CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761146Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Indication

Recommendation: BLA Approval

BLA Number: 761146
Review Number: 1
Review Date: May 20th, 2020

Drug Name/Dosage Form	Qwo (collagenase clostridium histolyticum-aaes) injection (solution)
Strength/Potency	0.23 mg/mL after reconstitution (0.92 mg/4 mL or 1.84 mg/8 mL)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Treatment of moderate to severe cellulite in the buttocks of adult women
Applicant/Sponsor	Endo Pharmaceuticals Inc.

Product Overview

Collagenase clostridium histolyticum (CCH) is a parenteral lyophilized product comprised of two collagenase enzymes in an approximate 1:1 mass ratio: Collagenase I (AUX-I; Clostridial type I collagenase) and Collagenase II (AUX-II; Clostridial type II collagenase). These collagenases are isolated and purified from the fermentation of the bacteria *Clostridium histolyticum.* Collagenase I and Collagenase II have molecular weights of ~ 114 kDa and ~ 113 kDa respectively. CCH is licensed for the treatment of Peyronie's Disease and Dupuytren's Contracture in BLA 125338. For this indication, the sponsor has generated a formulation containing (b) (4) mannitol (CCH Mannitol). Edematous fibrosclerotic panniculopathy (EFP), or cellulite, is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction and/or thickening of the collagen septa. The collagenases have synergistic cleaving activity towards the collagens, disrupting the thickening of the collagen septa. CCH Mannitol is a sterile, white, lyophilized powder for reconstitution in a clear, colorless sterile diluent consisting of 0.03% calcium chloride dihydrate in 0.6% sodium chloride. Each 5 mL vial of CCH Mannitol drug product (DP) contains 0.92 mg of CCH Mannitol lyophilized powder for reconstitution in 4 mL of sterile diluent. Each 10 mL vial of CCH Mannitol DP contains 1.84 mg of CCH Mannitol lyophilized powder for reconstitution in 8 mL of sterile diluent. The recommended dose is 0.84 mg per treatment area in 12 injections of 0.3 mL each delivered in three 0.1 mL aliquots. Treatment should be repeated every 21 days for 3 treatment visits.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance (DS)	Bruce Huang	OPQ/OBP/DBRRII
DP	Bruce Huang	OPQ/OBP/DBRRII
Immunogenicity	Bruce Huang	OPQ/OBP/DBRRII
Labeling	Vicky Borders Hemphill Bruce Huang	OPQ/OBP OPQ/OBP/DBRRII
DS Micro DS and Facilities	Ashley Queen	OPQ/OPMA/DBM2
DP Micro DP	Dupeh Palmer	OPQ/OPMA/DBM1
RBPM	Florence Aisida	OPQ/OPRO
Team Lead	Brian Roelofs	OPQ/OBP/DBRRII

	Candace Gomez-Broughton (Micro) Zhong Li (Facilities)	OPQ/OPMA/DBM1 OPQ/OPMA/DBM1
Application Technical Lead	Brian Roelofs	OPQ/OBP/DBRRII

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Craig Johnson	OND/ORO/DROII
Cross-disciplinary Team Lead	Gordana Diglisic	OND/OI/DDD
Medical Officer	Melinda McCord	OND/OII/DDD
Pharm/Tox	Jill Merrill/Barbara Hill	OND/OII/DPTII
Clinical Pharmacology	Liping Pan/Chinmay Shukla	OTS/OCP/DIIP
Statistics	Rebecca Hager/Mohamed Alosh	OTS/OB/DBIII

