

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761085Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

BLA Number: 761085

Review Number: 2

Review Date: January 18, 2019

Drug Name/Dosage Form	Jeuveau (prabotulinumtoxinA-xvfs)
Strength/Potency	100 Units/vial
Route of Administration	Intramuscular injection
Rx/OTC dispensed	Rx
Indication	Treatment of moderate to severe glabellar lines
Applicant/Sponsor	Evolus, Inc.

Product Overview

Jeuveau is a purified type A neurotoxin complex produced by anaerobic fermentation of *Clostridium botulinum* isolated from soil in South Korea. The 900 kDa complex is composed of a type A botulinum neurotoxin, (b) (4)

(b) (4). Jeuveau is supplied as a sterile, preservative free, (b) (4) vacuum dried powder for reconstitution in a single use vial containing 100 U of botulinum toxin type A neurotoxin complex, 0.5 mg of human albumin (HSA) and 0.9 mg of sodium chloride.

Jeuveau blocks neuromuscular transmission by binding to receptor sites on motor nerve terminals, entering the nerve terminals and inhibiting acetylcholine release. It is intended for intramuscular use. Jeuveau's biological activity is determined relative to a reference standard using an animal-based potency assay. One potency Unit of Jeuveau corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice. Due to specifics of the potency assay, Jeuveau potency Units cannot be converted into Units of other botulinum toxin assessed with different assays.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Ennan Guan/Susan Kirshner	DBRRIII/OBP
Drug Product	Davinna Ligons/Frances Namuswe	DBRRIII/OBP
Microbiology Drug Substance	Bo Chi/Patricia Hughes	Branch IV/DMA/OPF
Microbiology Drug Product	Aimee Cunningham/ Reyes Candau-Chacon	Branch IV/DMA/OPF
Facility	Viviana Matta/Zhihao (Peter) Qiu	DIA/OPF
Labeling	Vicky Borders-Hemphill	OBP
Immunogenicity	Davinna Ligons/Frances Namuswe/Susan Kirshner	DBRRIII/OBP
Application Team Lead	Frances Namuswe	DBRRIII/OBP
Application Tertiary reviewer	Susan Kirshner	DBRRIII/OBP
OPQ RBPM	Kelly Ballard	OPRO

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
OND RPM	Matthew White	ODEIII/DDDP
Cross-disciplinary Team Lead	David Kettl	ODEIII/DDDP
Medical Officer	Gary Chiang	ODEIII/DDDP
Pharm/Tox	Jianyong Wang	ODEIII/DDDP



Clinical Pharmacology	Jie Wang	OCP/DCPIII
Statistics	Marilena Flouri/Mohamed Alesh	OB/DBIII

1. Names:

Proprietary Name:	Jeuveau
Trade Name:	DWP-450 (botulinum toxin, Type A)
Non-Proprietary/USAN:	prabotulinumtoxinA-xvfs
CAS name and number:	93384-43-1
Common name:	Botulinum toxin
INN Name:	Botulinum toxin type A
Compendial Name:	<i>Botulinum</i> Toxin Type A for Injection (European pharmacopoeia)
OBP systematic name:	PROT P10845 (BXA1_CLOBO) BOTULINUM NEUROTOXIN TYPE A [DWP-450]

Submissions Reviewed

Sequence Number	Document Date	Review Completed	OPQ Office
SN 0001 (original submission)	May 15, 2017	Yes	All
SN 0003	July 05, 2017	Yes	DIA
SN 0005	July 07, 2017	Yes	DMA
SN 0013	September 28, 2017	Yes	OBP
SN 0014	September 28, 2017	Yes	OBP
SN 0015	October 2, 2017	Yes	OBP
SN 0016	October 17, 2017	Yes	OBP
SN 0017	November 3, 2017	Yes	DMA
SN 0018	December 1, 2017	Yes	OBP
SN 0019	December 15, 2017	Yes	DMA
SN 0020	December 20, 2017	Yes	OBP
SN 0021	December 22, 2017	Yes	DMA
SN 0023	January 08, 2018	Yes	OBP
SN 0024	January 16, 2018	Yes	DMA
SN 0025	January 31, 2018	Yes	DMA
SN 0026	February 23, 2018	Yes	DMA
SN 0027	March 05, 2018	Yes	OBP
SN 0029	March 09, 2018	Yes	OBP
SN 0033 (Resubmission)	August 02, 2018	Yes	All
SN 0034	September 05, 2018	Yes	DMA
SN 0035	September 28, 2018	Yes	DMA
SN 0036	October 12, 2018	Yes	DMA
SN 0038	October 25, 2018	Yes	OBP
SN 0039	October 29, 2018	Yes	OBP
SN 0041	November 30, 2018	Yes	All
SN 0042	December 28, 2018	Yes	DMA
SN 0044	January 15, 2019	Yes	OBP
SN 0045	January 17, 2019	Yes	All

Quality Review Data Sheet

1. Legal Basis for Submission: **351(a)**

2. Related/Supporting Documents

A. DMFs

DMF #	DMF Type	DMF Holder	Item referenced	Letter of Cross Reference	Code ¹	Status ²
(b) (4)	III	(b) (4)	(b) (4)	Yes	3	adequate
	III			Yes	3	adequate
	V			Yes	3	adequate
	III			Yes	1 3	adequate with additional information from DMF holder
				Yes	2	adequate

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
IND	121493	DWP-450 (Botulinum toxin type A)

3. Consults

OPQ did not issue formal consults for this BLA; however, during the first review cycle, OBP discussed the excess overfill in the drug product vial with DMEPA. Based on the recommended dose of 20 units (0.5 mL of the reconstituted solution), the 100 U (2.5 mL) single-dose vial contains an overfill of (b) (4). USP <1151> recommended overfill for a vial volume of 0.50 mL is 0.10 mL. One concern with excess overfill in single use vials is the possibility of multiple use, which could have safety implications. OBP and DMEPA determined that accepting this overfill does not set a precedence for this type of product because other botulinum toxin products on the market have a similar overfill, due primarily to the small amount of drug substance needed to manufacture drug product, which poses drug product manufacturing challenges. DMEPA is not aware of safety issues related to overfills in botulinum toxin products; therefore, the excess overfill will be accepted for Jouveau at this time to be consistent with similar products on the market.

For other botulinum toxin products marketed for the same indication as Jeuveau, a post marketing commitment (PMC) was issued to the Sponsor to develop a lower dose presentation if they did not already have one. We have not issued a PMC to Evolus to develop a lower dose presentation at this time because Evolus explained that they had technical difficulties developing a lower dose presentation. (b) (4)

(b) (4)

(b) (4). We have issued a PMC to develop an in vitro based potency assay. (b) (4)

(b) (4)

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality including Office of Biotechnology Products, Division of Microbiology Assessment, and the Division of Inspectional Assessment, CDER, recommends approval of STN 761085 for Jevueau manufactured by Daewoong Pharmaceutical, Co., for Evolus, Inc. The data and information submitted in this application are adequate to support a conclusion that the manufacture of Jevueau is well controlled and leads to a product that is pure and potent for the duration of the product shelf life. Office of Pharmaceutical Quality recommends 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: Daewoong Pharmaceutical, Co., Ltd. 35-14, Jeyakgongdan 4-Gil, Hyangnam-Eup, Hwaseong-si, Gyeonggi-Do, 18623, Republic of Korea
 - Drug Product: Daewoong Pharmaceutical, Co., Ltd. 35-14, Jeyakgongdan 4-Gil, Hyangnam-Eup, Hwaseong-si, Gyeonggi-Do, 18623, Republic of Korea
- Fill size and dosage form: 100 Units of vacuum-dried powder in a single-use vial for reconstitution
- Dating period:
 - Drug Substance: (b) (4)
 - Drug Product: 36 months at 2-8°C
 - For packaged Products: Not Packaged
- Exempt from lot release
 - No. Jevueau will be on lot release per 21 CFR 610.2

C. Benefit/Risk Considerations

Jevueau is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines in adult patients. It blocks neuromuscular transmission by binding to receptor sites on motor nerve terminals and inhibiting acetylcholine release. The therapeutic benefits include improved physical appearance. Potential side effects include but are not limited to problems swallowing and breathing due to spread of the toxin away from the injection site and weakening of associated muscles.

The data submitted in this application are sufficient to demonstrate that the manufacture of Jevueau is well-controlled and will lead to a product that is safe, pure and potent. Two post-marketing commitments (PMCs) were agreed upon with the sponsor to improve Jevueau's overall product control

strategy. PMC-1 is related to development and implementation of a non-animal-based potency assay. Potency of the drug substance and drug product is currently measured using an animal-based potency assay. Developing a non-animal-based assay will help reduce or limit animal use while improving assay reproducibility. PMC-2 is related to improvements in the drug substance reference material management program. The reference material qualification program is adequate to ensure that the reference materials are fit for intended use. However, the drug substance reference material management program is sub-optimal because the reference material batch size is small resulting in frequent replacement of the reference material, which increases the chances of product drift. PMC-2 is to scale-up the drug substance reference material batch size to generate a sufficient quantity of each reference material lot to prevent frequent replacement of the reference material. This will help improve the reference standard management program and overall control strategy for Jeuveau.

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

The following draft post marketing commitments have been proposed and accepted by the Sponsor:

PMC-1: To investigate the development and implementation of a non- animal- based potency assay for drug substance and drug product release and stability testing. A summary report together with any proposed modifications to the release and stability specifications should be submitted in a Prior Approval Supplement to the Agency by January 2021.

PMC-2: To scale-up the reference material batch size to generate a sufficient quantity of each reference material lot to prevent frequent replacement of the reference material. The study report together with any modifications to the reference material protocols and program will be submitted in a Prior Approval Supplement to the Agency by July 2021.

