Pharmacy Compounding Advisory Committee: Investigational New Drug (IND) Development and Expanded Access (EA)
December 4, 2024

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Disclosure

- **This speaker has no conflicts of interest to disclose**

Objectives

- Explain pathways under which investigational drugs can be studied and used for treatment based on questions raised in previous PCAC discussions
- Provide a brief overview of an Investigational New Drug (IND) submission
- Explain the primary purpose of Expanded Access (EA) and how it differs from clinical trials to study investigational products
- Discuss the three categories of Expanded Access available
- Identify useful resources for determining if Expanded Access is appropriate and preparing requests

Access to Drug Products Under an IND

- **Clinical Trials Under an IND**
  - **Provide necessary data to determine safety and effectiveness**
  - **Most efficient path to market and broad availability**
  - **Goal is research about the drug potentially leading to approval**
- **Expanded Access**
  - **Presents opportunity to access an investigational medical product for patients with a serious or immediately life-threatening disease or condition who have no comparable or satisfactory alternative therapies**
  - **Goal is access for treatment use**
- **Pathways distinct from 503A and 503B compounding**
  - **Availability of an IND is not a consideration in determining whether a nominated bulk drug substance is appropriate for inclusion on the 503A bulks list**

Some Key Content for IND Submissions

- FDA Forms for IND
  - Form FDA 1571 – Investigational New Drug Application/Form FDA 1572 – Statement of Investigator
  - Form FDA 3926 – Individual Patient Expanded Access Investigational New Drug Application
- Investigator Qualifications (CV)
  - Includes sub-investigators
- Drug substance and drug product information (all manufacturing sites) or Letter of Authorization (LOA) for
  - Identity, Purity, strength, and quality
  - Stability
  - Distribution

Some Key Content for IND Submissions (Continued)

- Safety
  - Evidence that the drug is reasonably safe at the dose and duration proposed
  - Nonclinical/Clinical
- Efficacy
  - Rationale for the intended use of the drug
- Protocol
  - Description of disease or condition
  - Proposed method of administration, dose, and duration
  - Eligibility criteria
  - Clinical procedures and monitoring to evaluate effects and minimize risk
- Informed consent form and Institutional Review Board (IRB) approval

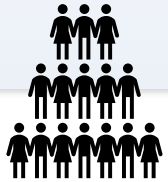
What is Expanded Access (EA)?

- **Expanded Access is the use of an investigational drug or biological product to treat a patient with a serious or immediately life-threatening disease or condition who does not have comparable or satisfactory alternative therapies to treat the disease or condition**
  - **Intent is clearly treatment**
- **Contrasts with investigational drug in a clinical trial where the primary intent is research**
  - **Systematic collection of data with the intent to analyze and learn about the drug**

Three General Categories of Expanded Access and Their Common Requirements

Individual patient
(includes non-emergency and emergency use)

Intermediate-size population



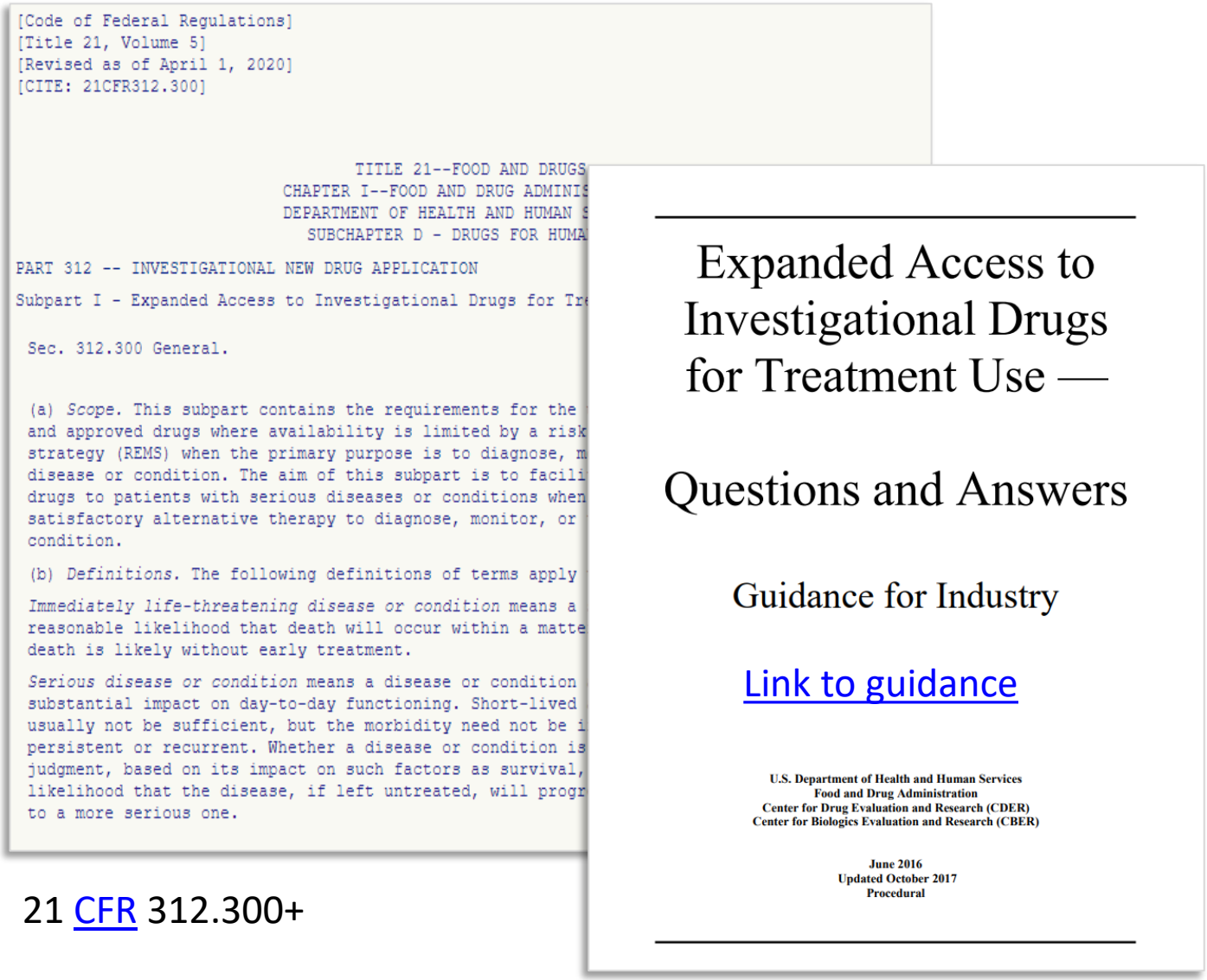
Treatment Investigational New Drug (IND) or Treatment Protocol

Common Requirements:*

1. Patients have serious or immediately life-threatening disease or condition
2. No comparable or satisfactory alternative therapy
3. Patient is unable to participate in a clinical trial for the investigational product
4. Potential benefits must justify the potential risks of the treatment
5. Providing the product under EA must not interfere with or compromise the potential development of the expanded access use

* Under EA, access to an investigational product additionally depends on a sponsor or manufacturer choosing to make the product available to patients.

Expanded Access Regulations and Guidance



[Code of Federal Regulations]
[Title 21, Volume 5]
[Revised as of April 1, 2020]
[CITE: 21CFR312.300]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINIS
DEPARTMENT OF HEALTH AND HUMAN S
SUBCHAPTER D - DRUGS FOR HUMA

PART 312 -- INVESTIGATIONAL NEW DRUG APPLICATION

Subpart I - Expanded Access to Investigational Drugs for Tr

Sec. 312.300 General.

(a) *Scope.* This subpart contains the requirements for the
and approved drugs where availability is limited by a risk
strategy (REMS) when the primary purpose is to diagnose, m
disease or condition. The aim of this subpart is to facili
drugs to patients with serious diseases or conditions when
satisfactory alternative therapy to diagnose, monitor, or
condition.

(b) *Definitions.* The following definitions of terms apply

Immediately life-threatening disease or condition means a
reasonable likelihood that death will occur within a matte
death is likely without early treatment.

Serious disease or condition means a disease or condition
substantial impact on day-to-day functioning. Short-lived
usually not be sufficient, but the morbidity need not be i
persistent or recurrent. Whether a disease or condition is
judgment, based on its impact on such factors as survival,
likelihood that the disease, if left untreated, will progr
to a more serious one.

Expanded Access to Investigational Drugs for Treatment Use —

Questions and Answers

Guidance for Industry

Link to guidance

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

June 2016
Updated October 2017
Procedural

21 CFR 312.300+

- **Describe the general criteria applicable to all categories of expanded access, and additional criteria that must be met for each expanded access category**
- **Describe the requirements for submission**
- **Describe the safeguards applicable to EA programs, such as informed consent, IRB review, and reporting requirements**

Human Subject Protections Apply to All EA Categories

- **Drugs in EA are *investigational drugs*, and they are subject to the following requirements from 21 CFR:**
  - Part 50 – **Protection of Human Subjects** (including informed consent)
  - Part 56 – **Institutional Review Board**
  - Part 312 – **IND Application** (including clinical holds based on safety, and reporting requirements (e.g., adverse event reports, annual reports))

EA Program Initiatives (Drugs and Biological Products)

- Creation of Form FDA 3926 for Individual Patient Expanded Access Investigational New Drug Application (IND) (2016)
- Updated guidances and website (2016, 2017, updated draft in 2022)
- Collaboration with the Reagan-Udall Foundation (RUF)
  - Expanded Access Navigator (2017)
  - Expanded Access eRequest mobile app (2020)
- Oncology Center of Excellence “Project Facilitate” (2019)
- Continual outreach efforts through publications, meetings, and webinars
- FDA EA Coordinating Committee (EACC)

User-friendly FDA Webpages for EA

Expanded Access

- Information for Patients
- Information for Physicians
- Information for Industry
- Information for Institutional Review Boards (IRBs)
- How to Submit a Request (Forms)
- Keywords, Definitions, and Resources
- Submission Data
- Contact Information

Español

Sometimes called “compassionate use”, expanded access is a potential pathway for a patient with a serious or immediately life-threatening disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

Expanded access may be appropriate when all the following apply:

- Patient has a serious or immediately life-threatening disease or condition.
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
- Patient enrollment in a clinical trial is not possible.
- Potential patient benefit justifies the potential risks of treatment.
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product’s development or marketing approval for the treatment indication.

Key Contact Information

1. During Normal Business Hours (8 a.m. - 4:30 p.m. ET, weekdays)

For **specific questions** during normal business hours:

- **Investigational drugs:** 301-796-3400 or druginfo@fda.hhs.gov [CDER's Division of Drug Information], or contact the appropriate review division, if known
  - **Oncology drugs:** 240-402-0004 or ONCProjectFacilitate@fda.hhs.gov
- **Investigational medical devices:** 301-796-7100 or DICE@fda.hhs.gov [CDRH's Division of Industry and Consumer Education]
- **Investigational biologics:** 240-402-8020 or 800-835-4709 or industry.biologics@fda.hhs.gov [CBER's Office of Communication, Outreach and Development]

For **general questions**, or if you are unsure of who to contact, contact the Patient Affairs Staff at 301-796-8460 or patientaffairs@fda.hhs.gov.