1. Names:
   a. Proprietary Name: Qwo
   b. Trade Name: Qwo™ (collagenase clostridium histolyticum-aaes) for injection
   c. Non-Proprietary Name/USAN: Collagenase clostridium histolyticum-aaes
   d. CAS Registry Number: *Clostridium histolyticum colG* gene product AUX-I: 955089-04-0
      Clostridium histolyticum colH gene product AUX-II: 955089-06-2
   e. Common Name: Collagenase AUX-I and Collagenase AUX-II, Clostridial Collagenase, Clostridial Collagenase for Injection
   f. INN Name: Not applicable
   g. OBP systematic name: PROT Q9X721 (Q9X721_CLOHI) & Q46085 (Q46085_CLOHI)[XIAFLEX]
   h. Other name(s): EN3835, AA4500, Enzyme Commission Number: EC 3.4.24.3

Submissions Reviewed:

Submission(s) Reviewed	**Document Date** (disciplines affected)
STN 761146/SN0001 (BLA submission)	September 6th, 2019 (OBP, OPMA)
STN 761146/SN0003 (Response to IR 1)	October 24th, 2019 (OPMA, OBP)
STN 761146/SN0007 (Response to IR 2)	December 5th, 2019 (OBP)
STN 761146/SN0013 (Response to IR 3)	January 31st, 2020 (OPMA)
STN 761146/SN0015 (Response to IR 4)	February 26th, 2020 (OBP)
STN 761146/SN0016 (Response to IR 5)	March 4th, 2020 (OPMA)
STN 761146/SN0017 (Response to IR 6)	March 6th, 2020 (OPMA)
STN 761146/SN0018 (Response to IR 7)	March 13th, 2020 (OPMA)
STN 761146/SN0025 (Response to IR 8)	April 7th, 2020 (OPMA)
STN 761146/SN0027 (Response to IR 9)	April 15th, 2020 (OPMA)
STN 761146/SN0029 (Response to IR 10)	April 30th, 2020 (OBP)
STN 761146/SN0031 (Response to IR 11)	May 8th, 2020 (OPMA)
STN 761446/SN0032 (Response to IR 12)	May 14th, 2020 (OPMA)
STN 761146/SN0033 (Response to IR 13)	May 19th, 2020 (OBP)

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed
(b) (4)	III		(b) (4)	3	Adequate	N/A
	V			3	Adequate	N/A
	III			3	Adequate	N/A
	V			3	Adequate	N/A
	III			3	Adequate	N/A
	III			3	Adequate	N/A

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
BLA	125338	In a Type B meeting held January 30th, 2019, under IND 110077, the sponsor proposed to file an original BLA for CCH for the treatment of EFP. The Agency responded with the advice to submit an Efficacy Supplement for the new indication. The sponsor stated their rationale for a separate BLA including anticipated differences in REMS requirements, labeling, methods of use, patient populations, lifecycle management and business reasons. The sponsor chose to submit the application as an original BLA and provided reference for modules 2.4,

		2.6, 3.2.S, 3.2.P, 4.2 and 5.3.6 from BLA 125338 for CCH. The DS manufacturing process in BLA 761146 differs (b) (4) to produce CCH in a new formulation containing (b) (4) mannitol at a pH of 8 (b) (4). The DP and DP sterile diluent (DPSD) manufacturing site used with BLA 761146 is a part of BLA 1253385, but only manufactures DPSD. Additionally, the DP process has a (b) (4) (b) (4).
IND	110077	Parent IND

3. Consults: None

4. Environmental Assessment

A categorical exclusion from submitting an Environmental Assessment of Qwo (collagenase clostridium histolyticum-aaes) is requested per 21 CFR 25, section 25.31(c). The protein molecule is a biodegradable product derived from a biological system. The small molecule side-chain has no known adverse effects on humans or the environment. The expected concentration at the point of entry into the aquatic environment is well below 1 part per billion. No extraordinary conditions exist.