II. Summary of Quality Assessments

Table 1 is a summary of critical quality attributes (CQA) that are intrinsic to the drug substance, their origin, and the associated risk and control strategies. Table 2 is a summary of CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy
Potency	Efficacy and safety	Intrinsic to the molecule.	(b) (4)
		(b) (4)	

		(b) (4)	(b) (4)
			A PMC was issued to develop and implement a non-animal-based potency assay to reduce animal use and improve assay reproducibility (b) (4)
Identity	Safety and Efficacy	Intrinsic to the molecule	
High molecular weight (HMW) species/Aggregates (product-related impurities)	Efficacy, potency, and immunogenicity The risk for immunogenicity is low because of the high purity of the product with respect to HMWS.	(b) (4)	
Low molecular weight species (product-related impurities)	Efficacy and potency		
Protein content	Specific activity calculation		

B. Drug Substance [prabotulinumtoxinA-xvfs] Quality Summary

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy
Host Cell DNA (Process-related impurity)	Safety		(b) (4)
Spores	Safety		
Bioburden	Safety, purity and		

	efficacy (degradation or modification of the product by contaminating microorganisms)	(b) (4)
Endotoxin	Safety and purity	
Leachables	Safety, product degradation	
Appearance	Safety	
Vegetative <i>Clostridium</i> bacteria	Safety	

a. Description

Jeuveau is a purified 900 kDa type A neurotoxin complex produced by anaerobic fermentation of the *Clostridium botulinum* bacterium isolated from soil in South Korea. The complex is composed of type A botulinum neurotoxin, (b) (4) (b) (4). The neurotoxin is a 1296 amino acid molecule consisting of a heavy chain and a light chain linked by a disulfide bond.

b. Mechanism of Action (MoA)

Jeuveau blocks neuromuscular transmission by binding to receptor sites on motor or sympathetic nerve terminals, entering the nerve terminal and inhibiting acetylcholine release. The activity of the toxin requires both the heavy chain (Hc) and light chain (Lc). The Hc mediates neuron-specific binding, up-take by receptor-mediated endocytosis and transport of the Lc across the endosomal membrane into the cytosol. In the cytosol the Lc, a zinc binding metallopeptidase, hydrolyzes a member of the SNARE protein complex, which is required for vesicle exocytosis.

The substrate for type A toxin is a 25-kD synaptosomal associated protein (SNAP-25). SNAP-25 is cleaved at the C-terminus (Q197-R) by BoNT/A, generating truncated SNAP-25 that cannot participate in formation of the SNARE core complex. When injected intramuscularly at

therapeutic doses, Jeuveau induces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. It is indicated for temporary improvement in the appearance of glabellar lines associated with corrugator or procerus muscle activity.

c. Potency Assay

The mouse lethal dose assay is used to assess the potency of the product. The assay is conducted by administration of pre-established dilutions of Jeuveau into groups of mice. The number of deaths that occur at each dilution is measured over a fixed period of time. The concentration that leads to death in half of the test animals is the lethal dose 50 (LD₅₀). The potency of botulinum toxin therapeutic preparations is expressed in LD₅₀ units, with one unit of activity defined as the amount of drug required to kill 50% of the animals. The assay is a good indicator of both light and heavy chain function since both are required for activity *in vivo*.

One drawback of this assay is that it is much more variable than cell-based assays and requires several mice for each potency measurement. Moreover, there is huge inter-product variability, precluding standardization of LD50 units among botulinum toxin products. A post marketing commitment was issued to develop and implement a non-animal-based potency assay.

d. Reference Materials



The criteria used to qualify the DS PRM and WRM are adequate to ensure that the drug substance reference material is fit for intended use. Of note, because the WRM is not used to determine potency of the DS, the stringent criteria typically needed to ensure accurate and precise potency of the reference material are not critical in this case. However, the DS reference material management program is sub-optimal because the reference material batch size is small, resulting in frequent replacement of the reference material, which could increase chances of product drift. A PMC was issued to scale-up the reference material batch size to generate a sufficient quantity of each reference material lot to prevent frequent replacement of the reference material.

e. Critical starting materials or intermediates



(b) (4)

f. Manufacturing process summary

(b) (4)

g.

h. Dating period and storage conditions

The dating period for the drug substance is (b) (4).

C. Drug Product [Jeuveau] Quality Summary:

Table 3 provides a summary of the CQAs that derive from the drug product manufacturing process and general drug product attributes, their origin and associated risk and control strategy.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy
Appearance	Safety, Efficacy, DP stability	(b) (4)	(b) (4)
Sterility	Safety risk to patients (infection), purity, and efficacy (degradation or potential modification of the product by microorganisms or their products)		
Endotoxin	Safety, purity and immunogenicity		

Container Closure Integrity (Sterility Assurance during storage)	Safety (Failure in container closure integrity may lead to contamination through a loss of sterility)
Water Content	Safety and Efficacy
Particulate Matter (Visible and Sub-Visible Particulates)	Safety/ Immunogenicity
pH	Safety and Efficacy
Total Protein	Efficacy (toxin) Stability (b) (4) (b) (4)
Solubility/ Reconstitution time	Dosing/efficacy
Leachables	Safety

<p>Overage</p>	<p>Safety</p> <p>Safety concerns are mitigated by the fact that DP containing the same overage was used in the pivotal clinical studies.</p>	<p>(b) (4)</p>
<p>Overfill and extractable volume</p>	<p>Safety and Efficacy /dosing. Excess overfill in single use vials may lead to the possibility of multiple use</p>	

a. Potency and Strength

Jeuveau is supplied as a 100 U of *C. botulinum* toxin A per vial for reconstitution. Potency is expressed in LD50 units, with one unit of activity defined as the amount of drug required to kill 50% of the animals. The potency assay is the same as described in the DS section of the memo. For DP, potency is reported relative to the reference standard.

b. Summary of Product Design

Jeuveau is supplied as a sterile, (b) (4) vacuum dried powder in a single use 10 mL vial. Each vial contains 100 Unit of *C. botulinum* toxin type A, 0.5 mg human albumin and 0.9 mg NaCl. There are no anti-microbial preservatives in the formulation. Prior to use, DP is reconstituted with 2.5mL of 0.9% sterile preservative free saline to a final concentration of 4 U/0.1 mL per injection. Reconstituted DP should be stored at 2-8°C and must be used within 24 hours of reconstitution. Data to support chemical and microbial stability of the reconstituted solution up to 24 h at 2-8°C were provided.

c. List of Excipients

The DP is formulated with 0.5 mg HSA (b) (4) and 0.9 mg sodium chloride (b) (4). The HSA is provided by (b) (4). The HSA is provided by an FDA approved provider, (b) (4).

d. Reference Materials

(b) (4)

e. Manufacturing process summary

(b) (4)

Therefore, the DWP-450 DP commercial manufacturing process is adequately controlled to ensure that DP manufacture is well-controlled and will lead to a product that is safe, pure and potent.

f. Container closure

DP is stored in a (b) (4) vial closed with a (b) (4) rubber stopper with a (b) (4) cap and an (b) (4) (b) (4) closure.

g. Dating period and storage conditions

The dating period for DP stored as a dried powder at 2-8°C is 36 months.

h. List of co-package components, if applicable: None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

Store unopened vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Prior to use, DP is reconstituted with 2.5mL of 0.9% preservative free saline. Reconstituted DP should be stored at 2-8°C (36°F to 46°F) in the original carton to protect from light for up to 24 hours until the time of use and discard any remaining solution after administration. Do not freeze reconstituted product.

F. Establishment Information

OVERALL RECOMMENDATION: Approve, pending final compliance assessment				
Drug Substance				
Function	Site Information	DUNS/FEI Number	Inspectional Observations	Final Recommendation
<ul style="list-style-type: none"> DS Manufacture Preparation of WCB Storage of MCB and WCB DS Primary Packaging QC Testing – Chemical /Physical, Biological, Microbiological, non-sterility DS Storage and distribution 	Daewoong Pharmaceutical, Co., Ltd. 35-14, Jeyakongdan 4-Gil, Hyangnam-Eup, Hwaseong-si, Gyeonggi-Do, 18623 Republic of Korea	3012333115	Pre-license inspection conducted on November 8-17, 2017. A 10 item FDA Form 483 was issued with an initial recommendation of withhold.	Acceptable
Drug Product				
Function	Site Information	DUNS/FEI Number	Inspectional Observations	Final Recommendation
<ul style="list-style-type: none"> DP Manufacture and release DP primary and secondary packaging Analytical testing for release Quality control testing (biological, Chemical /physical, microbiological) Stability testing Sterility testing Storage and distribution 	Daewoong Pharmaceutical Co., Ltd., 35-14, Jeyakongdan 4-Gil, Hyangnam-Eup, Hwaseong-si, Gyeonggi-Do, 18623 Republic of Korea	3012333115	Pre-license inspection conducted on November 8-17, 2017. A 10 item FDA Form 483 was issued with an initial recommendation of withhold	Acceptable

G. Facilities

DWP-450 DS and DP are manufactured, labeled and packaged at Daewoong Pharmaceutical Co., Ltd. in the Republic of Korea (FEI 3012333115). A Pre-license Inspection of the Daewoong facility was performed from 11/08/17 to 11/17/17. This inspection was system-based and covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 10-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection for the following reasons: inadequate investigations, inadequate test procedures, inadequate environmental monitoring, inadequate cleaning and disinfecting, inadequate procedures for microbiological contamination control, production operations not conducted in manner to prevent contamination, deviations from procedures not justified and inadequate training. The initial recommendation was withhold/OAI. The final facility and inspection EIR review recommendation is for approval because the proposed corrective actions appear adequate.