2. After 4:30 p.m. ET weekdays and all day on weekends

For **emergency requests** for all medical products (drugs, biologics, and medical devices) contact **FDA's Emergency Call Center** at 866-300-4374.

https://www.fda.gov/news-events/public-health-focus/expanded-access

Series of Informational Videos

Questions/Contact Us

- **CDER Division of Drug Information**
  druginfo@fda.hhs.gov

- **FDA's EA contact info**
  https://www.fda.gov/news-events/expanded-access/fdas-expanded-access-contact-information

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References

21 CFR part 312: Investigational New Drug Application. Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

21 CFR 312.300 on Expanded Access to Investigational Drugs for Treatment Use. Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.300.

Guidance for industry *Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers* (2017). Available at https://www.fda.gov/media/85675/download.

Guidance for industry *Individual Patient Expanded Access Applications: Form FDA 3926* (2017). Available at https://www.fda.gov/media/91160/download.


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Pharmacy Compounding Advisory Committee:

FDA Immunogenicity Risk of Compounded Peptides

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Disclosure

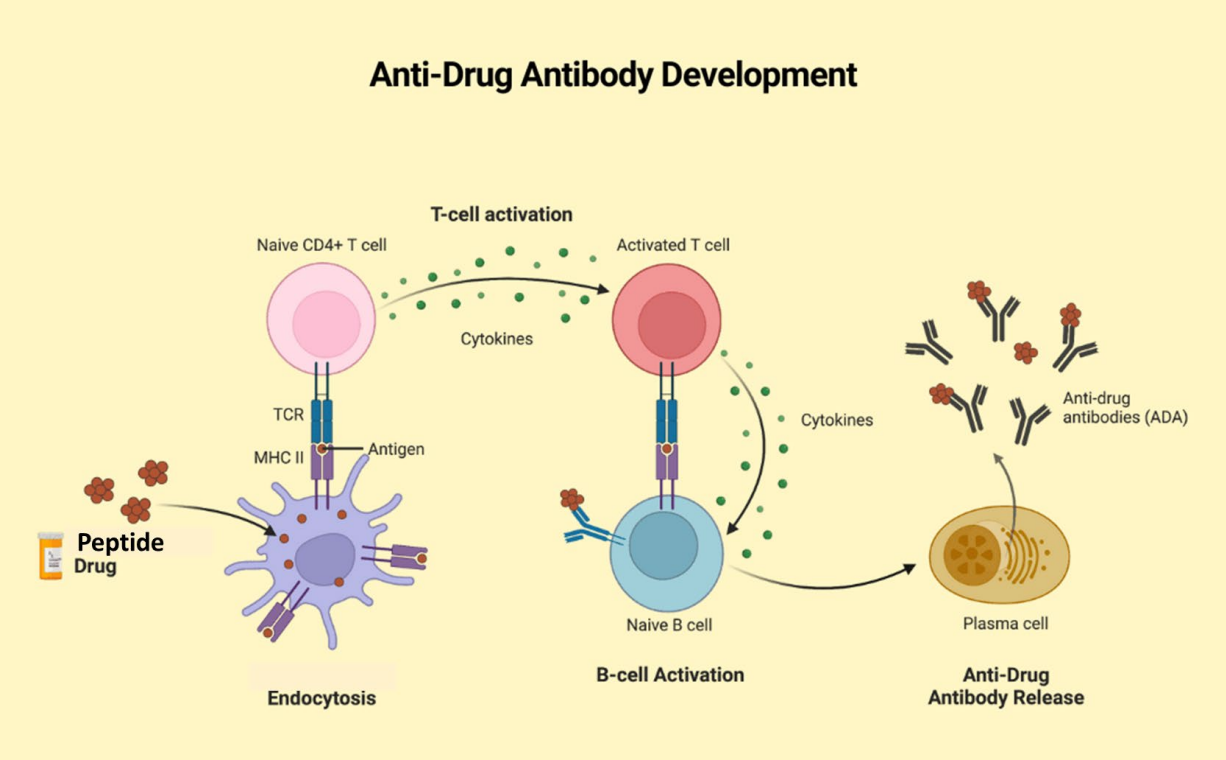
- **This speaker has no conflicts of interest to disclose**

Talk Map:

- **Product immunogenicity**
- **Describe the clinical immunogenicity concerns for peptides**
- **Brief introduction to the mechanisms involved in generating an immune response to a product**
- **Discuss the immunogenicity–related concerns for compounded complex peptide products**

Immunogenicity Concerns for Peptide Products

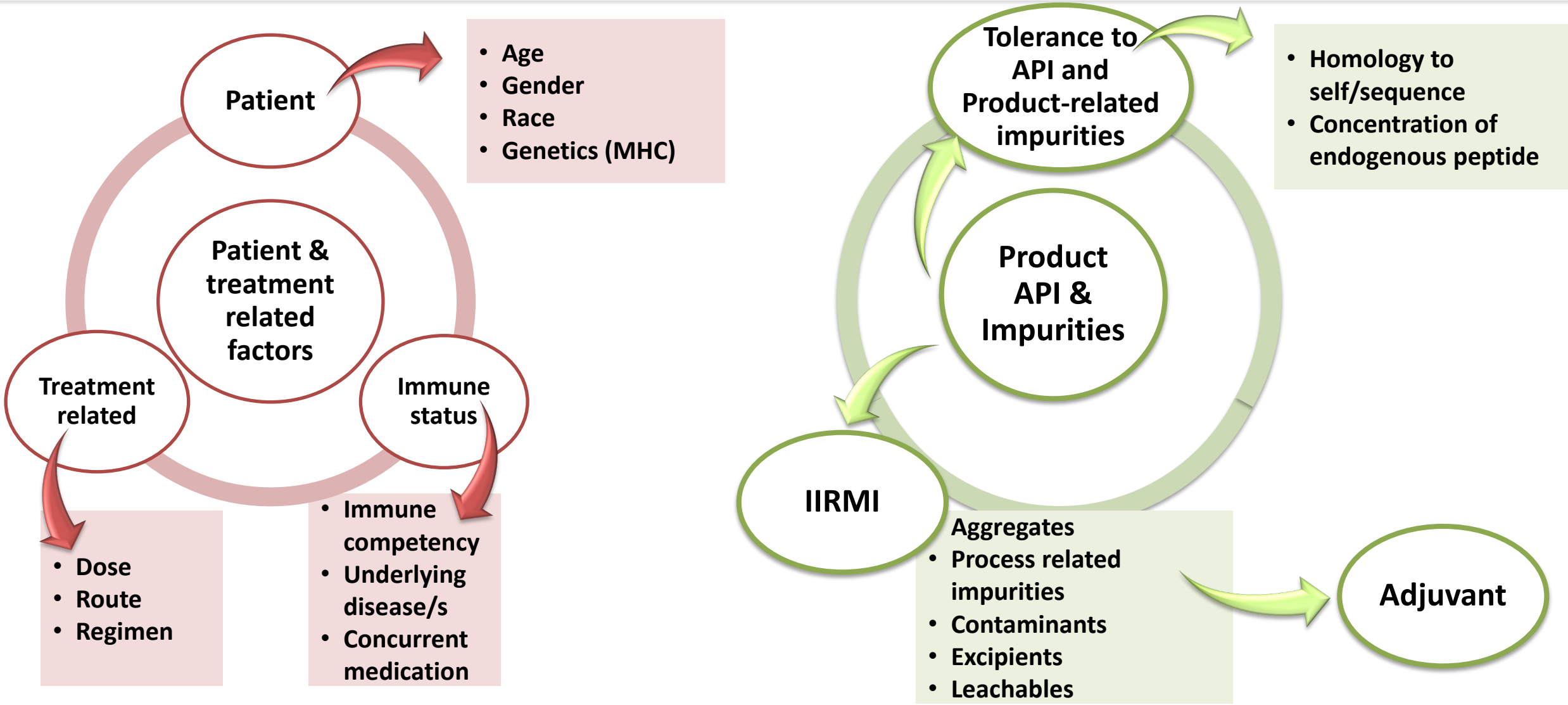
- **Immunogenicity is the unwanted development of an immune response, usually antibodies, elicited by a therapeutic product.**
- **Therapeutic peptides can induce an unwanted antigen(Ag)-specific immune response that can impact on safety and/or efficacy**



Clinical Immunogenicity Concerns for Peptide Products

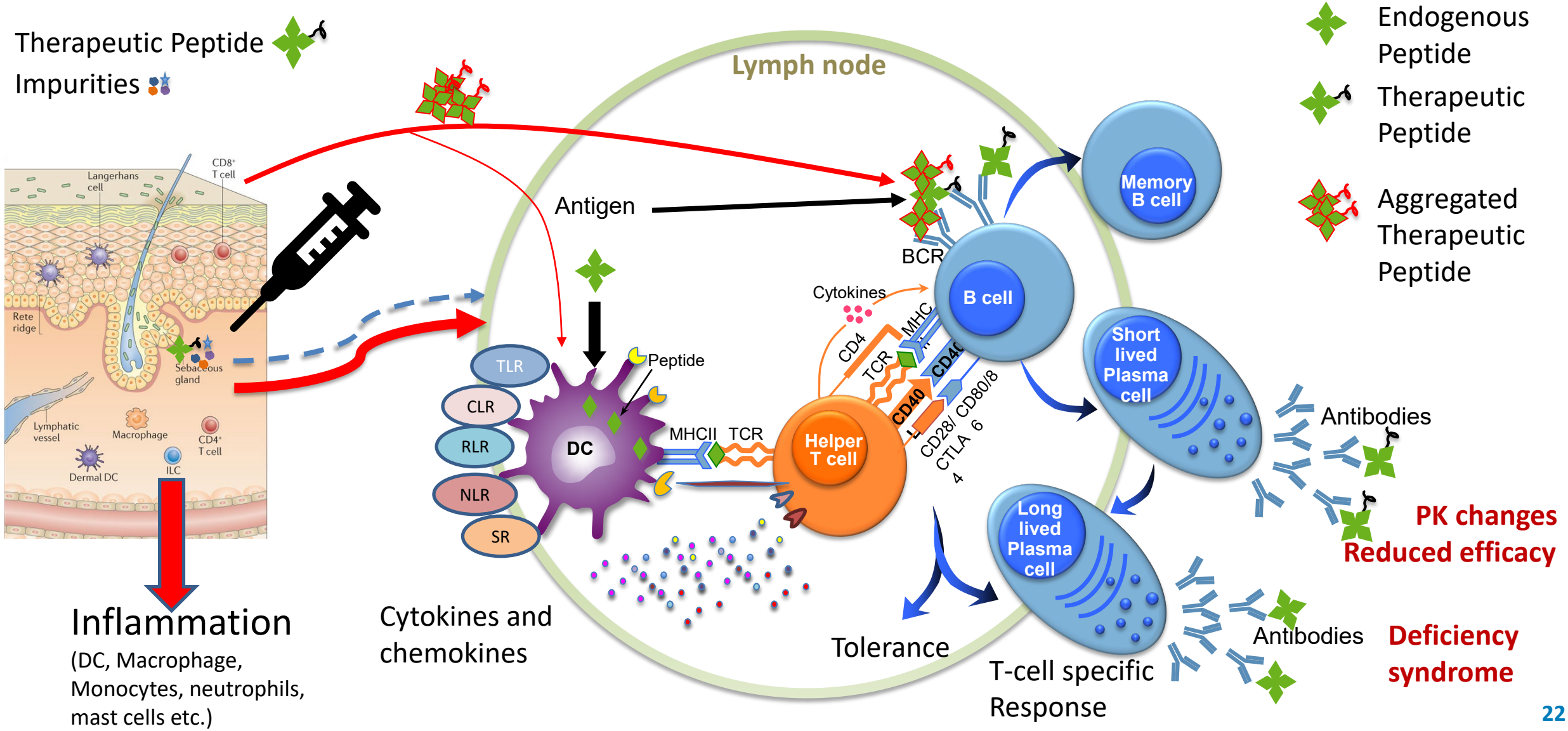
- None
  - No apparent effects
- Moderate
  - Alterations in pharmacokinetic/pharmacodynamic (PK/PD) leading to loss of efficacy or toxicity
- Severe
  - Hypersensitivity/Anaphylaxis (IgG or IgE)
  - Immune complex disease (IgG)
  - Neutralizing antibody, precludes efficacy of effective therapy
  - Cross-reactive neutralization of unique endogenous counterpart

