FDA Pharmacy Compounding Advisory Committee:

CJC-1295 Acetate

Presented by:

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Four Factor Inclusion Criteria

1) Is the substance well-characterized, physically and chemically?

   Is the substance identified consistently based on its physical and chemical characteristics?

2) Has the substance been used historically in compounding?

   Historical use of the substance in compounded products including peer reviewed medical literature about the medical conditions it has been used to treat. Widespread use, including use in other countries, favors inclusion.

3) Are there concerns about whether a substance is effective for a particular use?

   Available evidence of effectiveness of a drug product compounded with the substance. When the substance is used for a less serious disease FDA will be more concerned with safety. However, when the substance is proposed to treat a more serious or life-threatening disease the existence of an approved product would weigh against inclusion, even more so with minimal effectiveness data for the substance.

4) Are there concerns about the safety of the substance for use in compounding?

   Safety issues raised by the use of the substance in compounded product. Reports in peer reviewed medical literature about the substance's pharmacology, acute toxicity, repeat dose toxicity, mutagenicity, developmental and reproductive toxicity, and carcinogenicity. Reports and abstracts in literature about adverse reactions in humans.

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21 CFR § 216.23 **Bulk drug substances** that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act.

. . .

- (c) FDA will use the following criteria in evaluating substances considered for inclusion on the list set forth in paragraph (a) of this section:
  - (1) The physical and chemical characterization of the **substance**;
  - (2) Any safety issues raised by the use of the **substance** in compounded **drug products**;
  - (3) The available evidence of the effectiveness or lack of effectiveness of a **drug product** compounded with the **substance**, if any such evidence exists; and
  - (4) Historical use of the **substance** in compounded **drug products**, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

Four Factor Inclusion Criteria: CJC-1295 Acetate

1) Is the substance well-characterized, physically and chemically?

- FDA's own GSRS and NIH's own Pub Chem have listings for CJC-1295 Acetate that include information on the characterization of CJC-1295 Acetate both physically and chemically. The product was part of Phase II clinical trial listed on clinicaltrials.gov, meaning FDA reviewed an IND and protocols for the study of this product and recognized manufacturing and testing capabilities for the use of CJC-1295 in humans. We have also provided COAs in the written materials that show endotoxin testing, purity testing, etc. that are based on FDA's OWN guidance and ICH standards.
    - On Immunogenicity: you've heard from FDA– "Control of impurities, including aggregates, can mitigate this risk but requires sophisticated manufacturing and testing strategies."
        - Thus, there is no concern that cannot be controlled through testing and compounding processes.

2) Has the substance been used historically in compounding?

- We have provided RWE from pharmacies that have dispensed 449,184 prescriptions for CJC-1295 Acetate.

3) Are there concerns about whether a substance is effective for a particular use?

- CJC-1295 Acetate has been used 449,184 times and results have shown that it is effective.

4) Are there concerns about the safety of the substance for use in compounding?

- Our RWE and retrospective analysis found that out of 449,184 prescriptions providers report the drug as well tolerated.

Four Factor Inclusion Criteria: CJC-1295 Acetate

1) Is the substance well-characterized, physically and chemically?

Is the substance identified consistently based on its physical and chemical characteristics?

One potential example COA:

TESTS	SPECIFICATIONS		RESULTS
Appearance	White powder		White powder
Solubility	Soluble in water		Conforms
Amino Acid Composition (AAA)	Val	0.8 – 1.2	1.1
	Tyr	1.8 – 2.2	2.0
	Ala	3.6 – 4.4	4.1
	Arg	2.7 – 3.3	3.0
	Asp	1.8 – 2.2	1.9
	Ile	1.8 – 2.2	2.0
	Leu	4.5 – 5.5	4.9
	Phe	0.8 ÷ 1.2	1.0
	Thr	0.8 – 1.2	1.1
	Glu	2.7 – 3.3	3.2
	Ser	2.7 – 3.3	3.0
	Lys	1.8 – 2.2	2.1
Mass (MS)	3367.85 ± 1		3368.77
Water Content (KF)	≤ 8.00%		5.80%
Acetic Acid Content (HPLC)	≤ 18.0%		8.20%
Peptide Content (N%)	≥ 80.0%		82.9%
Peptide Purity (HPLC) (CP)	≥ 98.0%		98.7%
Related Substances (HPLC) (CP)	Total Impurities	≤ 2.00%	1.30%
	Largest Single Impurity	≤ 1.00%	0.60%
Residual Solvent (GC)	Formaldehyde	Negative	Conforms
Bacterial Endotoxins (USP)	≤ 10 EU/mg		< 10 EU/mg
Microbial Tests (USP)	Total Aerobic Microbial Count	$\leq 10^4$ CFU/g	< 20 CFU/g
	Total Yeast and Mold Count	$\leq 10^2$ CFU/g	< 20 CFU/g
	E. coli	Absent	Absent
Assay (On Anhydrous and Acetic Acid-Free Basis) (HPLC) (CP)	95.0 - 105.0%		99.6%