H. Lifecycle Knowledge Management

a. Drug Substance:

i. Protocols approved:

1. Annual stability protocol
2. Protocol for qualification of future working cell banks
3. Protocol for qualification and requalification of future reference standards
4. Protocol for assessment of leachables from the drug substance container closure system (*The protocol for assessment of leachables in the drug substance container closure system was initiated by the Sponsor and not requested by the Agency. As indicated in the CQA assessment above (Table 2), leachables from the drug substance container closure system present low risk for safety of this product.*)

ii. Outstanding review issues/residual risk:

1. See Post Marketing Commitments in Section 1D.

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

1. Annual stability protocol
2. Protocol for qualification and requalification of future reference standards
(b) (4)
(b) (4) *ICH Q6b guidance recommends a two-tier system for reference materials that includes a primary and working reference material to prevent drift in the reference material product quality attributes over time.* (b) (4)

(b) (4)
The DP reference material is only used to assess potency and a PMC was issued to change from an animal based to an in vitro potency assay. (b) (4)

3. Protocol for assessment of leachables from the drug product container closure system
- ii. Outstanding review issues/residual risk: None
 - iii. Future inspection points to consider: None



Frances
Namuswe

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Susan
Kirshner

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Addendum – Product Quality

Resubmission: BLA STN 761085

Primary Reviewer: Ennan Guan, M.D./Ph.D.

Secondary Reviewer: Frances Namuswe, Ph.D.

Tertiary Reviewer: Susan Kirshner, Ph.D., Chief

Product: **Jeuveau (probotulinumtoxinA)**

Indication Glabellar lines

Route of Admin: Intramuscular injection

Dose Regimen: 4 units intramuscularly injected into each of five sites in the mid-line of the procerus muscle for a total dose of 20 units

Labeled Strength: 100 Units/vial

Sponsor: Evolus, Inc

Clinical Division: CDER/OND/Division of Dental and Dermatology

Date Received: August 2, 2018

PDUFA Date: February 2, 2019

Recommendation

We recommend approval of the WBC qualification protocol. We also recommend approval of DWP-450 DS shelf life of (b) (4).

Justification

The information provided in the updated WBC qualification protocol adequately addressed the deficiencies identified during the original review and support the conclusion that consistent preparation of the future WCB will be well controlled by using this updated WCB qualification protocol.

The information provided in the updated DWP-450 DS stability data support the conclusion that the DWP-450 DS is stable at the recommended (b) (4) storage conditions at (b) (4).

Background

During review of the drug substance part of BLA761085 resubmission, an information request was sent to the Sponsor regarding their working cell bank (WCB) qualification protocol. In their response to the information request, the Sponsor stated they will submit an updated WCB qualification protocol at the end of November 2018. The adequacy of that protocol is addressed in this addendum to the review memo.

Updated WCB qualification protocol

The sponsor updated section 3.2.S.2.3 Control of materials to include the updated WCB qualification protocol (refer to the table below) under NPR02-003: Management of WCB. The WCB qualification protocol includes three parts 1) the test item and specification, 2) characterization of at least one lot of DS derived from the new WCB and 3) stability test of at least one lot of DS



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Response to this request is adequate. The reviewer recommends approval the WCB qualification protocol.

DS Shelf life update

This memo documents the submission and data used to support the shelf-life of the drug substance (DS) of (b) (4) months when stored at (b) (4). The data provided in the original BLA submission supported a shelf life of (b) (4) months. Additional data to support the proposed shelf life of (b) (4) months were submitted in a December 15, 2017 amendment to the BLA. Based on the updated DS stability data, the results of (b) (4) months of (b) (4) (b) (4) stability evaluation of three DWP-450 DS lots (794610, 974894, and 975140) met the acceptance criteria. These lots are stable with no adverse trends and the data support a shelf life of (b) (4) months for DWP-450 DS. The updated DS stability information is located in section 3.2. S. 3.1.

Drug product review addendum (Provided by Davinna Ligons)

In response to the complete response for product quality of drug product (DP), the Sponsor scaled up the batch formula from (b) (4) to allow for additional bioburden and endotoxin testing. This is acceptable because the scale-up is very small and the (b) (4) overage was not affected by the scale-up. In addition, an additional 6 months of long-

term storage stability data were provided for DP lots manufactured at commercial scale (991451, 991452, 991453); thus, a total of 18 months of stability data are provided for these lots. These data further support the stability of DP stored under long-term storage conditions and the long-term storage stability study for these lots will continue for up to 36 months which is the proposed shelf-life for DP.



Ennan
Guan

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Frances
Namuswe

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Susan
Kirshner

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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 1/8/2019
To: Administrative File, **STN 761085/0**
From: Bo Chi, Ph.D., CDER/OPQ/OPF/DMA/Branch IV
Endorsement: Reyes Candau-Chacon, Ph.D., Acting Quality Assessment Lead,
CDER/OPQ/OPF/DMA/Branch IV
Subject: Review of BLA resubmission in response to Complete Response Letter of May 15, 2018
Applicant: Evolus, Inc
US License: 2070
Facility: Daewoong Pharmaceutical Co., Ltd., Gyeonggi-do, Republic of Korea
FEI: 3012333115
Product: Botulinum toxin, Type A (DWP-450)
Dosage: Powder for solution, injection
Indications: Treatment of moderate to severe glabellar lines
PDUFA date: February 2, 2019

Recommendation: The drug substance part of this BLA is recommended for approval from a quality microbiology perspective.

Review Summary

This is a resubmission to Biologics License Application (BLA) STN 761085/0 DWP-450 (botulinum toxin, type A) for the treatment of moderate to severe glabellar lines. This resubmission addresses the deficiencies listed in the May 15, 2018 Complete Response Letter. This review assesses Evolus' response to eight CMC drug substance (DS) microbiology deficiency listed in the complete response letter.

The amendments reviewed are provided in the table below:

Sequence number	Date	Description
033	8/2/2018	BLA resubmission
042	12/28/2018	Response to IR

(b) (4)

Conclusion

- I. The drug substance part of this BLA is recommended for approval from a quality microbiology perspective.
- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the OBP reviewer.
- III. See Panorama for compliance status of the facilities.

DS Quality microbiology information request sent

IR #1

1. For the culture purity test conducted (b) (4) confirm (b) (4) (b) (4) during the routine test as proposed in the amendment dated 2/23/2018 (Sequence 26). Update the relevant section of the BLA.
2. You have proposed \leq (b) (4) CFU/mL as the in-process bioburden acceptance criterion (b) (4). Update the in-process bioburden acceptance criterion to (b) (4). Update Section 3.2.S.2.4 of the BLA.
3. With regard to your response to deficiency #5 listed in the May 15, 2018 Complete Response

Letter, you indicate that the bioburden qualification data are provided in Reports A-ZZR-DSHCl and A-ZZR-NBTN000B. However, the reports do not contain the information.

Provide the bioburden qualification data and report(s) [REDACTED] (b) (4)

[REDACTED] (b) (4) using

samples from three lots. The qualification studies should be conducted according to USP<61> [REDACTED] (b) (4)

(b) (4) The bioburden test method qualification is intended to demonstrate that the samples do not have inhibitory effect on recovering the USP microorganisms.

4. With regard to your response to deficiency #9 listed in the May 15, 2018 Complete Response Letter, based on the information provided in Section 3.2.S.4.3 and Report A-MVR-2018001, it appears that R&D batches NBT-18F007, NBT-18F008, and NBT-18F0010 were used for the qualification of the bioburden release sample. Clarify the difference between the R&D batches and commercial batches and if the R&D batches were manufactured at the commercial manufacturing site. If the R&D batches are significantly different from the commercial batches or if they were manufactured at a different site, provide bioburden qualification data of the DS sample using samples from three commercial batches. [REDACTED] (b) (4)

[REDACTED] (b) (4)



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Memorandum of Review – Complete Response Product Quality (Drug Product)

Resubmission: BLA STN 761085

Primary reviewers: Davinna L Lignons, Ph.D.
Secondary Reviewer: Frances Namuswe, Ph.D.

Product: Jeuveau (probotulinum toxin A)
Indication: Treatment of moderate to severe glabellar lines

Route of Admin: Intramuscular Injection
Dose Regimen: 4 units intramuscularly injected into each of five sites in the mid-line of the procerus muscle; Total dose: 20 units in 0.5mL

Labeled Strength: 100 Units/vial

Sponsor: Evolus, Inc

Clinical Division: ODEIII / DDDP

Received Date: August 2, 2018
PDUFA Date: February 2, 2019

Recommendation and Justification

We recommend approval of BLA 761085 from OBP's product quality perspective. The complete response (CR) review issues regarding the product quality of the drug product (DP) manufacturing process and control strategy have been adequately addressed.

CR Deficiencies- Drug Product

Question 18: In your December 1, 2017 response to the November 13, 2017 information request to update the DP stability testing protocols to include DP reconstitution time, it appears that additional changes were made to the post-approval stability protocol originally submitted in the BLA to remove the testing points at 3, 6, 9, and 18 months. You did not provide sufficient stability data to support a reduced stability testing program. Therefore, the updated annual post-approval stability protocol in section 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (Table 3.2.P.8.2-2) received on December 1, 2017 is not adequate to ensure that potential changes to commercial DP during storage are detected in a timely manner. Revise your

annual stability protocol to include testing at 3, 6, 9, and 18 months as recommended by ICH Q5C guidelines.

Sponsor's Response:

The annual stability protocol for future commercial lots stored under long-term storage conditions was corrected to include time points 0, 3, 6, 9, 12, 18, 24, and 36 months.

Reviewer comments:

The annual stability protocol is in agreement with ICH Q5C. No additional actions are required.

Question 19: In your March 9, 2018 response to the March 2, 2018 information request to describe Evolus' role in DWP-450 lot release, you stated that some of Evolus' quality responsibilities will be delegated via quality agreements and standard operating procedures (SOPs) to your "soon to be established distributor". Your response indicates that the distributor may be responsible for: visual inspection for shipping or water damage; verification of release certifications (Certificate of Analysis) from Daewoong Pharmaceuticals Co., Ltd.; verification of shipment quantity and lots numbers; and verification that appropriate temperature was maintained during shipment. You also state that you will rely on the distributor's SOPs and Quality Assurance unit for these activities. If your distributor is responsible for performing release operations for Evolus then they appear to fit the definition of a manufacturer rather than a distributor per 21 CFR 600.3 (t), (u), and (aa) and should be listed as a manufacturer in the license application.