The request for categorical exclusion is granted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:
The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761146 for Qwo (collagenase clostridium histolyticum-aaes) manufactured by Endo Pharmaceuticals, Incorporated. The data submitted in this application are adequate to support the conclusion that the manufacture of Qwo (collagenase clostridium histolyticum-aaes) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance:
    Auxilium Pharmaceuticals LLC, 102 Witmer Road, Horsham, Pennsylvania, 19044, United States of America (FEI: 3006537159)

  - Drug Product and Drug Product Sterile Diluent:
    (b) (4)

- Fill size and dosage form:
  - 0.92 mg for reconstitution in 4 mL of sterile diluent for one treatment area
  - 1.84 mg for reconstitution in 8 mL of sterile diluent for two treatment areas

- Dating period:
  - Drug Product: 24 months at 2 to 8°C
  - Drug Product Sterile Diluent: 24 months at 2 to 30˚C
  - Drug Substance: (b) (4)
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the process validation drug substance batches and drug product lots.
    - For stability protocols: We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release in accordance with 21 CFR 601.2a. CCH Mannitol is a specified product.

C. Benefit/Risk Considerations:

CCH is an approximate 1:1 mix of the collagenase gene products of *ColG and ColH* isolated and purified from the bacteria *Clostridium histolyticum*. CCH DP is a parenteral lyophilized product that is licensed for the treatment of Peyronie's Disease and Dupuytren's Contracture. EFP is

caused by herniation of subcutaneous fat lobules through the dermohypodermal junction and/or thickening of the collagen septa. There are currently no FDA approved pharmacologic therapies for the treatment of EFP.

Review of manufacturing has identified that the methodologies used for DS and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of CCH DS at Auxilium Pharmaceuticals, Horsham, Pennsylvania, USA and of CCH DP and DPSD at (b) (4) The OBP (Office of Biotechnology Products) product quality and immunogenicity assay assessments, OPMA (Office of Pharmaceutical Manufacturing Assessment) DS and DP microbiological and facility assessments, and OBP labeling technical assessments are located as separate documents in Panorama.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

1. Conduct a drug product (DP) transport qualification study shipping 5 mL and 10 mL vials of CCH Mannitol DP from (b) (4) to the (b) (4) packaging site (b) (4)

   Target completion date: June 30, 2021

2. The target filtration volume of (b) (4) mL was not achieved for one of the test filters (lot number: R6EA67189) in the bacterial retention study (b) (4) (b) (4). Conduct a bacterial retention study to simulate the target filtration volume and maximum flow rate throughout the study duration for all test filters.

   Target completion date: June 30, 2021

3. The validation runs (b) (4) (b) (4) (b) (4) in the "Manufacturing Equipment Validation Summary - Lyophilized Powder" document in section P.3.5). In response to the Agency's IR dated May 6, 2020, (b) (4) (b) (4) (b) (4). Provide data summaries from recent validation runs (b) (4) (b) (4)

   Target completion date: June 30, 2021

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Risk and Lifecyle Knowledge Management are also informed by the BLA 125338 for CCH.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Collagenase activity of AUX-I	Efficacy	Intrinsic activity to the enzyme	(b) (4)	CCH is an enzyme produced by *C. histolyticum* bacteria and therefore is not glycosylated.
Collagenase activity of AUX-II				
Synergistic collagenase activity of AUX-I and AUX-II				
Identity	Efficacy and Safety	Intrinsic to the enzyme		N/A
(b) (4) (fully characterized in BLA 125338)	Efficacy	Manufacturing process		Forced degradation studies assessing oxidation and deamidation revealed the presence of low molecular weight species impacting potency.
Thermal Stability	Efficacy	Manufacturing process, exposure to high temperature		N/A
Zinc binding (fully characterized in BLA 125338 assessment)	Efficacy	Intrinsic to the enzyme	Zinc is not required exogenously.	N/A
Calcium (fully characterized in BLA 125338 assessment)	Efficacy	Intrinsic to the enzyme	Controlled in the formulation buffer of the DPSD.	N/A
Purity	Efficacy, Safety	Manufacturing process	(b) (4)	N/A