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Physical and Chemical Characterization: CJC-1295 Acetate

- The issues raised by FDA relate to API concerns and not COMPOUNDING concerns
  - FDA should release a guidance on testing for APIs and not prohibit compounding for those that properly acquire and test the API.
  - API manufacturers are testing for potency, purity (and impurities including aggregates), and endotoxin testing
    - https://pmc.ncbi.nlm.nih.gov/articles/PMC7587993/
- National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 56841945, CJC-1295. Retrieved November 27, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/56841945
- FDA's GSRS listing for CJC-1295: https://precision.fda.gov/uniisearch/srs/unii/62RC32V9N7

Physical and Chemical Characterization: CJC-1295 Acetate

- See FDA Guidance on Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers.
- ICH Guidelines on:

Q3A - Q3E Impurities	
Q3A(R2)	Impurities in New Drug Substances
Q3B(R2)	Impurities in New Drug Products
Q3C(R9)	Guideline for Residual Solvents
Q3C(R10) Maintenance EWG	Maintenance of the Guideline for Residual Solvents
Q3D(R2)	Guideline for Elemental Impurities
Q3D(R3) Maintenance EWG	Maintenance of the Guideline for Elemental Impurities
Q3D training	Implementation of Guideline for Elemental Impurities
Q3E EWG	Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics

Physical and Chemical Characterization: CJC-1295 Acetate

The physical and chemical characterization of the **substance**. However, even if looking at the finished product:

- Impurities
  - Consistent with the small amount of unspecified peptide-related impurities observed in finished peptide drug products due to batch-to-batch variability, for any new specified peptide-related impurity, the level is no more than 0.5 percent of the drug substance.[1]
- Residual solvents
  - Limits are already set for common solvents.[2]
- The peptide can be taken orally.

1. ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin, Guidance for Industry, May 2021 https://www.fda.gov/media/107622/download
2. Companion document for the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance for industry Q3C Impurities: Residual Solvents. https://www.fda.gov/media/71737/download

Four Factor Inclusion Criteria: CJC-1295 Acetate

2) Has the substance been used historically in compounding?

Historical use of the substance in compounded products including peer reviewed medical literature about the medical conditions it has been used to treat. Widespread use, including use in other countries, favors inclusion.

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Historical Use in Compounding: CJC-1295 Acetate

- CJC-1295 Acetate has been researched by a pharma company.
- Outsourcing facility product reports sent to FDA show compounding in 2019 and 2020. [1]
- We have collected data from various pharmacies amounting to 449,184 dispenses of CJC-1295.

1. FDA Briefing Document, Pharmacy Compounding Advisory Committee, December 4, 2024. Page 24.

Real World Evidence (RWE)

- The clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real world data.[1]
- Oncology approvals from 2015 to 2020 were reviewed from FDA.gov.
  - 13 contained Real World Evidence.[2]
  - Sample size of RWE was from 14 to 908 patients.[2]
- NDAs and BLAs reviewed and approved by FDA from 2019 to 2021.
  - 13 examples of RWE were reviewed for insights into how RWE has been used to support regulatory submissions and the resulting feedback from FDA.[3]
  - Data included chart review for contextualization, retrospective observational cohort, electronic health record data for comparison to trial results. [3]
  - RWE has the potential to support inferences about safety and effectiveness.[4]

1. Framework for FDA's Real World Evidence Program. https://www.fda.gov/media/120060/download?attachment
2. Real-World Evidence in Support of Oncology Product Registration: A Systematic Review of New Drug Application and Biologics License Application Approvals from 2015–2020. Clin Cancer Res (2022) 28 (1): 27–35.
3. The Use of Real-World Evidence in FDA Regulatory Submissions: A Review. Nikita Raina & John Ko. Beam Therapeutics. https://www.ispor.org/docs/default-source/intl2023/ispor23rainaposter-pdf.pdf?sfvrsn=badb0da1_0
4. Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry. December 2023. https://www.fda.gov/media/154449/download