Sponsor's Response:

The Sponsor clarified the roles of Evolus and the U.S. distributor. Below is the list of roles. Evolus is responsible for release. Because the distributor in the U.S. is not responsible for release, the Sponsor did not list the distributor as a manufacturer on the license application.

Evolus Roles:

- Perform the final release on every shipment and production lot prior to being placed into inventory by our distributor
- Verify the lot and quantities are correct
- Verify the temperature maintenance requirements were met.
- Resolved shipping damage issues with the manufacturer
- Review the Certificate of Analysis provided by the manufacturer to ensure product specifications and release testing requirements have been met.
- Authorize the distributor to release the product from quarantine, if no discrepancies are identified

U.S. Distributor roles:

(b) (4)

(b) (4)

Reviewer comments:

The defined roles show that Evolus is responsible for Lot Release in the U.S. Thus, the distributor in the U.S. does not have to be listed as a manufacturer in the licensed application.

CR Additional Request- Drug Product

Question 8: We received unsolicited information in an amendment you submitted on December 15, 2017. This information includes process validation data from three new DP lots manufactured with an updated commercial DP manufacturing process. We did not review these data. In addition, we did not review the release and stability data from these new DP lots. If you plan to change the DP manufacturing process and these data support your changes, submit them to us through an appropriate mechanism.

Sponsor's Response:

Commercial scale DP batches generated with DS manufactured with the working cell bank were manufactured and tested to support the establishment of the working cell bank. In parallel with the verification of the DS derived from the working cell bank, revalidation of the DP manufacturing process was performed with DS derived from the WCB. The process validation studies conducted with the DP lots manufactured with the working cell bank derived drug substance incorporated and verified the operating parameters defined by the QbD studies.

Reviewer comments:

The control strategy described in Section 3.2.P.3.4 Controls of Critical Steps and Intermediates (Table 3.2.P.4.3-1) for the drug product (DP) manufacturing process is based on operating parameter ranges derived from quality by design (QbD) studies conducted after the initial validation of the commercial manufacturing process was completed. Because the QbD studies were performed at commercial scale, it is acceptable to use parameters established during these studies as control parameters for the commercial DP manufacturing process. Therefore, the proposed commercial DP manufacturing process control strategy is supported by the combination of the initial process validation studies conducted with DP derived from the master cell bank and the additional QbD studies.

(b) (4)

(b) (4). Overall from a product quality perspective, the new process validation data further support that the validated DP manufacturing process is capable of consistently producing DP that meets specifications, because all DP lots met the acceptance criteria for the release specifications as indicated in the Batch Analysis. (refer to Batch Analysis).

In the resubmission, a current version of an unexecuted batch record was added to the BLA.

Long-term Stability

Up to 12 months of long-term stability data were added to the BLA for the DP lots manufactured with DS produced from the working cell bank. These stability data were not reviewed during the initial review cycle, because they were considered unsolicited information.

Reviewer comments:

The 12 months of long-term stability data for DP lots manufactured with DS of the working cell bank have been reviewed as part of the CR review and they met all acceptance criteria. These data further support that the revised DP manufacturing process is capable of consistently manufacturing DP that meets specifications. In addition, these data support the comparability of the drug substance manufactured from the master cell bank and the working cell bank. The DP long-term stability testing will continue for up to 36 months for these lots.

Question 9: The commercial DP shipping validation studies you provided in the BLA include assessment of the temperature of the shipping containers and the physical integrity of the DP vials during the winter months. This validation study is inadequate and additional information is needed to assess the suitability of your commercial shipping process. Provide the following information:

- a. The validation results do not address the impact of shipping on product quality attributes of the DP. Provide product quality data from the winter shipping studies if they are available.

- b. During the pre-approval inspection of your facility in November 2017, you indicated that the summer shipping validation had been completed. Update the BLA to include the results from the summer shipping validation and provide product quality data from the summer shipping studies if they are available.

Sponsor's Response:

Commercial primary and secondary packaging configurations were used to evaluate the shipping conditions in the winter and summer. The winter validation study used DP vials and the summer shipping validation study used empty vials of the same materials and packaging used for commercial production. The objectives of the winter and summer shipping validation studies were to evaluate the impact of transport conditions on the container closure and qualification of the temperature control system. (b) (4)

(b) (4)

(b) (4) For both studies the temperature was maintained through the shipment and no broken vials were reported. However, no product quality data were provided for either the winter or the summer validation studies.

(b) (4)

(b) (4) All tests met the acceptance criteria.

Reviewer comments:

The additional shipping validation data submitted demonstrate that the shipping containers are able to maintain the correct temperature and physical integrity of the vials, and the shipping conditions do not impact product quality. No additional information is needed.

Question 10: In your December 1, 2017 response to the November 13, 2017 information request, you provided 12 months of leachables data for the DP container closure system and indicated that the leachable studies for the container closure system are ongoing. Provide updated leachable study results. If the levels of leachables detected are above the safety limits, provide a risk assessment of their impact to product quality and patient safety and justification for the continued use of the container closure system.

Sponsor's Response:

The leachable study is on-going and the next time point of 24 months will be in December 2018. The final time point of 36 months will be completed in December 2019. No additional leachable studies have been reported at the time of the resubmission. Section 3.2.P.2.4 Pharmaceutical Development (Container Closure System) was updated to contain the results from the 12 month time point, which was submitted and reviewed in the initial review cycle (refer to Table 3.2.P.2.4-8). In addition, 3.2.P.2.3.4 Pharmaceutical Development – Manufacturing Process Development (Risk Assessment of Potential Extractables/Leachables for Contact Materials) was updated to state that 6 months and 12 months stability data are available.

Reviewer comments:

There are no additional leachables data to review at this time, because data for the next time point are not available at this time. No additional information is required. If approved, updated leachables data should be provided in the annual report to the BLA.

Question 11: In your March 5, 2018 response to the February 21, 2018 information request to clarify what manufacturing steps are

(b) (4)
(b) (4)

(b) (4)

Reviewer comments:

The Sponsor adequately clarified (b) (4) and updated the BLA to indicate this information. From a product quality perspective, no additional information is required.

Question 12: Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls

(b) (4)

Question 14: The HSA excipient in the DP formulation is supplied by (b) (4). You provided a letter from (b) (4) authorizing you to reference (b) (4), US License No. (b) (4); however, throughout the BLA, you incorrectly refer to Plasma Master File (b) (4). Update your BLA to refer to (b) (4) for which you have a letter of authorization to cross reference.

Sponsor's Response:

Section 3.2.P.4.1 Control of Excipients – Specifications and other sections of the BLA were updated to correctly refer to (b) (4), US License No. (b) (4) for HSA.

Reviewer comments:

The BLA was correctly updated to reference the correct US License number for HSA. No further action is required.

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Memorandum of Review – Product Quality

Resubmission: BLA STN 761085

Primary Reviewer: Ennan Guan, M.D./Ph.D.
Secondary Reviewer: Susan Kirshner, Ph.D., Chief
Product: **Jeuveau (probotulinumtoxinA)**

Indication: Glabellar lines
Route of Admin: Intramuscular injection
Dose Regimen: 4 units intramuscularly injected into each of five sites in the mid-line of the procerus muscle for a total dose of 20 units
Labeled Strength: 100 Units/vial
Sponsor: Evolus, Inc
Clinical Division: CDER/OND/Division of Dental and Dermatology
Date Received: August 2, 2018
PDUFA Date: February 2, 2019

Product Quality Team: Ennan Guan, Frances Namuswe, Susan Kirshner
Davinna Ligons (Drug Product and Immunogenicity)

Recommendations

Recommendation

We recommend approval of this BLA from the chemistry perspective.

Justification

The data provided in this resubmission adequately addressed the deficiencies identified during the original review cycle and support the conclusion that the manufacture of purified *C. botulinum* neurotoxin type A (BoNT/A, complexed) naturally secreted by *C. botulinum*, is well controlled from the chemistry perspective.

In their response to an information request regarding question 5 the Sponsor stated they will submit an updated WCB qualification protocol at the end of November 2018. The adequacy of that protocol will be addressed in an addendum to this memo. WCB qualification protocols are not necessary for BLA approval because qualification of new WCB can be submitted as a prior approval supplement.

The Sponsor's reference material management program is still sub-optimal because the reference material batch size is small resulting in frequent reference material replacement and increasing the chances of product drift. However, because the risk is theoretical and the Sponsor has an adequate reference material qualification program the Sponsor can address this concern through a post-marketing commitment.

BLA resubmission review for product quality information request: Drug substance

FDA Request 1

(b) (4)



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Response to the information request is adequate.

FDA Request 4

A leachable study is underway for the DS container closure. Leachable substances can induce degradation, precipitation and changes in the product. To allow us to assess the impact of potential leachable substances on the DS, submit the leachable study results for the DS container closure to the BLA. In addition, provide the letters from the DMF holders authorizing you to cross reference Type III DMF (b) (4) and DMF (b) (4).

Evolus Response

Section 3.2.S.6 has been updated to include data from the on-going leachable study over 12-month of analysis as showed in the table below:



(b) (4)

The Sponsor states that the studies are on-going through 36 months and will submit the results in December, 2018.

Letters of authorization from the DMF holders to cross reference Type III DMF (b) (4) and DMF (b) (4) are not available. The Section 3.2.S.6 has been revised to remove these references.