B. Drug Substance [CCH] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: DS CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Endotoxin (contaminant)	Safety and Purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process.	(b) (4)	N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced by raw materials and throughout the manufacturing process.		N/A
Host Cell Protein (Process Related Impurity)	Safety (Immunogenicity)	Production cell line		N/A
Host cell DNA (Process related impurity)	Safety	Production cell line		N/A
(b) (4) (Process Related Impurity)	Efficacy and Safety	Manufacturing process		N/A
(b) (4) (Process Related Impurity)	Efficacy and Safety	Manufacturing process		N/A
Appearance	Stability	Formulation components and stability		N/A
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material and the DS container closure system (CCS)		Risk for leachables from CCS is low because the DS is stored frozen, and the same container is used with referenced BLA 125338.
Fermentation medium and buffer components	Safety	Cell bank cryopreservative medium, preculture medium, fermentation broth, process buffers		Levels are below toxicological concern based on the risk assessment.

Elemental impurities	Safety	Cell culture medium, product-contact surfaces, raw materials, excipients, and water	(b) (4)	The assessment for this process is consistent with data provided in the referenced BLA 125338.

- Description:
  CCH is comprised of two collagenase enzymes in an approximate 1:1 mass ratio: Collagenase I (AUX-I; Clostridial type I collagenase) and Collagenase II (AUX-II; Clostridial type II collagenase). These collagenases are isolated and purified from the fermentation of the bacteria *Clostridium histolyticum.* Collagenase I and Collagenase II have molecular weights of ~ 114 kDa and ~ 113 kDa respectively. CCH is licensed for the treatment of Peyronie's Disease and Dupuytren's Contracture in BLA 125338.

- Mechanism of Action (MoA):
  The MoA for CCH is the digestion of collagen. Collagenases are secreted as zymogens (inactive precursors), which are then activated extracellularly. As a mixture, AUX-I and AUX-II have approximately two-fold greater activity than individual enzymes on collagen. The cleavage of collagen can disrupt the thickening of the collagen septa that accompanies the development of EFP.

- Potency Assay:
  The assays developed to assess the potency of CCH in BLA 125338 are utilized with this BLA. Validation of the assays using the formulation for CCH proposed for this BLA confirmed their acceptability. To determine individual collagenase activity, two enzymatic digestion assays with fluorescence readouts are used. AUX-I collagenase activity is measured by the digestion of soluble rat-tail collagen (SRC) through the analysis of liberated peptides and fragments with fluorogenic fluorescamine. AUX-II collagenase activity is assessed by the digestion of a targeted substrate (Carbobenzyoxy-glycyl-L-prolyl-glycyl-glycl-prolyl-L-alanine) into two derivatives. The amount of liberated glycyl-L-prolyl-L-alanine fragment is measured with fluorescamine. In both cases, the amount of fluorescence in proportional to the collagenase activity and is reported relative to reference standard.

- Reference Materials:
  The reference material used for this BLA are identical to those used for CCH approved under BLA 125338. Reference materials are provided for the AUX-I intermediate, AUX-II intermediate and the DS based reference standard. The reference standards have been in place for the performance of the clinical trials under this IND and are representative of the clinical and manufacturing experience as well as BLA 125338 commercial experience. A protocol is provided for the qualification of future reference materials under BLA 125338. The protocols contain adequate testing and acceptance criteria (AC). The procedures to monitor the stability of the reference standards are appropriate.

- Critical Starting Materials or Intermediates:

The master cell bank (MCB) is derived from a *C. histolyticum* culture (ATCC 21000) originally deposited in the American Type Culture Collection (ATCC). Characterization and qualification protocols for the MCB in 2004 is provided in the referenced BLA 125338. The current working cell bank (WCB) was also established in 2004 under the referenced BLA 125338. Both the MCB and WCB were adequately tested to ensure product safety from adventitious agents. The procedures for release, stability testing and generation of new cell banks are provided in the referenced BLA 125338 and are adequate for the maintenance of product quality.
The (b) (4) DS manufacturing process are controlled by in-process control testing for appearance, pH, identity, concentration potency, endotoxin, and bioburden as described in BLA 125338.