Adverse Events (AE) and FDA Safety Evaluation

- We are unaware of any serious, let alone unexpected, adverse event directly attributable to drug products compounded from CJC-1295.
  - This includes RWE from pharmacies who have dispensed 449,184 prescriptions involving CJC-1295.
  - FDA has included in these materials, FDA's review of its FAERS and CAERS system, further evidencing the lack of adverse events associated with these peptides.
- The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for CJC-1295-related BDSs to include all reports through June 10, 2024. The search retrieved two reports, which were excluded due to insufficient information provided for case assessment (n=1) and no AE reported (n=1). They also conducted a literature search for case reports of AEs for CJC-1295-related BDSs that included all domestic case reports through June 11, 2024. This search did not retrieve any relevant domestic case reports describing AEs with the use of CJC-1295-related BDSs. [1]

1. FDA Briefing Document, Pharmacy Compounding Advisory Committee, December 4, 2024. Page 40

Summary of RWE and Safety

- Summary of Compounding Pharmacy Dispensing Data
    - This includes RWE from pharmacies who have dispensed 449,184 prescriptions involving CJC-1295.
    - We have collected and aggregated pharmacy dispensing data from compounding pharmacies for CJC-1295. We are not aware of any adverse event reported on CJC-1295.

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Uses and Efficacy: CJC-1295 Acetate

- Most Frequent Uses:
  - Body composition.
  - ConjuChem enrolled 192 participants in a clinical trial for HIV associated lipodystrophy.
- The company chose not to continue development due to the death of a trial subject from an Argentinian trial site.
  - The attending physician stated that his most likely explanation for the event was the patient had asymptomatic coronary artery disease with plaque rupture and occlusion. The study was terminated, and the data from that study has not been published.
- A study of 20 health men showed CJC-1295 increased trough and mean GH secretion and IGF-I production with preserved GH pulsatility.

FDA Briefing Document, Pharmacy Compounding Advisory Committee, December 4, 2024. Page 23.
See https://www.aidsmap.com/news/jul-2006/lipodystrophy-study-halted-after-patient-death. Accessed November 27, 2024.
Ionescu, Madalina et al. Pulsatile Secretion of Growth Hormone (GH) Persists during Continuous Stimulation by CJC-1295, a LongActing GH-Releasing Hormone Analog. J Clin Endocrinol Metab. 2006;91(12):4792-97. https://sci-hub.se/10.1210/jc.2006-1702
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Safety: CJC-1295 Acetate

- “No serious adverse effects were observed in any of the subjects. The most commonly observed effects were an increase in heart rate that was dose dependent and transient redness and tenderness at the injection site that appeared to be dose independent. All adverse effects were of short duration and not considered a problem by the subjects. None of the subjects experienced any of the adverse effects commonly associated with GH therapy.”

Ionescu, Madalina et al. Pulsatile Secretion of Growth Hormone (GH) Persists during Continuous Stimulation by CJC-1295, a LongActing GH-Releasing Hormone Analog. J Clin Endocrinol Metab. 2006;91(12):4792-97. https://sci-hub.se/10.1210/jc.2006-1702

Pharmacy Prescriptions Dispensed: CJC-1295 Acetate

- Total CJC-1295 Rxs dispensed = 449,184.

Safety: CJC-1295 Acetate

- The Office of Surveillance and Epidemiology conducted a search of the FAERS database for reports of adverse events (AEs) for CJC-1295-related BDSs to include all reports through June 10, 2024. The search retrieved two reports, which were excluded due to insufficient information provided for case assessment (n=1) and no AE reported (n=1). They also conducted a literature search for case reports of AEs for CJC-1295-related BDSs that included all domestic case reports through June 11, 2024. This search did not retrieve any relevant domestic case reports describing AEs with the use of CJC-1295-related BDSs.[1]
  - We conducted a search of the FAERS database for the period after June 11, 2024 and did not retrieve any reports.

- CFSAN collects reports of AEs involving food, cosmetics, and dietary supplements in the CAERS database. A search of CAERS was conducted for AEs associated with CJC-1295- related BDSs for dates 1/1/2004-4/22/2024 and retrieved no cases.
  - We conducted a search of the CAERS database for the period after April 22, 2024 (to July 2024, the most current data set) and did not retrieve any reports.

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Conclusion

1. Is the substance well-characterized, physically and chemically?
    - Yes, like all drug substances, any testing recommended by the Agency can be performed.
2) Has the substance been used historically in compounding?
    - Yes, literature supporting historical use and RWE.
3) Are there concerns about whether a substance is effective for a particular use?
    - No, there is literature and RWE supporting effectiveness.
4) Are there concerns about the safety of the substance for use in compounding?
    - None where risks outweigh benefits. Based on RWE, prescribers have determined that benefits outweigh risks for certain individual patients. Section 503A compounders compound and dispense based on individual patient prescriptions. RWE has not identified safety concerns that should prohibit patient access to compounded drug products using the substance as determined by the individual patient-prescriber relationship.