Immunogenicity Risk Factors:

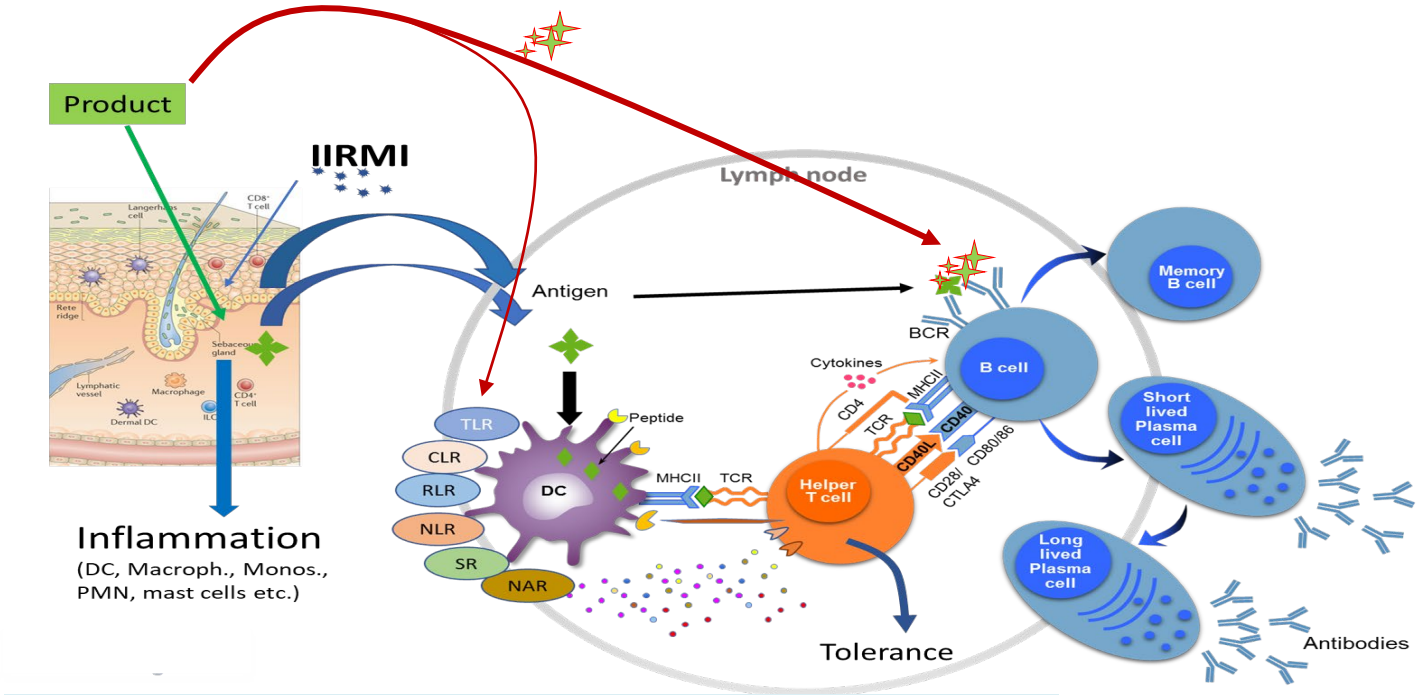


Abbreviations: API = active pharmaceutical ingredient, IIRMI = innate immune response modulating impurities, MHC = major histocompatibility complex

Impurities can increase the immunogenicity risk of peptides



Product and process related impurities impact on the immunogenicity risk for peptides



For most peptides capable of inducing an immune response, impurities can change the **quantity** and the **quality of the immune response**

Aggregation profile

Visible and subvisible particles

Process - related impurities	Leachables, LAL, residual solvents. Innate immune activation by IIRMI In vitro (IIRMI, Ag uptake, DC maturation)

Product – related impurities	LC-MS, MS-MS, Peptide mapping, etc. Methods that assess binding to MHC In silico In vitro (MHC binding, MAPPs) Methods that assess T cell activation In vitro (DC-T cell)

Immunogenicity risk of peptides

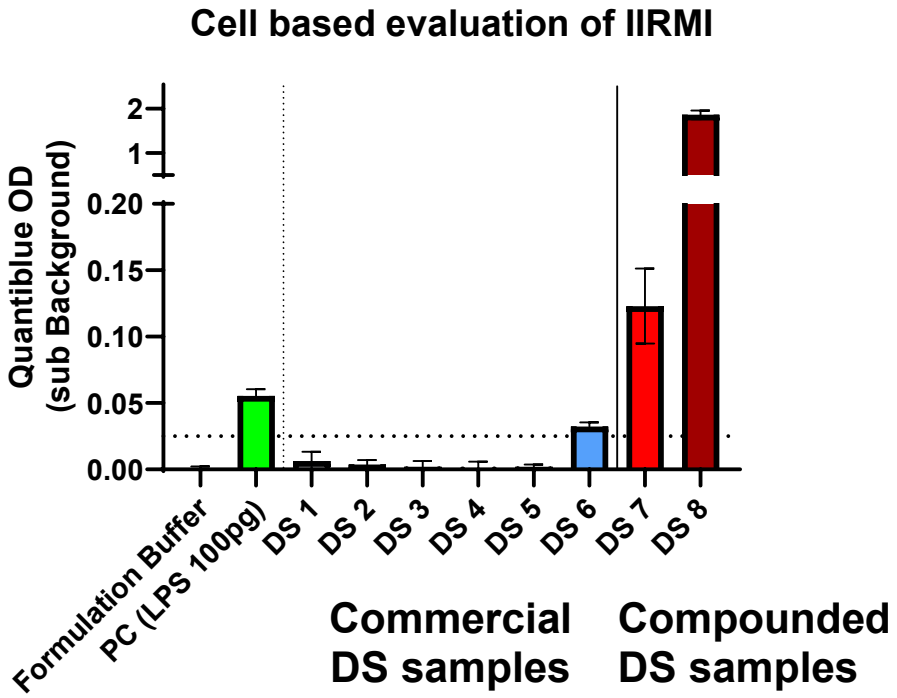
- **Level of concern with peptides is different than for small molecule: Peptide sequences can elicit an immune response, particularly if aggregated or presented on scaffolding.**
- **Peptides administered via subcutaneous, intravenous, intramuscular, intradermal, inhalation, and intravitreal routes have greater immunogenic risk than oral or transrectal peptides.**
- **Product formulation is critical to the quality and stability of peptide drug products. Formulation differences can modify peptide stability and immunogenicity.**
- **Peptide-related impurities may modify the target of the antibodies developed.**
- **Impurities or contaminants that activate immune cells may increase the immunogenicity of the API or result in immune responses that target new sequences that may cross-react with endogenous counterparts.**

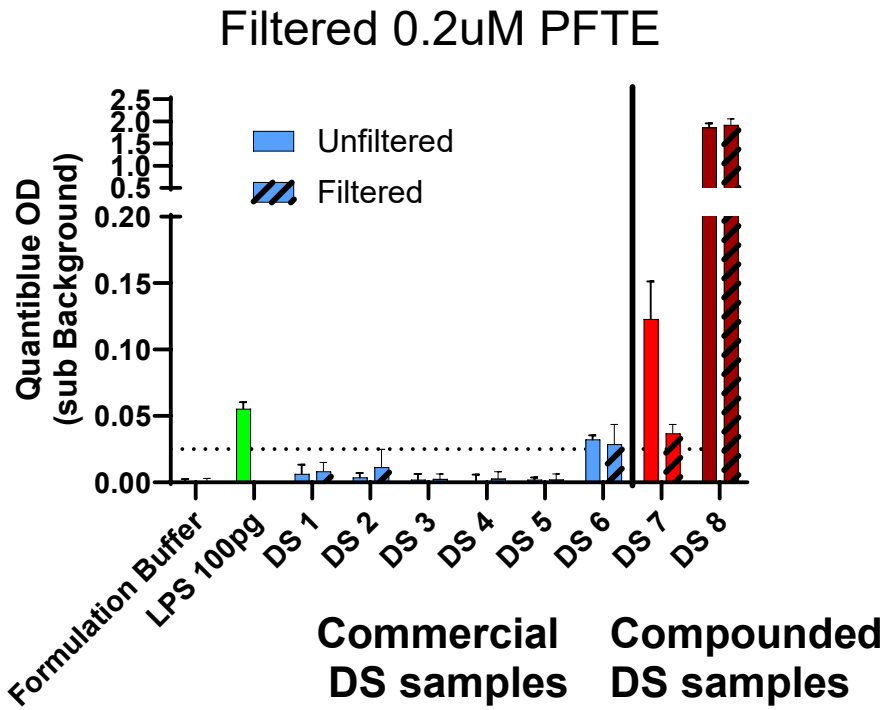
Immunogenicity risk of impurities in peptides

- **Peptide-related impurities can be difficult to detect, analyze, and control because the impurities can have similar amino acid sequences to the peptide itself, necessitating advanced analytical techniques, such as liquid chromatography-high resolution mass spectrometry, to detect, identify, and quantify impurities.**
- **Impurities and contaminants can activate the immune cells where the product is deposited increasing the immunogenicity risk at trace levels (pg-ng).**
- **Assessing the immunogenicity risk of the immunomodulatory impurities in peptides requires complex in silico and in vitro studies.**
- **Mitigating the immunogenicity risk of peptides requires sensitive assays and control of product and process impurities.**

Immunogenicity risk of peptides

- **The risk of Innate Immune Response Modulating Impurities may or may not be mitigated by the drug product (DP) manufacturing process.**