- Manufacturing Process Summary:
The manufacture of CCH Mannitol DS is identical to the process described in BLA 125338

(b) (4)

The DS manufacturing process is under adequate microbial control and each critical step is monitored for microbial quality. (b) (4)

(b) (4)

- Container Closure:
CCH Mannitol DS is stored in (b) (4) the same CCS as used in the referenced BLA 125338. The CCS is suitable for CCH Mannitol on the basis of stability data and the analysis of container closure integrity.

- Dating Period and Storage Conditions:

The dating period for the DS is (b) (4) The sponsor is monitoring stability of the CCH DS through 36 months as part of the process validation stability protocol and commits to testing through 36 months for their annual stability protocol.

C. Drug Product [CCH Mannitol] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for DP CQAs that derive from the DP manufacturing process and general DP attributes.

Table 3: DP CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity	(b) (4)	N/A
Endotoxin (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process		
Container closure integrity (contaminant)	Safety (maintenance of sterility during shelf-life)	Container closure breaches during storage		N/A
Quantity	Efficacy	Manufacturing process		N/A
Appearance of Lyophilized Powder (General)	Stability	Formulation components and stability		N/A
Appearance of Solution post reconstitution	Stability	Formulation components and stability		N/A
Reconstitution Time	Stability	Formulation components and stability		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A
Osmolality (General)	Stability	Composition of the DP		N/A
Volume in container (General)	Efficacy/Dosing	Fill process		N/A

Particulate matter for subvisible particles (b) (4) (b) (4)	Safety and Immunogenicity	Manufacturing process and CCS, (b) (4	(b) (4)	N/A
Moisture Content	Stability	Manufacturing process and CCS		N/A
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS	Leachables were assessed in the referenced BLA 125338 as well as by a risk assessment for this BLA. A real-time study is on-going and will be completed in Q2 of 2021.	The risk is deemed to be low, and the real-time study will be submitted as part of subsequent annual report.

- Potency and Strength:
  CCH Mannitol is provided as 0.92 mg in a 5 mL vial for reconstitution with 4 mL of sterile diluent or 1.84 mg in a 10 mL vial for reconstitution with 8 mL of sterile diluent. The strength of CCH Mannitol is 0.23 mg/mL after reconstitution in the provided sterile diluent. Potency is defined as the ratio of activity relative to the current CCH reference. The potency assays are the same as described in the DS section of this memo.

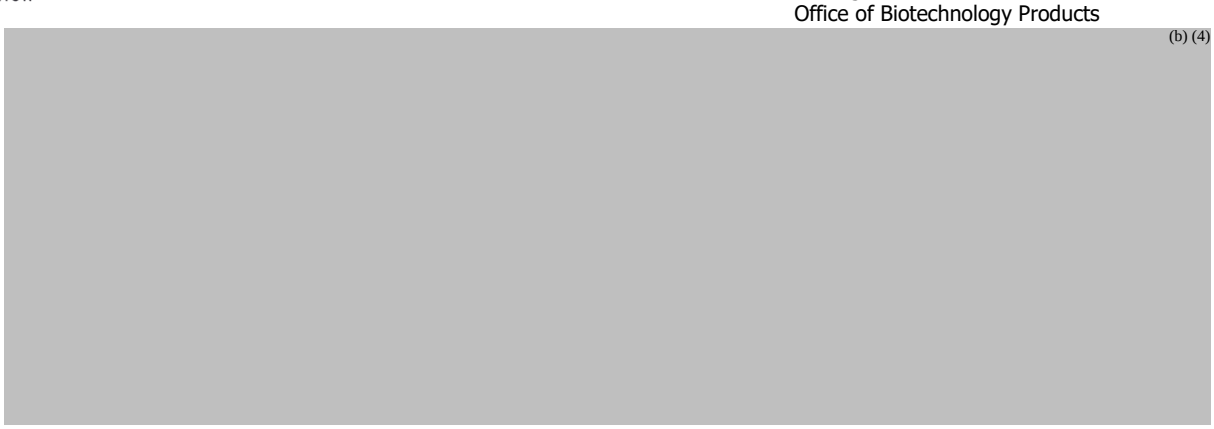
- Summary of Product Design:
  CCH Mannitol is supplied as 0.92 mg or 1.84 mg of lyophilized powder for reconstitution in sterile diluent to a final concentration of 0.23 mg/mL. CCH Mannitol is recommended for up to 12 injections of 0.3 mL (0.069 mg per injection) per treatment area. Reconstitution in 4 mL (0.92 mg) or 8 mL (1.84 mg) includes overfill to ensure sufficient volume for dose delivery.

