impurities in Calcitonin-Salmon Nasal Spray Using Data-Dependent LC-MS-MS And Data-Independent LC-MS^E, Yang, J., et. al., ASMS Poster, 2017.

Calcitonin-Salmon Impurity Analysis

- Instruments: UHPLC-MS (Thermo Q Exactive Orbitrap and Waters Synapt G2Si mass Spectrometers)
- To identify peptide impurities in all three groups
  - Impurities observed in total ion chromatogram (TIC)
  - Impurities co-eluting with the API or eluted at its peak tail (challenging for manual screening)
  - Impurities buried under the TIC baseline

Calcitonin Salmon Impurity Analysis

DIA LC-MS^E approach

Table 1. List of selected peptide impurities observed using DIA approach

Impurity	Rt (min)	M.W. (mono)	Δm/z	% ADC
1	5.8	2195.396	-1234.7	0.01
2		2213.408	-1216.7	0.08
3	21.3	3503.072	73.0	0.02
4		3333.996	-96.1	0.13
5	26.1	3412.084	-18.0	0.01
6	28.7	3412.032	-18.0	0.14
7		3315.960	-114.1	6.45
8		3297.972	-132.1	0.41
9		3477.048	47.0	0.01
10		3572.900	142.8	0.15
11		3214.884	-215.2	0.34
12	30.0	3468.080	38.0	2.18
13		3532.128	102.1	0.02
14		3232.920	-197.2	0.03
15		3501.096	71.0	0.02
16		3451.980	21.9	1.65
17	30.4	3430.072	0.0	0.78
18		2912.788	-517.3	0.01
19		3088.856	-341.2	0.09
20		3316.968	-113.1	0.05
21	31.5	2715.680	-714.4	0.04
22		3431.125	1.1	0.01
23		2930.784	-499.3	0.02
24		3316.968	-113.1	0.05
25		1691.986	-1738.1	0.13
26		3430.072	0.0	0.78
27		3453.000	22.9	0.01
28	32.5	3450.495	20.4	0.73

DDA LC-MS-MS approach

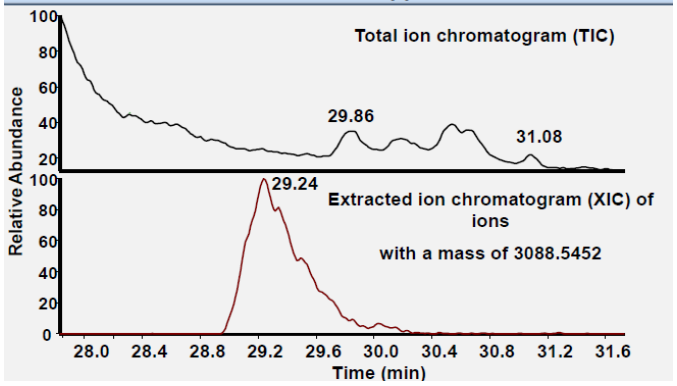
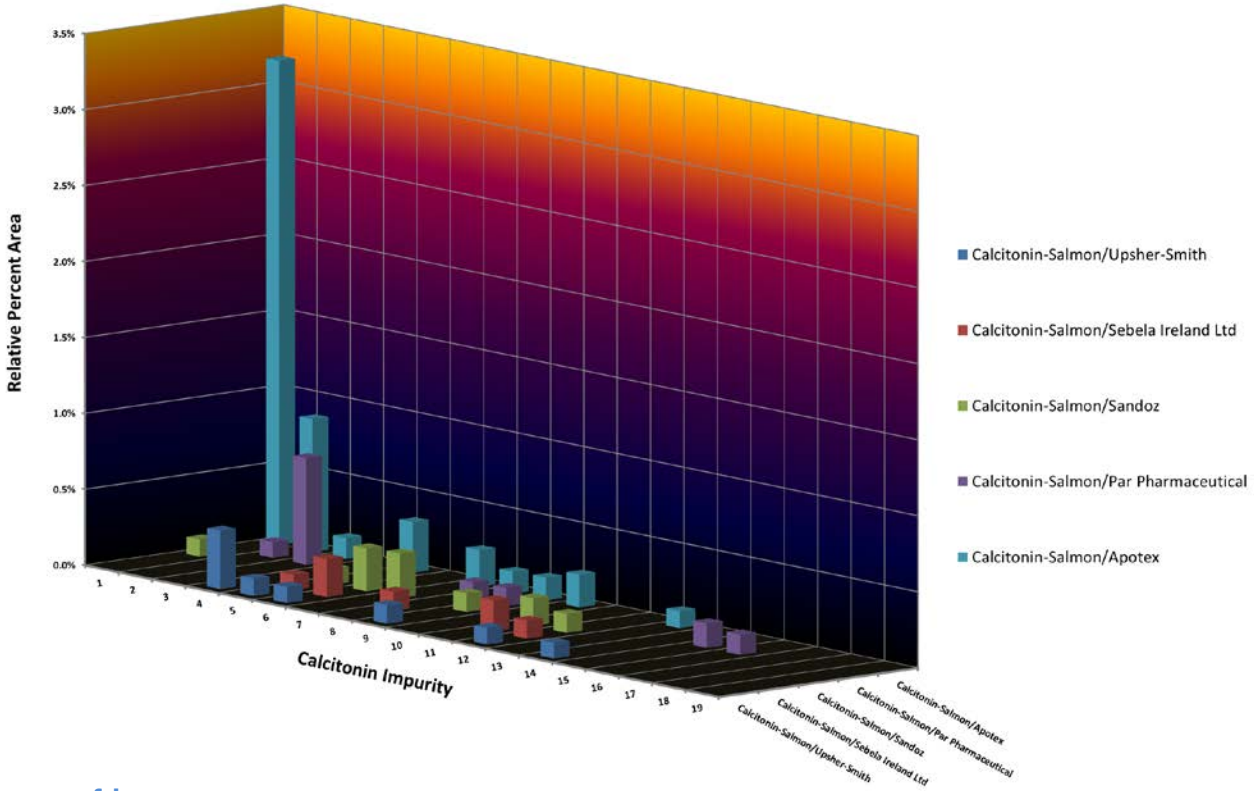