Abbreviations: DS = drug substance, LPS = lipopolysaccharide, PC = phosphorylcholine, PFTE = polytetrafluoroethylene

Summary

- **Product immunogenicity constitutes a risk for peptides, including compounded peptides, especially when delivered via certain routes of administration, which may result in significant risks of harm, including life-threatening reactions such as anaphylaxis. Control of impurities, including aggregates, can mitigate this risk but requires sophisticated manufacturing and testing strategies.**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Pharmacy Compounding Advisory Committee: Bulk Drug Substance (BDS) Discussion December 4, 2024

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Disclosure

- **This speaker has no conflicts of interest to disclose**

Rationale and Objectives

- **In an evaluation(s) presented today, FDA will discuss multiple "related" but distinct BDSs for inclusion on 503A Bulks List**

- **Despite the lack of clarity on which specific BDS was intended in the nominations, due to FDA's significant safety concerns related to the use of certain BDS in compounding drug products, FDA has decided to evaluate these multiple related BDSs on its own initiative**

- **Goals of this presentations**

  - **Explain regulatory definitions for BDS, active pharmaceutical ingredient (API) and active moiety (AM)**

  - **Explain how BDS differences have implications for the drug products made with them**

  - **Provide other relevant background**

A Thought Experiment…

- **How many BDS, API, and AM in the example below?**

- Diclofenac - Diclofenac Epolamine - Diclofenac Sodium - Diclofenac Potassium	- Naproxen - Naproxen Sodium

Statute and Regulations

- **Per 21 CFR 207.3, a BDS is the same an Active Pharmaceutical Ingredient (API). Section 207.3 reads "*Bulk drug substance*, as referenced in sections 503A(b)(1)(A) and 503B(a)(2) of the Federal Food, Drug, and Cosmetic Act, previously defined in § 207.3(a)(4), means the same as "active pharmaceutical ingredient" as defined in § 207.1."**

- **API is defined in FDA regulations at 21 CFR 207.1 and that section reads "*Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include intermediates used in the synthesis of the substance."**

BDS/API In Practical Terms

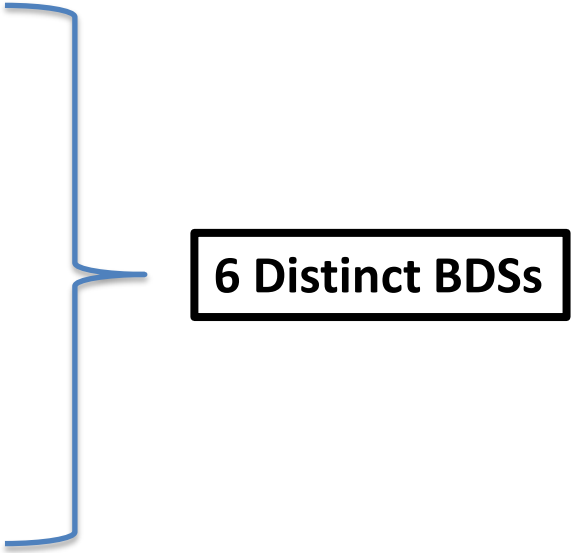
- The specific form of API used in a formulated product, is often a salt or an ester of a free base or active moiety; each a distinct API/BDS
- That “form” is chosen for its physical, chemical, or pharmacokinetic-pharmacodynamic (PKPD) characteristics which renders them more suitable for drug product/compounding processing
- The selection can be dosage form specific due to unique Critical Quality Attributes associated with a desired dosage form

What is an Active Moiety and Salt Form?

- **An active moiety is defined at 21 CFR 314.3 as "*Active moiety* means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance."**

- **Diclofenac – Free base and active moiety NSAID**
- **Diclofenac Epolamine – Epolamine salt of diclofenac free base**
- **Diclofenac Sodium – Sodium salt of diclofenac free base**
- **Diclofenac Potassium – Potassium salt of diclofenac free base**

- **Naproxen – Free base and active moiety NSAID**
- **Naproxen Sodium – Sodium salt of naproxen free base**



Why Does This Matter?

- **FDA has previously stated "when a salt or ester of an active moiety is listed, only that particular salt or ester may be used. The base compound and other salts or esters of the same active moiety must be evaluated separately for eligibility […].”**
  - **See 2016 proposed rule: https://www.federalregister.gov/d/2016-30109/p-108**
  - **This rule was finalized in 2019.**

Why Does This Matter?

- Different salts, esters and the free base can have very different properties
  - Physicochemical properties
    - Chemical formula/Molecular weight
    - Solid state stability
    - Solution stability
    - Solubility
    - Polymorphism
  - Pharm/Tox profile
  - PK/PD profile

- These definitions and distinctions are as important in compounding as they are in drug product manufacturing. This is not just a matter of regulations or definitions; this is a critical matter of chemistry as these different forms have different chemical structures as well as different physical, chemical, PK/PD characteristics. This can impact patient safety and product efficacy.

Physical and Chemical Characterization

- **[For] physical and chemical characterization of the substance, FDA would consider each substance's purity, identity, and quality. Based on attributes such as the substance's molecular structure, stability, melting point, appearance, likely impurities, and solubilities, FDA would determine whether the substance can be identified consistently based on its physical and chemical characteristics. If a substance cannot be well characterized chemically and physically, the Agency proposes that this *criterion weigh against its inclusion […] because there can be no assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities reported in the literature and considered by the Agency*."**
  - **2016 Proposed Rule, Docket No. FDA-2016-N-3464.**
  - **See 81 FR 91071**

Unique Identifiers and Related Databases

- Global Substance Registration System (GSRS)
  - Used by multiple worldwide regulatory agencies
  - Home of a Unique Ingredient Identifier (UNII)

- Chemical Abstracts Services
  - Home of unique identifier known as CAS Registry Number (CAS RN)

- Manufacturers/suppliers populate these databases
  - They provide structure and related information and request unique identifier
  - Regulators do not own or police the data contained therein

Conclusion

- **BDS is defined as the same as an API in the regulations. A free base form as well as each of the salt forms are each distinct BDS, each with unique physical, chemical and PK/PD characteristics which can impact patient safety and product efficacy**

- **Nominators, BDS Manufacturers, and Compounders need to be aware of what single BDS is nominated, manufactured, and used to formulate a compounded product**

- **UNII and CAS# are unique identifiers for API/BDSs but not controlled by FDA**

- **Our physical chemical characterization assessment and conclusion is specific to each unique BDS**

Final Thoughts

- **Botanical BDS are complex mixtures, and care must be taken to identify a single BDS**
- **Use of “common names” for nominated substance can be problematic and cause confusion**
- **Synthetic pathway considerations for more complex BDSs**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CJC-1295-related Bulk Drug Substances

Pharmacy Compounding Advisory Committee Meeting

December 4, 2024

Marianne San Antonio, DO

Physician

Pharmacy Compounding Review Team (PCRT), Office of Specialty Medicine (OSM), Office of New Drugs (OND)

and

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Special Thanks to:

Office of New Drugs - Division of General Endocrinology

Nomination

- Various CJC-1295-related bulk drug substances (BDSs) were nominated for inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
- CJC-1295-related BDSs were evaluated for treatment of:
  - Growth Hormone Deficiency (GHD)
- Proposed product:
  - subcutaneous (SC) injection administration in a 2,000 mcg/mL concentration
- The nominations were withdrawn, and FDA is evaluating the substances at its discretion

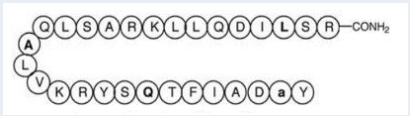
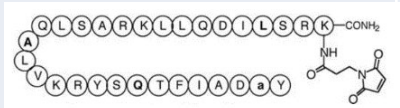
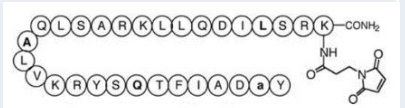
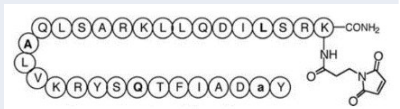
Evaluation Criteria

- Physical and chemical characterization
- Historical use in compounding
- Safety
- Available evidence of effectiveness or lack of effectiveness

Inconsistent Naming Conventions of the BDSs

- CJC-1295-related BDSs are analogues of growth hormone releasing hormone (GHRH)
- There have been many modifications to GHRH over time
- ConjuChem Biotechnologies may have developed CJC-1295 with Drug Affinity Complex (DAC) originally, DAC is a maleimidopropionamide-lysine (MPA-Lys) unit added at the C terminus which we refer to as “CJC-1295 DAC (free base)”
- However, there are other modifications of CJC-1295 that may have been studied including versions without the DAC complex
- It is not possible to know which compound/structure is intended when referenced as common names
- Common names being used for CJC-1295 related BDSs introduces risks: Safety risk for patients, error in chemical analysis

Summary of Basic Information on CJC-1295-related BDSs

	CJC-1295 (free base)	CJC-1295 Acetate	CJC-1295 DAC (free base)	CJC-1295 DAC Acetate	CJC-1295 DAC Trifluoroacetate (TFA)
UNII Code	Not available	Not available	62RC32V9N7	Not available	Not available
CAS No.	446036-97-1	Not available	446262-90-4	Not available	Not available
MF/ MW (g/mol)	$C_{152}H_{252}N_{44}O_{42}$ /3367.95	$C_{152}H_{252}N_{44}O_{42}$ xCH_3COOH /NA	$C_{165}H_{269}N_{47}O_{46}$ /3647.95	$C_{165}H_{269}N_{47}O_{46}$ xCH_3COOH /NA	$C_{165}H_{269}N_{47}O_{46}$ xCF_3COOH /NA
Chemical Structure		 .xCH_3COOH		 .xCH_3COOH	 .xCF_3COOH
Supplier	Yes	Yes	Yes	No	No
Active Moiety	CJC-1295 (free base)	CJC-1295 (free base)	CJC-1295 DAC (free base)	CJC-1295 DAC (free base)	CJC-1295 DAC (free base)

CAS = Chemical Abstracts Service; MF = molecular formula; MW = molecular weight

Summary of Information Submitted in Two Withdrawn Nominations

Nominator	1	2
Nominated BDS	CJC-1295 (free base)	CJC-1295 Acetate
BDS per UNII code	62RC32V9N7 *(matches CJC-1295 DAC (free base))*	62RC32V9N7 *(matches CJC-1295 DAC (free base))*
Certificate of Analysis (CoA)	Not provided	CoA provided for CJC-1295 Acetate
CAS No.	Not provided	863288-34-0 (deleted CAS)
MF	Not provided	$C_{152}H_{252}N_{44}O_{42}$ *(provided in the CoA) (matches CJC-1295 (free base))*
MW (g/mol)	Not provided	3367.97 (provided in the CoA) *(matches CJC-1295 (free base))*
Chemical Name	Information Provided Does Not Correspond to Any CJC-1295-related BDSs	Tyr-D-Ala-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Leu-Ser-Arg-NH_2 (*matches CJC-1295 (free base))*
Active Moiety in Clinical References	CJC-1295 DAC (free base)	CJC-1295 DAC (free base)

Italics in the table above represents the information identified by the FDA.