Reviewer comment: This reviewer considers that the leachable studies over 12-month period are sufficient enough



(b) (4)
(b) (4)

(b) (4). *As such, the container closure system is suitable for storing the DS at the proposed conditions. Response to this request is adequate.*

FDA Request 5

To ensure adequate characterization of a new working cell bank (WCB), qualification of a WCB should include manufacture and characterization of at least one drug substance lot at commercial scale. Update the WCB qualification protocol to include manufacture and characterization of at least one lot of DS and a commitment to place the first DS and DP lot manufactured from the new WCB on stability. Absent an Agency approved WCB qualification protocol, qualification of new WCB should be reported in a prior approval supplement.

Evolus Response

Evolus' response to the Agency request regarding the update the WCB qualification protocol is inadequate. Specifically, Evolus updated the relevant sections with a summary of a WCB characterization study reports from the original BLA submission. It appears that the Table 3.2.S.2.3-8 may be the qualification protocol for the new WCB. However, the applicant did not indicate which tests will be used for qualification of the future WCBs. For example, if the tests in Table 3.2.S.2.3-8 or other tables are part of their WCB qualification protocol. The following IR was sent to the Sponsor on Oct 23, 2018:

Your response to the Agency request to update the protocol for qualification of new working cell banks (WCB) to include manufacture and characterization of at least one drug substance (DS) lot at commercial scale is inadequate. Specifically, you updated the relevant sections of the BLA with information to support qualification of the current WCB and indicated the procedure that will be used to prepare a new WCB. However, based on the information provided, it is still not clear what tests will be performed to qualify a new or future WCB. In addition, it is not clear whether manufacture of DS will be part of future WCB qualification. Update Section 3.2.S.2.3 "Control of Materials" to clearly indicate which tests will be used for qualification of future WCBs. For example, if the tests in Table 3.2.S.2.3-8 or other tables are part of your WCB qualification protocol, clearly indicate this in the submission. In addition, update Section 3.2.S.2.3 to clearly indicate that qualification of the future WCBs should include manufacture and characterization of at least one lot of DS at commercial scale and a commitment to place the first DS and DP lot manufactured from the new WCB on stability.

On October 29, the Sponsor responded that they confirm the manufacture and characterization of at least one lot of DS at commercial scale and placement of the first DS and DP lot made from the new WCB on (b) (4) stability will be included in the

WCB qualification protocol. However, the Sponsor said that the updated WCB qualification protocol will be submitted by the end of November 2018.

(b) (4)

Reviewer comment: Waiting for the updated WCB qualification protocol from the Sponsor.

FDA request 6

The BLA includes a commitment to place one DS batch on a stability protocol under the (b) (4) storage condition annually (section 3.2. S.7.2). (b) (4)

(b) (4)
(b) (4). Incorporate studies with DS held under appropriate accelerated condition into the annual stability program.

Evolus Response

Section 3.2.S.7.2 has been updated (b) (4)
(b) (4)

Reviewer comment:

(b) (4)

(b) (4)

Response to this request is

adequate.

FDA request 7

Reference materials play a critical role in confirming the suitability of analytical tests and quality of the product during release and stability testing. The information you provided in the BLA suggests that your DS reference material management program does generate sufficient quantities of a given reference material lot to support all the required testing. Revise your reference material qualification procedures to ensure that you generate sufficient quantities of reference material to support all the necessary testing, including qualification of future reference materials. In addition, revise the DS reference material qualification and requalification protocol to include adequate stability monitoring of the reference materials.

Evolus Response

The revised DS reference qualification protocol is presented at far right of the table below:

(b) (4)

The test items and specifications of the updated protocol (at far right of the table) are similar to the test items and acceptance criteria in the updated DS release specification

(b) (4)
(b) (4)

The Sponsor has updated section 3.2. S.5. and 3.2.S.6 on qualification and requalification of reference standard material.

Reviewer comment: Response to this request is inadequate because the DS reference management program does not ensure that there is enough reference material for future stability monitoring, and calibration of the future primary reference materials. The Sponsor's reference material management program is still sub-optimal because the reference material batch size is small (Table 3.3.5.5-9) resulting in frequent reference material replacement and increasing the chances of product drift. This reviewer considers this as a post-marketing commitment to be negotiated with the Sponsor.

FDA Request 8

You indicated in the “Adventitious Agents Safety Evaluation Report” in Section 3.2.A.2 of the BLA that evaluation of viral clearance [REDACTED]

(b) (4) are on-going. If these studies are completed at the time of BLA resubmission, provide the results from these studies.

Evolus Response

The Sponsor completed the studies and updated the section 3.2.A.2 of the BLA to incorporate the completed viral clearance studies.



Reviewer comment: Botulinum products are naturally produced from Botulinum bacterial as such we do not ask the Sponsor to conduct the viral clearance studies. The Sponsor only needs to provide BSE certificates for animal derived materials. However, the Sponsor provided BSE certificates and completed a viral clearance study (b) (4). The results of viral clearance are adequate. Response to this request is adequate.



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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Aimee L. Cunningham, Ph.D., M.P.H.
Quality Assessment Lead: Reyes Candau-Chacon, Ph.D.

BLA: 761085/0
Applicant: Evolus, Inc.
US License Number: 2070
Submission Reviewed: Original BLA resubmission
Product: DWP-450 (prabotulinumtoxinA, Jeuveau)
Indication: moderate to severe glabellar lines
Dosage Form: 100 units/vial; powder for solution
Manufacturing Sites: Daewoong Pharmaceutical Co., Ltd. (FEI: 30123315)
FDA Receipt Date: 8/2/2018
Action Date: 2/2/2019

Conclusion and Approvability Recommendation

The drug product portion of this BLA was reviewed from a sterility assurance and product quality microbiology standpoint and is recommended for approval.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0033	08/02/2018	BLA resubmission
0034	09/05/2018	IR responses
0035	09/28/2018	IR responses
0036	10/12/2018	IR responses

Reviewer's Note: The original BLA was reviewed in the memo uploaded to Panorama on 04/06/2018. This memo reviews only the drug product (DP) deficiencies and additional comments communicated to the Sponsor in the CR letter.

Drug Product

Complete Response Items

Question 10

You performed validation (b) (4) using (b) (4) (b) (4) DWP-450 DP vials. No information was provided to assess (b) (4) (b) (4). Demonstrate that (b) (4) DWP-450 commercial DP vials (b) (4) effectively reduces endotoxin by a minimum of 3 logs and provide summary data and the validation report in the resubmission.

Review of Evolus Response

The resubmission includes validation of (b) (4) (b) (4) the vials used in routine DP manufacturing (b) (4)



SATISFACTORY

Question 11

You did not perform validation of the worst-case (b) (4) parameters on the DWP-450 DP vials to ensure that commercial vials are sealed appropriately, and that container closure is integral. The vials used in the commercial manufacture of DWP-450 DP were not used to validate the (b) (4) process. In addition, worst-case (b) (4) parameters were not used during validation. Submit container closure integrity data to support the proposed parameters in the BLA resubmission.

Review of Evolus Response



(b) (4)

Reviewer's Note: *The methodology of the dye ingress test used for CCIT is not described; it is unclear whether the validated method was used, if positive/negative controls were included and if samples were held under pressure or vacuum. An IR was sent on 08/29/2018 to clarify these points. In responses submitted 09/05/2018 (eCTD sequence 0034), Evolus clarified that positive and negative controls were not included in the (b) (4) validation study. An additional test was conducted and the report (C-R02PQR-CCAM01(01)) and associated protocol (C-R02PQP-CCAM01(02)) were submitted in amendment 0035 on 09/28/2018 (described below).*

(b) (4)

Reviewer's Note: *Report C-R02PQR-CCAM01(01) shows photos of vials following dye ingress testing, which demonstrate that all acceptance criteria were met for the repeat validation using (b) (4) vials to be used in DWP-450 routine manufacturing. The repeated validation study is adequate.*

SATISFACTORY

Question 12

You performed the (b) (4) validation study with (b) (4) (b) (4) the DWP-450 DP vials. No information was provided to assess (b) (4) (b) (4). Demonstrate (b) (4) the DWP-450 DP vials is effective (b) (4) and provide summary data and the validation report in the BLA resubmission

Review of Evolus Response

(b) (4)

(b) (4)

SATISFACTORY

Question 13

The maximum sterile hold of (b) (4) for DWP-450 DP is not supported (b) (4). Provide data (b) (4) to support the sterile hold of (b) (4) for DWP-450 DP (b) (4). Include a summary of the (b) (4) (b) (4) environmental monitoring data in the BLA resubmission.

Review of Evolus Response

(b) (4)

(b) (4)

SATISFACTORY

Question 14

You did not demonstrate that the container closure integrity test detects breaches that may allow for bacterial ingress. You did not include positive controls in the method validation. Submit information to demonstrate that the container closure integrity testing can detect breaches \leq ^{(b) (4)} μm and include positive controls during routine testing.

Review of Evolus Response

(b) (4)

Reviewer's Note: It does not appear that negative controls are included in the validation. An IR was sent on 08/29/2018 to ask that these also be routinely included in CCIT. Evolus agreed to include negative controls (vials not immersed in dye) in the routine CCIT test. A revised SOP # NPR03-030 which includes the use of the negative control was submitted in amendment 0035 on 09/28/2018.

SATISFACTORY

Question 15

You did not perform low endotoxin recovery (LER) testing of DWP-450 DP to assess whether the bacterial endotoxin test can consistently detect endotoxin in the drug product. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> Bacterial Endotoxin Test (BET). Evaluate the effect of hold time on endotoxin detection by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted DP and test for recoverable endotoxin over time (b) (4). Submit the report in the BLA resubmission.

Review of Evolus Response

LER was performed on 3 batches of undiluted DP dissolved in 2.5 mL NaCl injection (identical parameters to routine use) or 1 mL LAL reagent water. Endotoxin was spiked at 1.2, 30, and 50 EU/mL. Samples were maintained at 2-8°C for 0, 1, 2, 3, 4, 7, and 8 days and tested for endotoxin. Results provided in the updated P.5.3 section are found in Table 3.2.P.5.3-2; reports DWP450-32p52-REP-002E and DWP450-32p52-DAT-002E were provided in the resubmission. As recovery of the endotoxin meets acceptance criteria of $\geq \frac{(b)}{(4)}\%$ (all recoveries were (b) (4) %), no LER effects were observed in DWP-450 drug product.