Table 2. List of selected peptide impurities observed in TIC

Index	TIC Peak Retention Time (min)	Monoisotopic Mass	Detected by DDA	Area %
1	5.77	2213.1206	Yes	0.06
2	18.49	1321.6378	No	0.009
3	19.44	1578.7394	No	0.005
4	20.6	3447.7259	Yes	1.17
5		1234.6048	Yes	0.05
6		3333.6461	Yes	0.02
7	24.32	1828.8825	No	0.02
8	24.99	3412.6908	Yes	0.23
9	29.86	2930.4755	Yes	0.04
10	30.4	2715.3867	Yes	0.02
11	30.54	2070.0608	Yes	0.12
12	31.08	1691.8229	Yes	0.06
13	32.71	3471.7261	Yes	0.17
14	35.84	3428.6858	Yes	0.08
15	37.99	3471.7261	Yes	0.02
16	57.07	Only Singly-charged ions observed		
17	58.8	Only Singly-charged ions observed		

API Rt = 28.7 min

Calcitonin-Salmon Impurity Analysis



- 13 nasal spray drug products analyzed
- Over 100 peptide impurities detected by LC/MS
- 4 were above 0.5%
- 16 were above 0.1%

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: generally not higher than those found in the RLD
- New peptide impurities: need to identify and characterize if above certain threshold
- 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

Facilitating Generic Drug Development and Approval: the Pre-ANDA Program

- 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
  - Product-Specific Guidances (PSGs)
  - ANDA Meetings on complex products
  - Controlled Correspondence (CC)

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

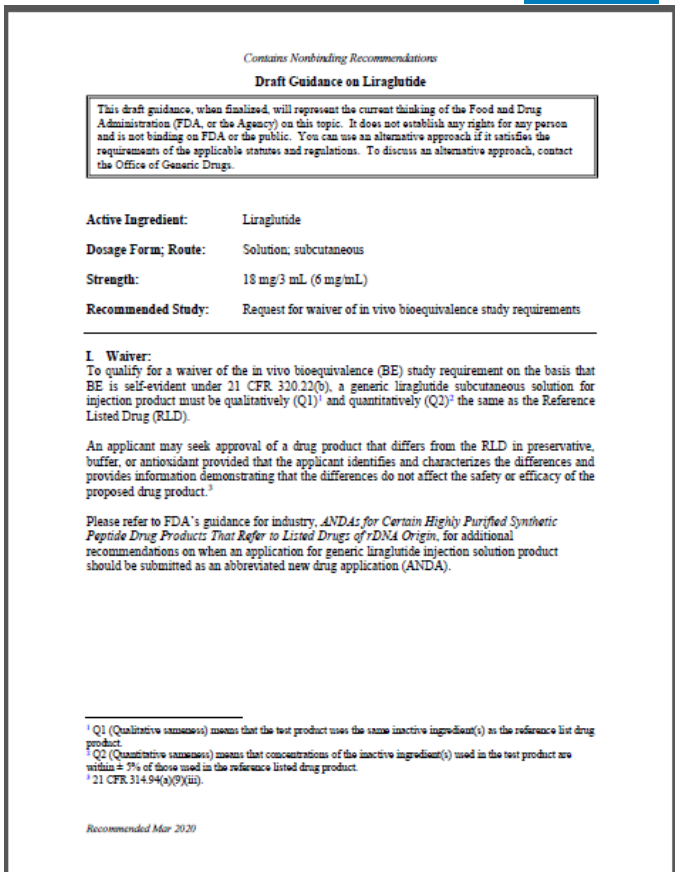
*GDUFA II started Oct 1, 2017 and is a 5 year agreement (FY18-22)

Complex Products

COMPLEX…	Example	Example Products
Active ingredients	Peptides, complex mixtures, natural source products	Glucagon
Formulations	Liposomes, emulsions	Liposomal formulation
Routes of Delivery	Locally acting drugs such as dermatological products and complex ophthalmological products	Acyclovir cream
Dosage Forms	Transdermal systems, extended release injectables	Paliperidone palmitate extended release suspension
Drug-Device Combinations	Dry powder inhalers, nasal sprays, transdermal systems	Mometasone Nasal Spray
Other products	Complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement	Abuse deterrent opioid formulations

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 2020, there are 1,903 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/

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 meetings (PDEV)
  - Early engagement in product development program
- Pre-Submission meetings (PSUB)
  - Ready to or close to submitting ANDA application
- Mid-review-cycle meetings (MRCM)
  - After ANDA has been submitted

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

Meeting vs Controlled Correspondence

- Controlled Correspondence (CC)* generally has single or a small group of closely related questions requesting information on a specific element of generic drug development
- Meetings are best for multidisciplinary questions
- Response timelines:
  - Standard CC within 60 days; Complex CC within 120 days
  - Meeting: within 120 days of being granted

* Guidance for Industry *Controlled Correspondence Related to Generic Drug Development* https://www.fda.gov/media/89456/download

Summary

- 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.

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

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