Physical and Chemical Characterization (1)

CJC-1295 Acetate

- Acetate salt of CJC-1295 (free base), that is synthetic 29 amino acid analogue (Tyr-DAla-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Leu-Ser-Arg-NH2) of GHRH.
- White lyophilized powder; soluble in water at 5 mg/mL
- No USP drug substance monograph
- BDS storage and stability
  - Manufacturer recommends long-term storage at 2 °C - 8 °C in a refrigerator or freezer
  - Remain stable up to 3 years when stored at -20 °C
  - Sensitive to product formulation, process and environment conditions which may lead to aggregation and degradation
- Potential for Impurities
  - Peptide-related impurities and peptide synthesis process-related impurities (e.g., starting materials, residual solvents, coupling reagents, activators, catalysts)

Physical and Chemical Characterization (2)

- Potential for immunogenicity
  - CoA includes peptide purity, largest single impurity limit less than 2.0%, but no information regarding the nature of individual impurities or aggregates
  - Lack of information on the potential of peptide aggregation, especially when formulated in an injectable dosage form for SC administration

Conclusion: CJC-1295 Acetate is not well-characterized

- Concerns arising from inconsistent naming conventions exist for the BDS
- Lack of certain critical characterization data (impurities, aggregates, and bioburden/endotoxin levels)
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities.

Physical and Chemical Characterization (3)

CJC-1295 (Free Base)

- Synthetic 29 amino acid analogue (Tyr-DAla-Asp-Ala-Ile-Phe-Thr-Gln-Ser-Tyr-Arg-Lys-Val-Leu-Ala-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Leu-Ser-Arg-NH2) of GHRH
- White lyophilized powder; limited solubility in water (soluble in 1% acetic acid)
- No USP drug substance monograph
- BDS storage and stability
  - Manufacturer recommends storage at -20 °C
  - Sensitive to product formulation, process and environment conditions which may lead to aggregation and degradation
- Potential for Impurities
  - Peptide-related impurities and peptide synthesis process-related impurities (e.g., starting materials, residual solvents, coupling reagents, activators, catalysts)

Physical and Chemical Characterization (4)

- Potential for immunogenicity
  - No CoA for CJC-1295 (free base) in the nominations
  - No information on impurity limits/testing results as critical attribute control in the CoA reported in public domain
  - Lack of information on the potential of peptide aggregation, especially when formulated in an injectable dosage form for SC administration

Conclusion: CJC-1295 (free base) is not well-characterized

- Concerns arising from inconsistent naming conventions exist for the BDS
- Lack of certain critical characterization data (impurities, aggregates, and bioburden/endotoxin levels)
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities.
- Limited water solubility makes it difficult to formulate proposed injectable dosage form at the concentration of 2 mg/mL using water as a solvent.

Physical and Chemical Characterization (5)

CJC-1295 DAC (Free Base)

- CJC-1295 (free base) with an MPA-Lys unit added at the C terminus
- White lyophilized powder; soluble in water at 2 mg/mL
- No USP drug substance monograph

- BDS storage and stability
  - Manufacturer recommends long-term storage at -20°C
  - The reconstituted peptide can be stored at 4°C
  - Sensitive to product formulation, process and environment conditions which may lead to aggregation and degradation

- Potential for Impurities
  - Peptide-related impurities and peptide synthesis process-related impurities (e.g., starting materials, residual solvents, coupling reagents, activators, catalysts)

Physical and Chemical Characterization (6)

- Potential for immunogenicity
  - No CoA for CJC-1295 DAC (free base) in the nominations
  - Literature search showed that most of the CoAs for CJC-1295 DAC (free base) only contain purity testing result, no impurity attribute control in the CoA to demonstrate the impurity profiles
  - Lack of information on the potential of peptide aggregation, especially when formulated in an injectable dosage form for SC administration

Conclusion: CJC-1295 DAC (free base) is not well-characterized

- Concerns arising from inconsistent naming conventions exist for the BDS
- Lack of certain critical characterization data (impurities, aggregates, and bioburden/endotoxin levels)
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities.

Physical and Chemical Characterization (7)

CJC-1295 DAC Acetate, CJC-1295 DAC TFA

- Salts of CJC-1295 DAC (free base)
- No USP drug substance monograph
- We have not identified publicly available information for these BDSs
- It appears that there is no supplier for these BDSs which likely contributes to the lack of data or any CoA available.

Conclusion: CJC-1295 DAC Acetate, CJC-1295 DAC TFA are not well-characterized

- Concerns arising from inconsistent naming conventions exist for the BDS
- Lack of certain critical characterization data (impurities, aggregates, and bioburden/endotoxin levels)
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities.

Historical Use in Compounding (1)

CJC-1295-related BDSs:

- CJC-1295 DAC
  - Identified in 2005 by ConjuChem Biotechnology as part of the development of maleimido derivatives of human $GHRH_{1-29}$ to overcome the short half-life of human $GHRH_{1-29}$
  - Studies conducted in healthy human subjects were first published in 2006
- CJC-1295 without DAC
  - First referenced in the literature in 2010 with the identification of an unknown pharmaceutical preparation that was seized by Norwegian police and customs
- Compounding with forms of CJC-1295 can be traced back to at least 2018
  - No studies were identified that used a compounded formulation of CJC-1295

Historical Use in Compounding (2)

- An analysis of online discussion forums to identify trends in popularity of doping products identified that CJC-1295 emerged as a topic of discussion after 2005 and the number of discussions regarding its use have continued to trend upward (Pinaeau et al. 2016)
  - There are reports of illicit use in professional sports
- CJC-1295-related BDSs are marketed online:
  - For weight loss, muscle building, and anti-aging as a subcutaneous injection, oral tablet, or troche
  - In combination with other peptides such as ipamorelin acetate
  - Some sites state that an appointment can be scheduled to discuss CJC-1295 therapy
    - Unclear if compounded CJC-1295 is used but a few sites state that it is compounded by a compounding pharmacy
  - Some sites sell products containing CJC-1295 that are listed for research use only
- Not recognized in the European or Japanese Pharmacopeias or in any of the National Medical Registries searched

Conclusion: The extent to which CJC-1295-related BDSs have been used in compounding is unclear. Currently available data is too limited to understand the historical use in compounding.

Nonclinical General Pharmacology

- Like $GHRH_{1-29}$, CJC-1295 DAC acts as a growth hormone (GH) secretagogue (GHS) (Jette et al. 2005)

- CJC-1295 DAC is more stable and has a longer half-life than $GHRH_{1-29}$ (Jette et al. 2005)
  - Researchers suggested that the DAC modification accounts for the greater stability of CJC-1295 DAC

- In rats, CJC-1295 DAC TFA (1 µmol/kg, SC) increased plasma GH levels. However, after peaking at 30 minutes, plasma GH levels declined to baseline by 2 hours post-injection while CJC-1295 DAC levels could still be measured up to 72 hours post-injection.
  - The loss of the GH secretagogue activity in the presence of CJC-1295 DAC in the plasma could be due to:
    - CJC-1295 DAC-induced down-regulation of GHRH receptors in the anterior pituitary gland
    - A decline in pituitary GH content, and/or
    - CJC-1295 DAC-induced activation of a negative feedback loop regulated by somatostatin and the insulin-like growth factor (IGF)-1

- FDA did not identify pharmacological studies of CJC-1295 (free base) or CJC-1295 acetate

Nonclinical Safety (1)

- Acute Toxicity [unspecified form of CJC-1295 DAC]
  - In rats (2-8 mg/kg, intravenously (IV)): Reduced food intake, increased soft/mucoid stools, and/or decreased activity (Iordanova et al. 2004)
  - In dogs (8-40 mg/kg, SC): Emesis and transiently reduced activity (Iordanova et al. 2005)

- Repeat-Dose Toxicity [unspecified form of CJC-1295 DAC]
  - In rats (0.25-4 mg/kg/day, IV) and in dogs (2-18 mg/kg/day, SC) treated for 14 days, safety signals included but were not limited to (Iordanova et al. 2004; Iordanova et al. 2005):
    - Reduced food intake and water consumption, increased soft/mucoid stools, and decreased activity in rats
    - Emesis and decreased activity in dogs
    - Reduced hemoglobin at all tested doses in both species
    - Increased levels of cholesterol (suggestive of altered lipid metabolism) in both species
    - Injection site irritation, with evidence of inflammation, hemorrhage, and minimal to mild necrosis, in both species at all doses

Nonclinical Safety (2)

- Genotoxicity
  - CJC-1295 DAC (unspecified form) induced DNA damage (Ben-Shlomo et al. 2020):
    - In vitro (in mouse pituitary cells in culture)
    - In vivo (in the anterior pituitary gland of mice treated with 10 µg/kg/day, SC, 8 weeks)

- Developmental and Reproductive Toxicity
  - No embryofetal toxicity was observed in pregnant rats treated with CJC-1295 DAC (unspecified form) from gestation days 7 to 17 (Iordanova et al. 2006)
  - FDA did not identify studies assessing potential effects of CJC-1295-related BDSs within a complete reproductive cycle and on peri- and postnatal development

- Carcinogenicity
  - FDA did not identify nonclinical 2-year carcinogenicity studies of CJC-1295-related BDSs

Nonclinical Safety (3)

Conclusions:

- While CJC-1295 DAC-related substances act as GH secretagogues, it is unknown if CJC-1295 (free base) and CJC-1295 acetate are pharmacologically active

- Safety signals reported in nonclinical toxicological studies of CJC-1295 DAC (unspecified form) included, but were not limited to:
  - Local irritation signals characterized by different degrees of hemorrhage, inflammation, and necrosis at the sites of injection in rats and dogs
  - Genotoxicity signals characterized by DNA damage in vitro and in vivo

- Due to lack of carcinogenicity studies, the potential for pituitary gland hyperplasia and tumors to develop due to overstimulation of somatotrophs by different forms of CJC-1295 DAC cannot be ruled out

- There is a lack of nonclinical studies to inform safety considerations for potential clinical uses of CJC-1295 (free base) and CJC-1295 acetate

Clinical Safety (1)
Pharmacokinetics

- Pharmacokinetics (PK)
  - No PK data for children (healthy or with GHD)
  - No PK data for adults with GHD
  - PK data for CJC-1295 DAC (unspecified form) SC administration in healthy adults
    - Teichman et al. 2006
      - Study 1
        - » Placebo (n=7), 30, 60, 125, 250 mcg/kg SC injections in single doses (total n=42)
      - Study 2
        - » n=24, SC injections given 2-3 times over 14 days
        - » Placebo, 20 mcg/kg (3 doses), 30 mcg/kg (2 or 3 doses), 60 mcg/kg (2 doses)
    - Ionescu and Frohman 2006
      - Twelve healthy adult men
      - 60 (n=4 subjects) or 90 (n=8 subjects) mcg/kg SC dose of CJC-1295 DAC (unspecified form)