Reviewer's Note: LER studies should be performed under process-relevant conditions with recoveries calculated compared to a nominal spike or spiked LAL reagent water. This study was performed at 2-8°C with recoveries calculated compared to time 0 recovery since the spiked LAL water control was not held past time 0. Another study will not be requested since LER risk in the product is low, as the formulation does not contain polysorbate.

SATISFACTORY

Question 16

You did not routinely monitor bioburden (b) (4) to verify continued microbial control of the drug product (b) (4). Implement routine bioburden monitoring (b) (4). In addition, provide a description of the bioburden test method and provide method qualification, summary data, and the qualification report.

Review of Evolus Response

Routine in-process testing of bioburden has been established and will be implemented to monitor bioburden (b) (4). The BLA has been updated in P.3.3 to reflect this additional IPC, and in P.3.4 with a description of test method and method qualification. (b) (4)

(b) (4) These acceptance criteria include TAMC and TYMC.

(b) (4)

(b) (4) Results are documented in Table 3.2.P.3.4-6 and show no CFU detected for TAMC or TYMC.

SATISFACTORY

Additional Items

Request 16

(b) (4)

Review of Evolus Response

(b) (4)

SATISFACTORY

Request 17

Provide endotoxin action limits for the DWP-450 (b) (4) .

Review of Evolus Response

Bioburden and endotoxin action limits (b) (4) have been set and updated in P.3.4. The endotoxin acceptance criteria is NMT (b) (4) EU/mL.

SATISFACTORY

Request 18

(b) (4)

Review of Evolus Response

(b) (4)

(b) (4)

SATISFACTORY

Request 19

Provide justification (b) (4) that the F_H acceptance criteria is sufficient to reduce endotoxin by 3 logs.

Review of Evolus Response

Section P.3.5 has been updated with additional information regarding (b) (4) validation (b) (4); reference was made to deficiency #10 (addressed above). F_H values greatly exceed the (b) (4) acceptance criteria, and this is acceptable.

SATISFACTORY

Request 20

Clarify whether the formulated DP may be held (b) (4). If there is a hold which exceeds (b) (4), provide data to support microbial control (b) (4).

Review of Evolus Response

There is no hold of formulated DP (b) (4). See deficiency #8 (addressed above).

SATISFACTORY

Request 21

(b) (4)

Review of Evolus Response

(b) (4)



SATISFACTORY

Conclusion

1. The BLA resubmission was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval.
2. Product quality aspects other than microbiology should be reviewed by OBP.
3. No inspection follow-up items were identified; refer to Panorama for the updated status of all facilities.

DP Quality Microbiology Information Requests Sent and Date

IR #1, sent 08/29/2018

1. CR item 11: Clarify whether the validated dye ingress test method was used to assess worst-case (b) (4) parameters, and whether positive and negative controls were included in the assay.
2. (b) (4)

(b) (4)

3. CR item 14: Include negative controls (vials not immersed in dye) in your routine CCIT testing.

4.

(b) (4)

5.



Aimee
Cunningham

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Reyes
Candau-Chacon

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Date: 11/15/2018 03:14:25PM
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Memorandum of Review – Product Quality

Original BLA STN 761085/0

Primary Reviewer: Ennan Guan, M.D./Ph.D.

Secondary Reviewer: Frances Namuswe, Ph.D.

Product: **Jeuveau (probotulinumtoxinA)**

Indication Glabellar lines

Route of Admin: Intramuscular injection

Dose Regimen: 4 units intramuscularly injected into each of five sites in the mid-line of the procerus muscle for a total dose of 20 units

Labeled Strength: 100 Units/vial

Sponsor: Evolus, Inc

Clinical Division: CDER/OND/Division of Dental and Dermatology

Date Received: May 15, 2017

PDUFA Date: May 15, 2018

Product Quality Team: Ennan Guan, Frances Namuswe, Susan Kirshner
Davinna Ligons (Drug Product and Immunogenicity)

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Recommendations

Recommendation

We do not recommend approval of this BLA from the chemistry perspective with the CR and non-CR comments below to be communicated to the Sponsor. The evaluation of immunogenicity assays is covered in a separate review.

Justification

The data submitted in this application do not support the conclusion that the manufacture of purified *C. botulinum* neurotoxin type A (BoNT/A, complexed) naturally secreted by *C. botulinum*, is well controlled from the chemistry perspective (refer to the CR-comment below).

CR-comment to the applicant

1. DS reference materials play a critical role in confirming the suitability of analytical tests and the quality of the DS during DS release and stability testing. However, your DS reference material program is not adequate to ensure the adequate control of the drug substance during release and stability monitoring. In addition, the reference material qualification and requalification protocol needs to be revised to include stability monitoring of reference materials and to have enough reserved reference materials for calibration of the future reference standards.

Unresolved non-CR review issues to be included in the letter to the applicant

1. The acceptance criteria (b) (4) (b) (4) (b) (4) are not adequate to control the quality of the product (b) (4) (b) (4). The DS identity specification (b) (4) should be updated (b) (4), (b) (4). The DS purity specification (b) (4) should be updated (b) (4) (b) (4)
2. (b) (4)

(b) (4)

Update the DS purity specification (b) (4) to specify the acceptable limits

(b) (4)

3. The validation exercise for the DS (b) (4) did not include demonstration of specificity (b) (4) (b) (4)
- (b) (4). Update the BLA to include demonstration of specificity (b) (4)
4. A leachable study is underway for the DS container closure. Leachable substances can induce degradation, precipitation and changes in the product. To mitigate the potential leachable substances that may cause adverse impact on the DS, submit the leachable study results for the DS container closure to the BLA.
5. To ensure adequate characterization of a new working cell bank (WCB), qualification of a WCB should include manufacture and characterization of at least one drug substance lot at commercial scale. Update the WCB qualification protocol to include manufacture and characterization of at least one lot of DS and a commitment to place the first DS and DP lot manufactured from the new WCB on stability. Absent an Agency approved WCB qualification protocol, qualification of new WCB should be reported in a prior approval supplement.

Administrative

Primary Review Team

Medical Officer:

Gary Chiang

Pharm/Tox:

Jianyong Wang

DMA Drug Substance:

Bo Chi

DMA Drug Product:

Aimee Cunningham

OBP Drug Substance

Ennan Guan

OBP Drug Product:

Davinna Ligons

Immunogenicity:

Davinna Ligons

Facilities:

Vivian Mattas

Clinical Pharmacology:

Jie Wang

Statistics:

Matthew Guerra and Marilena Flouri

OBP Labeling:

Vicky Borders-Hemphill

OBP RPM:

Kelly Ballard

OSE RPM:

Trim Bui Nguyen

Regulatory Project Manager:

Strother Dixon

GRMP Review Deadlines

Filing Meeting:	June 26, 2017
Mid-Cycle Meeting:	October 11, 2017 (Internal)
Late-Cycle Meeting:	December 12, 2017 (Internal)
Primary Review Due:	April 11, 2018
Secondary Review Due:	April 17, 2018
CDTL Memo Due:	
PDUFA Action Date:	May 15, 2018

Environmental Assessment Or Claim Of Categorical Exclusion

A categorical exclusion is claimed from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). The claim of categorical exemption is accepted because the amount of botulinum toxin (b) (4)

(b) (4) found in an unused vial of DWP-450 will not significantly alter environmental concentrations of botulinum neurotoxin A. Clostridium botulinum, which produces BoNT/A is commonly found in the environment throughout the US, as well as most of the world. C. botulinum is frequently found in food and soil in the US, occasionally at levels high enough to cause botulism in children and animals. Used vials are disposed of as medical waste and therefore will not contribute to environmental exposure.

Communication with Sponsor (Drug Substance and Drug Product)

Communication/Document	Date Sent
Information Request #1	August 29, 2017
Information Request # 1 resent	September 12, 2017
Information Request # 2	September 22, 2017
Information Request # 3	September 27, 2017
Mid-cycle communication	October 30, 2017
Information Request #4	November 13, 2017
Information Request #5	November 28, 2017
Information Request #6	January 4, 2018
Late-cycle communication	January 9, 2018
Information Request#7	February 12, 2018
Information Request #8	February 21, 2018
Information Request #9	March 2, 2018

Submissions Reviewed

Submission	Date Received	Review Completed (Yes/No)
Original Submission	May 12, 2017	Yes
SN 0013	September 28, 2017	Yes
SN 0014	September 28, 2017	
SN 0015	September 28, 2017	Yes
SN 0016	October 17, 2017	Yes
SN 0020	January 31, 2018	Yes

SN 0030	March 30, 2018	No
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Quality by Design Elements

	Design Space
	Design of Experiments
	Formal Risk Assessment / Risk Management
X	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

Chemistry Executive Summary

A. Description of the Drug Product and Drug Substance

Structure

The active pharmaceutical ingredient in Jeuveau is a purified type A neurotoxin complex with a molecular weight of 900 kDa and is produced by the anaerobic fermentation of the bacterium *Clostridium botulinum* isolated from soil in S. Korea. The neurotoxin complex is a dimeric molecule linked by disulfide bonds. Each monomer consists of the neurotoxin moiety, (b) (4)

(b) (4) The neurotoxin moiety is a 1296 amino acid dimer molecule consisting of a heavy chain and a light chain linked by a disulfide bond. The final product is a vacuum dried material containing the type A toxin complex, and human albumin.