- List of Excipients:
  The CCH Mannitol DP excipients are (b) (4) tromethamine (Tris), (b) (4) sucrose and (b) (4) mannitol. The DPSD excipients are 0.03% calcium chloride dihydrate and 0.6% sodium chloride. After reconstitution, the pH is 8 (b) (4)

- Reference Materials:
  The same reference standards are used for DS and DP.

- Manufacturing Process Summary:
  The manufacturing process for CCH Mannitol DP includes the following steps:

(b) (4)



- Container Closure:
  The primary container closure systems for CCH Mannitol consist of the following presentations:
  - 0.92 mg Lyophilized Powder: A 5 mL Type I (b) (4) glass vial closed with a 13 mm (b) (4) stopper. The stopper is sealed (b) (4).
  - 1.84 mg Lyophilized Powder: A 10 mL Type I (b) (4) glass vial closed with a 20 mm (b) (4) stopper. The stopper is sealed (b) (4).
  - 4 mL Sterile Diluent: A 5 mL Type I (b) (4) vial closed with a 20 mm (b) (4) (b) (4) stopper. The stopper is sealed (b) (4) (b) (4).
  - 8 mL Sterile Diluent: A 10 mL Type I (b) (4) vial closed with a 20 mm (b) (4) (b) (4) stopper. The stopper is sealed (b) (4) (b) (4).

  Appropriate compatibility studies were performed for identical materials used with the primary CCS in BLA 125338.

- Dating Period and Storage Conditions:
  The dating period for the DP and the DPSD is 24 months when stored at 2-8°C. The data included in the BLA support storage for up to 24 hours when stored at temperatures below 25°C once removed from refrigerator, as described in the labeling or up to (b) (4) hours in the refrigerator at 2-8˚C. The in-use stability testing was performed with the solution reconstituted in the vial, not in the injection syringe. The reconstituted solution is not meant to be stored in the syringe.

- Commercial Presentation:
  The intended commercial presentation will be vials containing 0.92 mg or 1.84 mg of CCH Mannitol lyophilized powder along with vials containing 4 mL or 8 mL of sterile diluent for reconstitution.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:
   - Store in a refrigerator at 2°C to 8°C
   - Do not freeze

- The reconstituted solution can be kept in the vial at room temperature (20-25°C) for up to 8 hours or refrigerated for up to 72 hours in the vial prior to administration
- Do not store in the syringe, administer immediately upon withdrawing from the vial

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Storage of MCB and WCB; Analytical testing of MCB and WCB; CCH Mannitol DS Manufacturer; Release and stability testing of DS; Storage of raw materials, samples, solutions for fermentation and purification, in-process materials, bulk DS and stability samples Dispensing of raw materials	Auxilium Pharmaceuticals, LLC 102 Witmer Road Horsham, PA, 19044 USA Warehouse located at: 102 Rock Road Horsham, PA, 19044 USA	DUNS: 801535787 FEI: 3006537159	Acceptable based on file review	PLI waived	Approve
Bacteriophage testing of cell banks and in-process testing of DS	(b) (4)		Acceptable based on profile	N/A	Approve
Release and stability testing of DS (back-up)			Acceptable based on profile	N/A	Approve
Residual DNA testing of DS			Acceptable based on profile	N/A	Approve
Storage of bulk DS			Acceptable based on profile	N/A	Approve