Clinical Safety (2)
PK

- PK study outcomes (Teichman et al. 2006; Ionescu and Frohman 2006):
  - Half-life of up to 8 days (Teichman et al. 2006)
  - Measurable drug concentrations for 10–13 days (Teichman et al. 2006)
  - Elevated serum GH and IGF-1 concentrations in both studies
  - IGF-1 exceeded normal levels in subjects who received 250 mcg/kg (Teichman et al. 2006)

Clinical Safety (3)
FAERS, CAERS

- FDA Adverse Event Reporting System (FAERS)
  - Two reports, excluded due to:
    - insufficient information provided for case assessment (n=1)
    - no AE reported (n=1)
- CFSAN Adverse Event Reporting System (CAERS)
  - No cases

Clinical Safety (4)
Clinical Studies in Healthy Adults

- Teichman et al. 2006:
  - Study 1, AEs reported in 94% subjects in the CJC-1295 DAC (unspecified form) group and in 29% subjects in the placebo group:
    - Injection site reactions
    - Transient urticarial rashes at the injection site
    - Headache
    - Diarrhea
    - Systemic vasodilatory reactions (flushing, warmth, and transient hypotension)
    - All AEs (except for transient urticarial rashes) were more common at higher doses
  - Study 2:
    - Injection site reactions reported in all subjects who received CJC-1295 DAC (unspecified form)
    - Flushing
    - Headache
    - Nausea or abdominal pain
    - Transient involuntary leg muscle contractions and some loss of coordination
    - Transient dizziness and hypotension
- Ionescu and Frohman 2006:
    - Increase in heart rate (dose dependent)
    - Transient redness and tenderness at the injection site (dose independent)

Clinical Safety (5)
Anecdotal Reports

- Phase 2 clinical trial* conducted by ConjuChem Biotechnologies Inc.
- CJC-1295, DAC:GRF
- 192 subjects with HIV lipodystrophy enrolled and randomized
- Once-weekly injections of either:
  - Three-week escalating low dose of CJC-1295 (DAC:GRF) (at 60, 90, 120 mcg/kg)
  - Three-week escalating high dose (at 60, 120, 240 mcg/kg)
  - Placebo
  - Then continue for a further nine weeks
- AE: Two hours after receiving an 11th weekly dose of CJC-1295 (DAC:GRF), one subject
  - Chest discomfort, electrocardiogram (ECG) confirmed acute myocardial infarction
  - The subject died approximately one hour later
  - The attending physician explanation for the event was the patient had asymptomatic coronary artery disease with plaque rupture and occlusion
- The study was terminated, and data from that study has not been published
- No further information about the other study subjects or about AEs was available

*See two internet anecdotal reports: https://www.aidsmap.com/news/jul-2006/lipodystrophy-study-halted-after-patient-death, accessed on 5/7/2024 and https://web.archive.org/web/20171106065138/http://www.natap.org/2006/newsUpdates/081106_02.htm accessed on 5/7/2024.

Other Safety Concerns

- Teichman et al. 2006 and Ionescu and Frohman 2006 reported that increased GH and IGF-1 levels were observed following administration of CJC-1295 DAC (unspecified form) to study subjects
- There are known potential risks associated with elevated GH and IGF-1 levels, and these risks are included in all FDA-approved recombinant human GH (rhGH) product labeling
  - Increased risk of neoplasm
  - Glucose intolerance and diabetes mellitus
  - Intracranial hypertension
  - Fluid retention
  - Hypoadrenalism
  - Hypothyroidism
  - Slipped capital femoral epiphysis in pediatric patients
  - Progression of preexisting scoliosis in pediatric patients
  - Pancreatitis
- There is a risk of QT prolongation associated with the use of the approved GH stimulator macimorelin acetate (Macrilen oral solution)
- FDA has not identified data or information to suggest that the CJC-1295-related BDSs would not present similar risks

Immunogenicity (1)

- Teichman et al. 2006 assessed the presence of antibodies to CJC-1295 DAC (unspecified form) in the PK study in healthy adult subjects, most of whom were exposed to CJC-1295 DAC (unspecified form) once
- The authors stated that “no significant antibody formation was detected in subjects who received the active study drug”

Limitations:

- The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay
- The authors do not discuss the sensitivity of the assay used to detect antibodies in the study
- It is not known how this assay was validated making it difficult to interpret the findings of no “significant” antibody formation
- Although the authors state that “significant” antibody formation was not observed, they do not specify whether there was no antibody formation
- The lack of “significant” anti-CJC-1295 DAC antibodies does not mean that there is no risk for antibody formation because data for long-term, repeated exposure is lacking
- There is concern that the high degree of homology that CJC-1295-related BDSs have with endogenous GHRH (86%) could result in cross reactivity with endogenous GHRH if antibodies to CJC-1295-related BDS were to form

Clinical Safety Conclusions

- The available clinical safety information is derived from:
  - Published studies conducted in healthy adults
  - Anecdotal reports of exposure in subjects with HIV lipodystrophy
- It is unclear which substance was used in the clinical studies
  - The active moiety may have been CJC-1295 DAC (free base), but no salt was specified
- AEs
  - Most commonly reported AEs in healthy subjects were injection site reactions
  - Other AEs: systemic vasodilatory reactions, headache, nausea, abdominal pain, diarrhea, transient involuntary leg muscle contractions and some loss of coordination, transient dizziness, hypotension, increase in heart rate
- Immunogenicity
  - The lack of "significant" anti-CJC-1295 DAC antibodies does not mean that there is no risk for antibody formation because data for long-term, repeated exposure is lacking
- CJC-1295-related BDSs are nominated to treat a chronic condition (GHD), but their long-term safety profile in humans is unknown
- There were no data to inform safety for use in the pediatric population

Overview of Growth Hormone Deficiency (GHD)

- **Growth Hormone Deficiency**
  - Characterized by inadequate secretion of GH from pituitary gland
  - Can be congenital or acquired
    - Some cases have no known cause (idiopathic) and may be childhood- or adult-onset
  - Can be complete (inability to secrete GH) or partial
- Diagnosis: signs and symptoms and GH stimulation tests using provocative agents
  - Random GH level is not useful because levels fluctuate throughout day
  - IGF-1 levels are helpful in screening
- Signs and symptoms may include:
  - Childhood: low blood glucose levels in infants, growth failure, short stature
  - Adulthood: reduced energy levels, altered body composition, osteoporosis, reduced muscle strength, lipid abnormalities, insulin resistance, and impaired cardiac function

Treatment of GHD

- Multiple rhGH preparations approved for children with growth failure due to inadequate secretion of endogenous GH and adults with GHD

- In pediatric patients with GHD:
  - GH is used to normalize annual growth velocity and final adult height
  - Doses are titrated based on growth response. IGF-1 levels monitor adherence and safety

- In adults with GHD:
  - GH offers benefits in body composition, exercise capacity, and quality of life (Molitch et al. 2011)
  - GH dose is titrated according to clinical response, side effects, and IGF-1

Clinical Effectiveness- GHD (1)

- No articles discussed the effectiveness of CJC-1295-related BDSs in humans with GHD

- Patients with GHD will most likely not respond to GHSs, including CJC-1295-related BDSs, unless these patients have partially preserved pituitary function (partial GHD). Patients with complete GHD will not respond to GHSs.

- Studies conducted in humans were in healthy adults (Teichman et al. 2006, Ionescu and Frohman 2006, Sackmann-Sala et al. 2009)
  - It is unclear which substance was used, the active moiety may have been CJC-1295 DAC (free base)
  - They did not measure endpoints such as changes in body composition (lean body mass and fat mass) in adults or height velocity in children with short stature due to GHD

Clinical Effectiveness – Other Disorders (3)

- In Teichman et al. 2006 and Ionescu and Frohman 2006, the authors stated:
  - "GH has also been used for therapy of disorders in children and adults in which pituitary function is either intact or only slightly impaired" (Teichman et al. 2006)
  - "used in conditions with presumed functional GH deficiency" (Ionescu and Frohman 2006)
- There is no information concerning effectiveness to support use of SC CJC-1295-related BDSs for the treatment of
  - Prader-Willi Syndrome
  - Turner Syndrome
  - Small for gestational age (SGA)
  - Idiopathic short stature (ISS)
  - HIV associated lipodystrophy
  - Wasting syndrome
  - Severe burns
- An anecdotal report of a trial in humans with HIV lipodystrophy who received CJC-1295 (DAC:GRF) was reportedly stopped early after a subject who received CJC-1295 (DAC:GRF) died, and the data were not published

Clinical Effectiveness – GHD (2)

Conclusion:

- There is no information concerning effectiveness to support use of SC CJC-1295-related BDSs for the treatment of GHD
- Professional society guidelines do not discuss the use of CJC-1295-related BDSs for GHD
- There are FDA-approved therapies with established efficacy for GHD

Evaluation Summary (1)

- **Physical and Chemical Characterization**
  - The CJC-1295-related BDS are not well characterized due to:
    - Concerns arising from inconsistent naming conventions for the BDS
    - Lack of certain critical characterization data (impurities, aggregates, bacterial endotoxin levels)
    - Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation and peptide-related impurities
- **Historical Use in Compounding**
  - The extent to which CJC-1295-related BDSs has been used in compounding is unclear
  - Currently available data is too limited to understand the historical use in compounding

Evaluation Summary (2)

- There is no nonclinical or clinical data to assess safety and effectiveness of CJC-1295 (free base) or CJC-1295 acetate

- Safety and effectiveness assessment discusses CJC-1295 DAC-related BDSs

- The salt forms of the CJC-1295 DAC-related BDSs are not specified in the clinical references

Evaluation Summary (3)

Safety

Nonclinical:

- While CJC-1295 DAC-related substances act as GH secretagogues, nonclinical studies were not identified to establish if CJC-1295 (free base) and CJC-1295 acetate are pharmacologically active
- Safety signals induced by CJC-1295 DAC (unspecified form) included, but were not limited to:
  - Local irritation signals
  - Genotoxicity signals characterized by DNA damage in pituitary cells
- Due to lack of carcinogenicity studies, the potential for pituitary gland hyperplasia and tumors to develop due to CJC-1295 DAC-induced overstimulation of somatotrophs cannot be ruled out

Evaluation Summary (4)

Safety

Clinical:

- The available clinical safety information is derived from:
  - Published studies conducted in healthy adults
  - Anecdotal reports of exposure in subjects with HIV lipodystrophy
- AEs, especially injection site reactions, were reported in almost all study participants who received CJC-1295 DAC (unspecified form)
- CJC-1295-related BDSs are nominated to treat a chronic condition (GHD), but their long-term safety profile in humans is unknown
- There were no data to inform safety for use in the pediatric population

Evaluation Summary (5)

- **Effectiveness**
  - There is no information concerning effectiveness to support use of subcutaneous CJC-1295-related BDSs for the treatment of GHD
  - Professional society guidelines do not discuss the use of CJC-1295-related BDSs for GHD
  - There are FDA-approved therapies with established efficacy for GHD