Biological activity

Jeuveau blocks neuromuscular transmission by binding to receptor sites on motor or sympathetic nerve terminals, entering the nerve terminal and inhibiting neurotransmitter (acetylcholine) release. The full activity of the toxin requires both the heavy (Hc) and light (Lc) chains. The Hc mediates neuron-specific binding, uptake by receptor-mediated endocytosis and transport of Lc across the endosomal membrane into the cytosol. In the cytosol the Lc, a zinc binding metalloproteinase, hydrolyzes a member of the SNARE protein complex, which is required for vesicle exocytosis. The Zn²⁺ binding sequence within each Lc, H-E-X-X-H, is a distinct minimal amino acid motif conserved within this toxin family.

The substrate for type A toxin is a 25-kD synaptosomal associated protein (SNAP-25). SNAP-25 is cleaved at the C-terminus (Q197-R) by BoNT/A, generating truncated SNAP-25 that cannot participate in formation of the SNARE core complex. When injected i.m. at therapeutic doses, Jeuveau induces partial chemical denervation of the

muscle resulting in a localized reduction in muscle activity. It is indicated for temporary improvement in the appearance of glabellar lines associated with corrugator or procerus muscle activity.

Potency Assays to Measure Activity

The mouse lethal dose assay is used to assess product activity. The assay is conducted by administration of pre-established dilutions of Jeuveau into groups of mice. The number of deaths that occur at each dilution is measured over a fixed period of time. The concentration that leads to death in half of the test animals is the lethal dose 50 (LD₅₀). The potency of botulinum toxin therapeutic preparations is expressed in LD₅₀ units, with one unit of activity defined as the amount of drug required to kill 50% of the animals. The assay is a good indicator of both light and heavy chain function since both are required for activity *in vivo*. A major drawback of this assay is that it is much more variable than cell based assays, requiring sacrifice of hundreds of mice for each potency activity measurement. Moreover, there is huge inter-laboratory variability, precluding standardization of LD50 units between products. If this product is approved, the post marketing commitment for development and implementation of the cell-based potency assay will be issued.

Drug Product Presentation

Jeuveau is supplied as a sterile single use vial. Each 100 Unit vial contains vacuum dried *C.botulinum* toxin type A, and human albumin (500ug). The DP is packaged in (b) (4) vials with (b) (4) rubber closure and sealed (b) (4). As each vial is for single patient use, no anti-microbial preservatives are included in the formulation.

Excipients

The product is formulated with human albumin. Human albumin is manufactured by (b) (4) and is a FDA approved medicinal product in the US. Human plasma was received from selected donation centers in the US, authorized by FDA.

Drug Product Storage

Drug product is stored as a dried powder at 2-8 °C. Drug product must be used within 24 h of reconstitution and should be stored at 2°C – 8°C.

DS Manufacture:

(b) (4)



(b) (4)

DS Release Tests

The tests for release of DS include the following: appearance (b) (4); protein content (b) (4); immunological identity (b) (4); (b) (4); protein profile (b) (4); (b) (4); bioburden ($< \frac{(b)}{(4)}$ cfu/ml); and endotoxin ($< \frac{(b)}{(4)}$ IU/ml). Drug product is formulated with (b) (4) HSA and DS is present in nanogram quantities. Therefore, it is not possible to test DP for aggregates. Since presence of aggregates can promote immunogenicity, this is a safety concern, albeit a limited one because the drug is administered intramuscularly at low dose and is highly diluted. The immunogenicity rate is less than 0.1 percent for this product in the clinical studies (refer to immunogenicity review of this BLA)

Development

The drug substance manufacturing process was developed at Daewoong Pharmaceutical Co., Ltd, South Korea. There are no significant changes in the manufacturing process development.

Stability

Real time stability data indicate that drug substance is (b) (4)
(b) (4)

The proposed drug substance shelf life (b) (4) is supported by stability data.

B. CR-comment to the applicant

DS reference materials play a critical role in confirming the suitability of analytical tests and the quality of the DS during DS release and stability testing. However, your DS reference material program is not adequate to ensure the

adequate control of the drug substance for release and stability monitoring. In addition, the reference material qualification and requalification protocol needs to be revised to include stability monitoring of reference materials and to have enough reserved reference materials for calibration of the future reference standard.

C. Unresolved non-CR review issues to be included in the letter to the applicant

1.

(b) (4)

2.

3.

4. A leachable study is underway for DS container closure. Leachable substances can induce degradation, precipitation and changes in the product. To mitigate the potential leachable substances that may cause adverse impact on the DS, submit the leachable study results for the DS container closure to the BLA.

5. Qualification protocol for new working cell bank (WCB) lacks a commitment to place the first DS and DP lot manufactured from the new WCB on stability. To ensure adequate control of the new WCB and the product derived from the new WCB, update the BLA to include a commitment to place the first DS lot manufactured from the new WCB on long term stability and submit the release and long term stability results to the BLA Annual Report.

C. Inspection Activities

A pre-license inspection was conducted from November 8, 2017 through November 17, 2017 at the Daewoong Pharmaceutical Co., Ltd, drug substance and drug product manufacturing site in South Korea for BLA 761085. The inspection covered Quality, Facility and Equipment, Production, Material, and Laboratory systems. Ennan Guan and Davinna Ligon of OBP participated in the inspection. A ten-item Form FDA 483 was issued to the firm at the close of the inspection on November 17, 2017, with the following observations:

(b) (4)



The initial recommendation was official action indicated (OAI) and is now downgraded to VAI.

REVIEW DRUG SUBSTANCE

3.2. S. 1.1 Nomenclature

INN	Botulinum toxin type A
Compendial name*	<i>Botulinum</i> Toxin Type A for Injection
Chemical Name	BoNT/A
Company or laboratory code	DWP-450
Chemical Abstracts Service (CAS) registry number	93384-43-1
Anatomical Therapeutic Chemical Classification (ATC)	M03AX01

USAN Jeuveau (probotulinumtoxinA)

3.2. S.1.2 General information

Structure

DWP-450 Drug substance (DS) is produced from fermentation of clostridium botulinum type A strain. It is purified as a complex with toxin A protein, (b) (4). (b) (4).

The molecular weight of the DWP Botulinum toxin type A complex is 900kDa. The toxin A molecule is a 150 kDa protein (1296 amino acids) composed of a 100 kDa heavy chain (Hc) and a 50 kDa light chain (Lc) linked by a disulfide bond. The structure and composition of DS is presented in the following figure and table.



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Ennan
Guan

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Frances
Namuswe

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Date: 4/11/2018 05:08:16PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

US Food & Drug Administration
Center for Drug Evaluation & Research
Office of Biotechnology Products
Division of Biotechnology Review and Research III

Memorandum of Review - Product Quality (Drug Product)

Primary reviewers: Davinna L Ligons, Ph.D.
Secondary Reviewer: Frances Namuswe, Ph.D.

Product: Jeuveau (probotulinum toxin A)
Indication: Treatment of moderate to severe glabellar lines

Route of Admin: Intramuscular Injection
Dose Regimen: 4 units intramuscularly injected into each of five sites in the mid-line of the procerus muscle; Total dose: 20 units in 0.5mL

Labeled Strength: 100 Units/vial

Sponsor: Evolus, Inc

Clinical Division: ODEIII / DDDP

Received Date: May 15, 2017
Target Date:
PDUFA Date May 15, 2018

Recommendation and Justification

We do not recommend approval of BLA761085 from a product quality perspective. The current drug product annual post-approval stability protocol is not acceptable because it does not include appropriate testing intervals to ensure that potential changes to commercial drug product during storage are detected in a timely manner. The protocol originally submitted to the BLA was acceptable. However, the Sponsor changed this protocol during the review cycle to remove the testing time points at 3, 6, 9, and 18 months. The sponsor does not have sufficient manufacturing experience to support a reduced stability program at this time. A CR comment will be added to the CR letter to advise the Sponsor to submit a drug product annual stability protocol consistent with the ICH Q5C guidelines.

Drug product executive Summary

Jeuveau (DWP-450; botulinum toxin, Type A) drug product is a sterile vacuum dried (b) (4) (b) (4) powder supplied as a 100 U product in a (b) (4) (b) (4) glass vial. The vial is closed with a (b) (4) stopper (b) (4) (b) (4) and sealed with a (b) (4) cap and (b) (4) closure. The drug product is formulated with human serum albumin (HSA) and sodium chloride. The HSA is supplied by an FDA approved manufacturer, (b) (4).

Drug product is stored as a dried powder at 2-8°C for up to 36 months. Prior to use, the DP is reconstituted with 2.5mL of 0.9% preservative free saline to a final concentration of 4 U/0.1mL per injection. Reconstituted drug product should be stored at 2 – 8°C and must be used within 24 h of reconstitution.

The drug product manufacturing process involves (b) (4)

(b) (4). Overall, the DWP-450 DP commercial manufacturing process is adequately controlled. The lots manufactured at commercial scale are comparable to the lots used in the clinical study. The Sponsor provided 36 months real time stability results for process validation batches manufactured at small scale and 12 months real time stability for process validation batches manufactured at the commercial scale. These results support the proposed 36 months expiry for DWP-450 DP.

As noted above, the drug product annual post-approval stability protocol is not acceptable because it does not include appropriate testing intervals to ensure that potential changes to commercial drug product during storage are detected in a timely manner. This will be communicated to the Sponsor as a CR item. In addition, several non-approvability issues listed below will be communicated to the Sponsor.

The following CR item is to be communicated to the Sponsor:

In response to a November 13, 2017 information request to update the drug product stability testing protocols with the solubility test for drug product, it appears that additional changes were made to the post-approval stability protocol originally submitted in the BLA to remove the testing points at 3, 6, 9, and 18 months. You do not have sufficient manufacturing experience and stability data to support a reduced stability testing program. The updated annual post-approval stability protocol in section 3.2.P.8.2 *Post-approval Stability Protocol and Stability Commitment* (Table 3.2.P.8.2-2) submitted on 12/01/2017 is not adequate to ensure that potential changes to commercial drug product during storage are detected in a timely manner. Revise your annual stability protocol to be consistent with ICH Q5C guidelines.