16S ribosomal DNA sequence analysis for qualification of MCB and WCB	(b) (4)		Acceptable based on profile	N/A	Approve
DNA isolation, nucleotide sequencing and assemblage of the DNA consensus sequences as part of amino acid sequencing of putative toxins for qualification of WCB			No Evaluation Necessary	N/A	N/A
Backup storage of MCB and WCB			No Evaluation Necessary	N/A	N/A
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacturer Release Testing Packager (bulk vials, secondary packaging)	(b) (4)		Acceptable based on file review	PLI waived	Approve
Release and stability testing Storage of unlabeled vials	Auxilium Pharmaceuticals, LLC 102 Witmer Road Horsham, PA, 19044 USA Warehouse located at: 102 Rock Road Horsham, PA, 19044 USA	DUNS: 801535787 FEI: 3006537159	Acceptable based on file review	N/A	Approve
Alternate site for release and stability testing of DP	(b) (4)		Acceptable based on profile	N/A	Approve
Alternate release and stability testing for particulate matter and sterility			Acceptable based on profile	N/A	Approve
Container/closure integrity by helium leak test for stability			Acceptable based on profile	N/A	Approve

	(b) (4)			
Secondary packaging of DP		No Evaluation Necessary	N/A	N/A

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided or referenced to BLA 761146 for Auxilium Pharmaceuticals (FEI 3006537159) and (b) (4), proposed for CCH DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.S.7.2	Annual stability protocol for DS with shelf-life extension	At -70˚C, at least one batch per year at 0, 3, 6, 9, 12, 18, 24, 30 and 36 months, as well as at -20˚C at least one batch per year at 0, 6, 12, 24 and 36 months according to the tests and acceptance criteria (AC) listed in 3.2.S.7.2.	Stability updates will be provided annually as part of the **Annual Report**

ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.P.2	Leachables study on stability samples of the CCH Mannitol DP packaged in the container closure system	A study of potential volatile leachables after 36 months of long term storage at 2-8˚C for CCH Mannitol DP lots 307984, 307985 and 313877 with a targeted completion of March 2021.	Study results will be submitted as part of the **Annual Report**

3.2.P.8.2	Annual stability protocol for DP with shelf-life extension	At 5°C, at least one lot per year at 0, 3, 6, 9, 12, 18, 24, 30 and 36 months, as well as at 25°C at least one batch per year at 0, 6, 12, 24 and 36 months according to the tests and AC listed in 3.2.P.8.2 for lyophilized powder.	Stability updates will be provided annually as part of the **Annual Report**
3.2.P.8.2	Annual stability protocol for DPSD with shelf-life extension	At 5°C, at least one lot per year at 0, 3, 6, 9, 12, 18, 24, 30, 36 and 48 months, as well as at 30°C at least one batch per year at 0, 6, 12, 24, 36 and 48 months according to the tests and AC listed in 3.2.P.8.2 for DPSD.	Stability updates will be provided annually as part of the **Annual Report**

ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product			X	
2.	Naturally Derived Product			X	
3.	Botanical			X	
4.	Human Cell Substrate/source material			X	
5.	Non-Human Primate Cell Substrate/Source Material			X	
6.	Non-Primate Mammalian Cell Substrate/source material			X	
7.	Non-Mammalian Cell Substrate/Source Material		X		
8.	Transgenic Animal source			X	
9.	Transgenic Plant source			X	
10.	New Molecular Entity			X	
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]		X		
	The sponsor references their other licensed application for collagenase clostridium histolyticum (BLA 125338) for a significant portion of the file covering drug substance and drug product manufacture.				
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-NDA Agreements			X	
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name		X		
20.	Other [fill in]				X
	Quality Considerations				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			X	
27.	Real Time release testing (RTRT)			X	
28.	Parametric release in lieu of Sterility testing			X	
29.	Alternative Microbiological test methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial analytical procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other {fill-in}				X

Brian Roelofs

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