Recommendation

After considering the information currently available, a balancing of the four evaluation criteria weighs **against** the following CJC-1295-related BDSs being added to the 503A Bulks List:

- CJC-1295 (free base)
- CJC-1295 acetate
- CJC-1295 DAC (free base)
- CJC-1295 DAC acetate
- CJC-1295 DAC TFA


FDA
U.S. FOOD & DRUG
ADMINISTRATION

AOD-9604-related Bulk Drug Substances

Pharmacy Compounding Advisory Committee Meeting

December 4, 2024

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Clinical Analyst
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Office of Specialty Medicine (OSM), Office of New Drugs (OND)
and
Bini Mathew, PhD
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Center for Drug Evaluation and Research (CDER), FDA

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Special Thanks to: **Office of New Drugs - Division of Diabetes, Lipid Disorders, and Obesity**

Nomination

- AOD-9604 related bulk drug substances (BDSs) were nominated for inclusion on the list of bulk drug substances that can be used to compound products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (503A Bulks List)
- The nominations provided inconsistent information regarding the specific BDS proposed
  - AOD-9604 (free base) or AOD-9604 acetate
- Evaluated for treatment of obesity
- Proposed drug products:
  - 600 mcg oral capsule
  - 1,200 mcg/mL subcutaneous (SC) injection
  - 600 mcg/g transdermal topical cream
- The nominations were withdrawn, and FDA is evaluating the substances at its discretion

Evaluation Criteria

- Physical and chemical characterization
- Historical use in compounding
- Available evidence of effectiveness or lack of effectiveness
- Safety

Physical and Chemical Characterization

Summary of Basic Information on AOD-9604 (Free Base) and AOD-9604 Acetate

	AOD-9604 (free base)	AOD-9604 Acetate
UNII Code	7UP768IP4M	Not available
CAS No	221231-10-3	Not available
MF/MW (g/mol)	$C_{78}H_{123}N_{23}O_{23}S_2$/1,815.09	$C_{78}H_{123}N_{23}O_{23}S_2 \cdot CH_3COOH$/ 1,875.1
Chemical Structure	Tyr-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe cyclic (7->14)-disulfide	Tyr-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe cyclic (7->14)-disulfide $\cdot CH_3COOH$
Supplier Availability	Yes	Yes
Active Moiety	AOD-9604 (free base)	AOD-9604 (free base)

CAS = Chemical Abstracts Service; MF = molecular formula; MW = molecular weight

Summary of Information Submitted in Two Withdrawn Nominations

Nominator	1	2
Nominated BDS	AOD-9604	AOD-9604
BDS per UNII code	Not provided	7UP768IP4M *(matches AOD-9604 free base)*
Certificate of Analysis (CoA)	CoA provided for AOD-9604	CoA provided for AOD-9604 Acetate
CAS No.	221231-10-3 *(matches AOD-9604 free base)*	221231-10-3 *(matches AOD-9604 free base)*
MF	$C_{78}H_{123}N_{23}O_{23}S_2$ *(provided in the CoA) (matches AOD-9604 free base)*	$C_{78}H_{123}N_{23}O_{23}S_2$ *(provided in the nomination package and CoA) (matches AOD-9604 free base)*
MW (g/mol)	1,815.1 *(provided in the CoA) (matches AOD-9604 free base)*	1,815.1 *(provided in the CoA) (matches AOD-9604 free base)*
Chemical Name	L-tyrosyl-L-leucyl-L-arginyl-L-isoleucyl-L-valyl-L-glutaminyl-L-cysteinyl-L-arginyl-L-seryl-L-valyl-L-alpha-glutamyl-glycyl-L-seryl-L-cysteinyl-glycyl-L-phenylalanine (7->14)-disulfide *(matches AOD-9604 free base)*	L-tyrosyl-L-leucyl-L-arginyl-L-isoleucyl-L-valyl-L-glutaminyl-L-cysteinyl-Larginyl-L-seryl-L-valyl-L-alpha-glutamyl-glycyl-L-seryl-L-cysteinyl-glycyl-Lphenylalanine (7->14)-disulfide *(matches AOD-9604 free base)*
Active Moiety in Clinical References	AOD-9604 (free base)	AOD-9604 (free base)

Italics in the table above represents the information identified by the FDA.

Physical and Chemical Characterization

AOD-9604 (Free Base)

- Hexadecapeptide (Tyr-Leu-Arg-Ile-Val-Gln-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe cyclic (7->14)-disulfide):
  - Tyrosine at the N-terminal end of 15 amino acids fragment of human growth hormone (hGH)
  - Disulfide bridge between two cysteine amino acids may lead to peptide degradation
- White solid powder, soluble in water [up to 2 mg of AOD-9604 (free base) in 1 mL water]
- Has no USP drug substance monograph
- BDS Storage and Stability:
  - Manufacturer recommends storing in a dry place to protect against water and moisture
  - Manufacturer recommends storing in closed containers at temperatures of -18 °C for 3 years, 0-7 °C for 1 year, and 7-30 °C for half a year
  - Sensitive to product formulation, process and environment conditions which may lead to aggregation and degradation

Physical and Chemical Characterization (2)

- Potential for Impurities
  - Peptide-related degradation impurities and peptide synthesis process-related impurities (e.g., starting materials, residual solvents, coupling reagents, activators, catalysts)
- Potential for immunogenicity
  - CoA includes appearance, solubility, identification, peptide purity, water content and assay but no testing result for the control on impurities
  - Lack of information on the potential of peptide aggregation, especially when formulated in an injectable dosage form for SC administration
- Lack of information on critical attributes associated with other proposed pharmaceutical dosage forms such as transdermal cream and oral capsule

Conclusion: AOD-9604 (free base) is not well-characterized

- Lack of certain critical characterization data specific to AOD-9604 (free base), including impurities, aggregates, bioburden, and bacterial endotoxins
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities
- Lack of information on critical attributes associated with other proposed pharmaceutical dosage forms such as transdermal cream and oral capsule

Physical and Chemical Characterization (3)

AOD-9604 acetate

- Acetate salt of the Hexadecapeptide AOD-9604
- White powder, soluble in water [up to 2 mg of AOD-9604 acetate in 1 mL water]
- Has no USP drug substance monograph
- BDS Storage and Stability:
  - Manufacturers recommend storing in a sealed container at 2-8 °C for less than 6-month storage and at -20 °C for more than 6-month storage
  - Sensitive to product formulation, process and environment conditions which may lead to aggregation and degradation
- Potential for Impurities
  - Peptide-related degradation impurities and peptide synthesis process-related impurities (e.g. starting materials, residual solvents, coupling reagents, activators, catalysts)

Physical and Chemical Characterization (4)

- Potential for immunogenicity
  - CoA provided includes identification, purity, peptide content, water content, residual solvent, Bacterial Endotoxins and related substance, controlled largest single impurity at ≤1.0% and total impurities at ≤2.0%; however, lack of information on the nature of individual impurities that can be present at ≤1.0%
  - Lack of information on the potential of peptide aggregation, especially when formulated in an injectable dosage form for SC administration
- Lack of information on critical attributes associated with other proposed pharmaceutical dosage forms such as transdermal cream and oral capsule

Conclusion: AOD-9604 acetate is not well-characterized

- Lack of certain critical characterization data specific to AOD-9604 acetate, including aggregate and bioburden
- Potential for immunogenicity when formulated in an injectable dosage form for SC administration due to potential for aggregation as well as peptide-related impurities
- Lack of information on critical attributes associated with other proposed pharmaceutical dosage forms such as transdermal cream and oral capsule

AOD-9604 (Free Base) or AOD-9604 Acetate

- The nonclinical and clinical references reviewed do not clearly identify whether the substance discussed is the AOD-9604 (free base) or AOD-9604 acetate

- In the next sections, the substances will be generally referred to as AOD-9604

Historical Use in Compounding (1)

AOD-9604-related bulk drug substances:

- First developed by Metabolic Pharmaceuticals (Metabolic Pharma) in the late 1990s (in Australia)
- Has been studied for use in obesity
- Based on outsourcing facility reports, none reported compounding any drug products containing AOD-9604
- The extent to which it has been used in compounding is unclear
- Have been widely advertised by medical spas and wellness clinics
  - Unclear if compounded AOD-9604 is used; however, one wellness clinic indicated that “peptides are prepared and delivered to your doorstep from a 503B compounding pharmacy”

Historical Use in Compounding (2)

- Are marketed online:
  - For osteoarthritis, osteoporosis, worn cartilage, bone damage, hypercholesteremia, diabetes, depression, anti-aging, skin care, boost metabolism, and support weight loss
  - In combination with other APIs (aminophylline, N-acetyl BPC-157, topiramate, etc.)
  - As injectable and oral formulations
- Have been used in sports as a doping agent
- Not recognized in the National Medical Registries, European Medicines Agency website, European, Chinese, Indian, or Japanese Pharmacopoeias

Historical Use in Compounding (3)

Conclusion: There is some evidence of compounded AOD-9604's use in humans. Internet search results show that compounders have prepared AOD-9604 in injectable and oral formulations for certain uses. These formulations of AOD-9604 are being marketed by medical spas and wellness clinics.

General Pharmacology

- Like hGH, AOD-9604 decreases lipogenesis and increases lipolysis in obese rodents:
  - In obese Zucker rats, AOD-9604 (500 µg/kg/day, oral gavage, 19 days):
    - ↓Body weight gain and ↑lipolytic activity in adipose tissue (Ng et al. 2000)
  - In obese mice, AOD-9604 (250 µg/kg/day, SC minipump infusion, 14 days):
    - ↓Body weight gain, ↑plasma glycerol levels (an index of lipolysis), and ↓ white and brown adipose tissue (Heffernan et al. 2001a, 2001b)
- In contrast to hGH, AOD-9604 has no effect on plasma glucose and insulin levels, or glucose oxidation in rats and mice
- Mechanism of action
  - Unknown, but unlikely to involve growth hormone receptors
  - Depends, at least in part, on intact β3 adrenergic receptor signaling

Pharmacokinetics

- **Nonclinical**
  - In vitro (Cox et al. 2015)
    - AOD-9604 was no longer detected after 1-h incubation in human serum at 37°C, as it was hydrolyzed into 6 smaller peptides
  - In vivo (Moré and Kenley 2014)
    - In pigs, AOD-9604 (intravenous (IV)) had a half-life ($t_{1/2}$) of ~3 min
    - In pigs, oral AOD-9604 (2 mg/kg) appeared to have high bioavailability
      - High data variability likely to account for the estimated oral bioavailability (~170%), which exceeds the theoretical maximal 100%
- **Clinical**
  - FDA did not identify clinical studies in humans assessing pharmacokinetics or pharmacodynamics of AOD-9604 via any route of administration (ROA)

Overview of Obesity

- Chronic health condition that increases the risk for heart disease and is linked to other health problems, such as type 2 diabetes and cancer
- Diagnosis based on medical history and high body mass index (BMI) (for adults, ≥ 30 kg/m^2)
- Treatment may involve:
  - Diet, exercise, behavioral modification, and surgery
  - FDA-approved drug products as adjunctive therapy for weight reduction in patients with obesity, including:
    - Glucagon-like peptide-1 (GLP-1) receptor agonist (liraglutide (Saxenda), semaglutide (Wegovy))
    - Glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist (tirzepatide (Zepbound))
    - Naltrexone HCl and bupropion HCl (Contrave), an opioid antagonist (naltrexone) and an aminoketone antidepressant (bupropion)
    - Inhibitor of gastrointestinal lipases orlistat (Xenical) (Alli OTC)
    - A sympathomimetic amine anorectic (phentermine) with a sulfamate-substituted monosaccharide (topiramate) (Qsymia)

Clinical Effectiveness (1)

Wilding 2004:

- Briefly described 3 studies as part of drug development by Metabolic Pharma for the potential treatment in adult patients with obesity
  - IV: AOD-9604 (25, 50, or 100 mcg/kg) or placebo, once weekly x 4 weeks, N=23
  - Oral: AOD-9604 (9, 27, and 54 mg) or placebo, once weekly x 4 weeks, N=16
  - ROA not specified: AOD-9604 (10, 30, or 60 mg) or placebo for 1 week, dosing frequency not specified, N=36
- Authors noted AOD-9604 did not show any statistically significant weight loss in patients with obesity compared to placebo
- Study limitations: insufficient details about methodology and study results, small sample size, and unclear study parameters

Clinical Effectiveness (2)

Herd et al. 2005:

- Double blind (DB), randomized (R), placebo-controlled (PC) study: 300 adults with obesity (abstract only)
  - Received oral AOD-9604 (1, 5, 10, 20, or 30 mg/day) or placebo x 12 weeks
  - Mean weight loss per week: 1 mg (0.22 kg); 20 mg (0.13 kg); 30 mg (0.15 kg); placebo (0.07 kg); no details provided for 5 and 10 mg groups
  - Authors state: Weight loss over 12 weeks was greater with AOD-9604 than placebo, "…with a non-linear dose response…" The largest effect occurred in the 1 mg dose
- We note that the authors claim of weight reduction is based on small difference between AOD-9604 and placebo groups which has unclear meaningful therapeutic effects
- Interpretation of this study is limited by the minimal data in the abstract; insufficient details about the study methodology and results

Clinical Effectiveness (3)

OPTIONS Study (conducted by Metabolic Pharma):

- DB, R, PC study in 502 adults (536 enrolled) with obesity (BMI 30-45 kg/m^2)
- Subjects received:
  - Oral AOD-9604 (0.25, 0.5, or 1 mg) or placebo once daily x 24 weeks, and
  - Dietician-supervised diet and exercise program
- The primary efficacy endpoints:
  - Weight loss after 12 weeks of treatment; safety and tolerability
  - Study was powered for an 80% chance of achieving significance on the primary endpoint if the weight loss compared to placebo was 1.8 kg
- Study Results: No significant difference in weight loss between placebo and AOD-9604. Per company, "Weight loss compared to placebo… was too low to reach statistical significance."

Clinical Effectiveness (4)

OPTIONS Study (continued):

- In 2007, study summary and results were publicly announced by Metabolic Pharma:

  "…the Phase 2B trial results for its drug, AOD9604, do not support the commercial viability of the drug as a treatment for obesity. Development of the drug for this condition is terminated"[1]

- We did not find details of the study design and preliminary efficacy results in the published medical literature

[1] Submission to the Australian Stock Exchange and Australian Security and Investment Commission on 2/21/2007.

Clinical Effectiveness – Conclusion

- In most of the studies we identified, AOD-9604 *failed* to show benefit for weight reduction when compared to placebo
- A study that enrolled 536 patients with obesity did not find significant weight loss with AOD-9604 treatment compared to placebo. Development of the drug was terminated for obesity because of the failed study
- There is lack of evidence to support the effectiveness of AOD-9604 (free base) and AOD-9604 acetate for the treatment of patients with obesity
- There are multiple FDA-approved drug products indicated for weight reduction in patients with obesity

Nonclinical Safety

- Moré and Kenley 2014 provide a descriptive narrative of findings from studies with AOD-9604
  - Four-week toxicity study in rats (intravenous (IV) doses: 0.1, 1.0, 10 mg/kg)
    - ↓Body weight gain at ≥1.0 mg/kg
    - ↓Thymus mass and ↓thymic cortical width (at 10 mg/kg)
  - Six-month toxicity study in rats (Oral doses: 0.5, 20, 100 mg/kg/day)
    - ↓Lymphocyte count (females at all doses)
    - Serum osteocalcin levels ↓ at week 13 and ↑ at week 26 in females
    - ↑Serum creatinine and triglyceride levels (males at 100 mg/kg)
  - Nine-month toxicity study in Cynomolgus monkeys (Oral doses: 0.5, 10, 50 mg/kg/day)
    - Vacuolation in periportal hepatocytes (females at all doses; all females at highest dose)
  - Equivocal signals in in-vitro and in-vivo genotoxicity assays
- Because the article does not provide the underlying data, it is difficult to interpret the author's conclusion that no-adverse-effect-levels (NOAELs) are the highest tested doses

Nonclinical Safety – Conclusion

- The molecular target and the mechanism of action underlying the pharmacological effects of AOD-9604 remain unknown (slide 16), making it difficult to assess the biological plausibility of the pharmacological effects reported in the different studies

- Nonclinical findings suggest that clinically relevant safety signals may develop with systemic exposures to AOD-9604

- Nonclinical studies available at the time of this evaluation were too limited to inform safety considerations for the potential clinical uses of AOD-9604 (free base) or AOD-9604 acetate delivered via the nominated oral, SC, and topical ROAs

Clinical Safety – FAERS and CAERS

- FDA Adverse Event Reporting System (FAERS):
  - Search retrieved no adverse event (AE) reports for AOD-9604[2]

- Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System (CAERS):
  - Search retrieved no reports for AOD-9604

[2] Note the lack of reports for AOD-9604 does not imply that the substance is safe or lacks toxicities; FAERS data have limitations

Clinical Safety – Clinical Studies (1)

Stier et al. 2013:

- Presented safety summary of IV and oral AOD-9604 obtained in six R, DB, PC clinical studies
- Safety monitoring included:
  - Interview of subjects for AEs
  - Measurement of vital signs, laboratory parameters (hematology; biochemistry, urinalysis, lipid analysis), glucose tolerance, and ECG
  - Anti-AOD-9604 antibodies in the blood (in selected patients on oral AOD-9604) and serum levels of IGF-1
- Studies were funded by Metabolic Pharma

Clinical Safety – Clinical Studies (2)

Stier et al. 2013 (continued): IV

- 2 studies:
  - 15 males (no obesity), single dose 25 – 400 mcg/kg and placebo (METAOD001)
  - 23 males with obesity, single dose 25, 50, 100 mcg/kg or placebo (METAOD002)
- AEs reported:
  - 3 AEs severe in intensity:
    - 1 AE "feeling of chest tightness" possibly related to AOD-9604 per authors
    - 2 AEs in the placebo group with no additional details provided
  - AEs most commonly reported
    - Hypoglycemia unspecified, headache, euphoria, fatigue, dizziness, nasopharyngitis, cough
- Authors concluded safety profile of AOD-9604 was comparable in all treatment groups

Clinical Safety – Clinical Studies (3)

Stier et al. 2013 (continued): Oral

- 4 studies in subjects with obesity, AOD-9604 doses 0.25 to 54 mg/day for up to 24 weeks (METAOD003, N=17; METAOD004, N=36; METAOD005, N=300; METAOD006, N=502)

- Serious AEs reported in subjects receiving AOD-9604:
  - Single dose studies:
    - Diarrhea – possibly related to AOD-9604 per authors (54 mg dose)
    - Pneumonia – unrelated to treatment per authors (54 mg dose)
  - 12 weeks study:
    - Basal cell carcinoma, moderate lipoma and squamous cell carcinoma (20 mg)
    - Malignant melanoma (10 mg), Breast cancer (5 mg)

    Authors considered these not related to AOD-9604
  - 24 weeks study:
    - Distribution of SAEs were similar among groups; no details provided

- AEs reported:
  - Diarrhea (severe intensity) - possibly related to AOD-9604 per authors
  - Most common: headache, diarrhea, flatulence, increased appetite, nausea

- Authors concluded safety profile of AOD-9604 was comparable in all treatment groups

Clinical Safety – Clinical Studies (4)

Stier et al. 2013 Continued

- Authors noted for all studies:
  - No “statistically significant” changes in laboratory parameters, ECG changes, or vital signs in any treatment group (Note no details provided)
  - No “statistically significant differences” in IGF-1 levels among the treatment groups and placebo group were detected
  - Anti-AOD-9604 antibodies were not detected in selected patients who received oral AOD-9604 for up to 24 weeks

- We note the limitations of the study include lack of sufficient details such as detailed description and breakdown of AEs, intervention and outcome, and/or a short-term study duration

Additional safety information – Immunogenicity Concerns

- AOD-9604 (free base) and AOD-9604 acetate consists of 16 amino acids
- Peptides may elicit an immune response; this response may be enhanced when peptides are given via the SC ROA
- AOD-9604 pose a risk for immunogenicity, potentially amplified by aggregation as well as potential peptide-related impurities
  - The nomination did not include, and FDA did not identify, information about AOD-9604 (free base) or AOD-9604 acetate to suggest that the substances do not present these risks

Clinical Safety - Conclusion

- Based on available studies in humans who received oral AOD-9604, serious AEs include diarrhea, chest tightness, and various types of cancers
- FDA did not find information on the proposed SC and transdermal use of AOD-9604 (free base) and AOD-9604 acetate in humans
- Obesity is a chronic condition which may need long-term repeated treatment; there is insufficient information to support the long-term use of AOD-9604 in patients with obesity
- There is limited information to assess immunogenic safety risk for AOD-9604 for the oral route of administration and there is no information to assess immunogenic safety risk for the subcutaneous and transdermal topical routes
- AOD-9604 (free base) and AOD-9604 acetate are peptides containing 16 amino acids and peptide sequences of this length have the potential to be immunogenic
- There are multiple currently available FDA-approved drug products indicated for weight reduction in patients with obesity

Evaluation Summary

On balance, physicochemical characterization, information on historical use, lack of evidence of effectiveness, and safety information **weigh against** both AOD-9604 (free base) and AOD-9604 acetate being added to the 503A Bulks list

Although available data suggests that these substances have historically been used in compounding, FDA's proposal is based on a lack of data related to physical and chemical characterization and additional concerns related to potential immunogenicity risk, lack of evidence of effectiveness for use in patients with obesity, insufficient safety information on the use of the substances

The lack of evidence of effectiveness and limited safety data and the existence of FDA-approved drugs for use in patients with obesity, particularly in light of the fact that obesity increases the risk for many serious diseases and health conditions, weigh against AOD-9604-related BDSs being added to the 503A Bulks List

Recommendation

After considering the information currently available, a balancing of the four evaluation criteria weighs **against** AOD-9604 (free base) or AOD-9604 acetate being added to the 503A Bulks List.


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