The following non-CR items are to be communicated to the Sponsor:

1. The Agency received unsolicited information in an amendment received on December 15, 2017. This information includes process validation data from three new drug product lots manufactured with an updated commercial drug product manufacturing process. These data were not reviewed. In addition, the release and stability data from these new drug product lots were not reviewed. If you plan to change the drug product manufacturing process and these data support your changes, they should be submitted to the Agency through an appropriate mechanism.
2. Data to show that there is no impact on product quality during shipping of drug product were not submitted in the BLA. These data were requested in a January 4, 2018

information request and the data were received on April 10, 2018. These data were not reviewed and should be resubmitted.

3. In response to the November 13, 2017 information request, you provided 12 months of leachables data for the drug product container closure system and indicated that the leachable studies for the container closure system are ongoing. Provide updated leachable study results. If the levels of leachables detected are above the safety limits, provide a risk assessment of their impact to product quality and patient safety and justification for the continued use of the container closure system.

4. In your response to a February 21, 2018 IR to clarify what manufacturing steps are

(b) (4)

5. *Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls* states that

(b) (4)

- 6.

(b) (4)

7. The HSA excipient in the drug product formulation is supplied by (b) (4). The letter from (b) (4) authorizing you to reference master file (b) (4) is included in the submission; however, throughout the BLA, you refer to Plasma Master File (b) (4). Update the BLA with references to the correct Plasma Master File.

Administrative

Primary Review Team

Medical Officer: Gary Chiang
Pharm/Tox: Jianyong Wang
DMA Drug Substance: Bo Chi
DMA Drug Product: Aimee Cunningham
OBP Drug Substance: Ennan Guan
OBP Drug Product: Davinna Ligonis
Immunogenicity: Davinna Ligonis
Facilities: Viviana Matta
Clinical Pharmacology: Jie Wang
Statistics: Matthew Guerra
Statistics: Marilena Flouri
OBP Labeling: Vicky Borders-Hemphill
OBP RPM: Kelly Ballard
OSE RPM: Trim Bui Nguyen
Regulatory Project Manager: Strother Dixon

GRMP Review Deadlines

Filing Meeting: June 26, 2017
Mid-Cycle Meeting (Internal): October 11, 2017
Late-Cycle Meeting (Internal): December 12, 2017
Primary Review Due: April 11, 2018
Secondary Review Due: April 17, 2018
CDTL Memo Due:
PDUFA Action Date: May 15, 2018

Communication with Sponsor (Drug Substance and Drug Product)

Communication/Document	Date Sent
Information Request # 1	September 12, 2017
Information Request # 2	September 22, 2017
Information Request # 3	September 27, 2017
Mid-cycle communication	October 30, 2017 (meeting October 11, 2017)
Information Request # 4	November 13, 2017
Information Request # 5	January 4, 2018
Late-cycle communication	January 9, 2018 (meeting December 12, 2017)
Information Request # 6	February 21, 2018
Information Request #7	March 2, 2018

Submissions Reviewed

Submission	Date Received	Review Completed (Yes/No)
SN 0001	May 15, 2017	Yes
SN 0014	September 28, 2017	Yes

SN 0015	September 28, 2017	Yes
SN 0016	October 17, 2017	Yes
SN 0018	December 1, 2017	Yes
SN 0023	January 08, 2018	Yes
SN 0027	March 05, 2018	Yes
SN 0029	March 09, 2017	Yes (see secondary review)

Request for a Waiver to Perform an Environment Evaluation

Refer to the drug substance review.

Quality by Design Elements

(b) (4)

X	Design Space
	Design of Experiments
X	Formal Risk Assessment / Risk Management
X	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

Drug Product Referenced Drug Master Files (DMF)

DMF number	Holder	Item referenced	Letter of cross-reference	Comments
(b) (4)			Yes	None
			Yes	None
			Yes	None
			Yes	None

Reference is made to Type V DMF (b) (4). The review of this DMF is deferred to DMA.

Drug Product Inspectional Activity

Refer to Appendix 2 for a list of the 483 inspectional observations.

Drug Product Consults Requested by OBP

There are no consults requested by OBP for drug product.

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REVIEW (Drug Product)

Proprietary Name: Jeuveau
Company Code: DWP-450
Non-Proprietary/USAN: prabotulinumtoxinA-xvfs
CAS name and number: 93384-43-1
Common name: Botulinum toxin
INN Name: Botulinum toxin type A
Compendial Name: *Botulinum Toxin Type A* for Injection
OBP systematic name: PROT P10845 (BXA1_CLOBO) BOTULINUM NEUROTOXIN TYPE A [DWP450]

P.1 Description and Composition of the Drug Product

DWP-450 (Botulinum toxin, Type A) drug product is a sterile vacuum dried (b) (4) powder supplied as a 100 U product in a (b) (4) vial. The vial is closed with a (b) (4) stopper (b) (4). A (b) (4) cap and (b) (4) closure seals the rubber stopper to the vial. The DP is reconstituted with 2.5mL of 0.9% preservative free saline yielding a final concentration of 4 U/0.1mL per injection. The saline is not provided with the product.

Table 3.2.P.1-1. Components of DWP-450 Drug Product

Component	Function	Quantity per Vial	Reference to Standards
Botulinum toxin, Type A	Active ingredient	100 Units	In-house*
Human serum albumin	(b) (4)	0.5 mg	Ph. Eur./USP [†]
Sodium chloride	(b) (4)	0.9 mg	Ph. Eur./USP [‡]
(b) (4)			

* The In-house Specification include all Ph. Eur. monograph requirements and additional company imposed quality requirements.

† The manufacturer (b) (4) has a Plasma Master File (PMF) filed with the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) that complies with USP and Ph. Eur. The PMF certificate numbers are (b) (4) respectively.

‡ The product is for global distribution. As the USP and Ph. Eur. are not completely harmonized, chemical constituents and test methods used to support the quality attributes are tested against both pharmacopoeia monograph requirements.

(b) (4)

N/A = Not applicable; NF = National Formulary

Reviewer comments:

The description of the components of the drug product is complete and satisfactory. The excipients used in the drug product provide stability and isotonicity and are acceptable for those purposes. Assessment of HSA as an excipient is provided in the appropriate sections below.

P.2 Pharmaceutical Development

P.2.1 Components of the Drug Product

P.2.1.1 Drug Substance

DWP-450 is purified from *Clostridium botulinum*, Type A which is composed of a neurotoxin, non-toxic, (b) (4) with a molecular weight of 900 kDa. DWP-450 drug substance is identical to wild type botulinum toxin, Type A. Figure 3.2.P.2.1-1 shows the structure of the toxin.



Figure 3.2.P.2.1-1. Structure of Botulinum toxin, Type A (900 kDa)

Reviewer comments:

The manufacturing process for the drug substance is discussed in Section 3.2.S.2.2. The drug substance was characterized for structure and composition, physiochemical properties, immunochemical property and biological property in Section 3.2.S.3.1. Refer to the drug substance review. The excipients added to drug substance are described below in Section 3.2.P.2.1.2 and the compatibility of drug substance with excipients is evaluated through drug product stability assessment in Section 3.2.P.8.3.

P.2.1.2 Excipients

Human serum albumin (HSA) is used (b) (4)

(b) (4) Sodium chloride is added (b) (4)

(b) (4)

(b) (4) Table 3.2.P.2.1-1 summarizes the excipients found in the drug product.

Table 3.2.P.2.1-1. Excipients of DWP-450 DP

Excipient Component	Function	Contents (per 1 vial)	Specification
Human Serum Albumin	(b) (4)	0.5 mg	Ph. Eur./USP*
Sodium Chloride	(b) (4)	0.9 mg	Ph. Eur./USP†
(b) (4)			

*The manufacturer (b) (4) has a Plasma Master File filed with the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) that complies with United States Pharmacopeia (USP) and European Pharmacopoeia, Ph. Eur. The PMF certificate numbers are (b) (4).

† The product is for global distribution. As the USP and Ph. Eur. are not completely harmonized, chemical constituents and test methods used to support the quality attributes are tested against both pharmacopoeia monograph requirements.

(b) (4)

Reviewer comments:

The excipients used for DWP-450 DP are common pharmaceutical excipients and are also used for other approved botulinum toxin A products. The Sponsor notes that other suppliers of the toxins approved in the US and globally use a similar formulation containing HSA and sodium chloride. The Sponsor mentions that there is low immunogenicity of human serum albumin as an excipient which is consistent with the low level of immunogenicity observed for HSA. The HSA is supplied by an FDA approved supplier, (b) (4). A letter authorizing the Sponsor to reference master file (b) (4) is included in the Submission and it indicates that (b) (4) is used as an excipient. However, throughout the BLA, the Sponsor refers to DMF (b) (4). In the review, I report (b) (4) to be consistent with the letter of authorization. Since the HSA is approved by the FDA for human use, its quality and safety were previously evaluated and found acceptable by the Agency. For more on qualification of HSA, see Section 3.2 P.4 Control of Excipients. It is acceptable to use HSA and sodium chloride as excipients (b) (4), respectively.

P.2.2 Drug Product**P.2.2.1 Formulation Development**

The formulation of the drug product is based on previous studies with the toxin and is informed by the formulation of the toxin used by other suppliers. According to information provided by Evolus, Allergan the producer of BOTOX uses 100U of purified botulinum toxin, Type A complex, 0.5 mg of HSA and 0.9% of sodium chloride which is the same formulation used for DWP-450 DP in this BLA submission. Evolus also notes that Dysport and Xeomin, other suppliers of the toxin, use HSA and sodium chloride in their formulation. (b) (4)

(b) (4)

(b) (4)



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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date:
To: Administrative File, STN 761085/0
From: Viviana Matta, Consumer Safety Officer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: 2070
Applicant: Evolus Inc.
Mfg Facility: Drug Substance and Product: Daewoong Pharmaceutical Co., Ltd., Korea (FEI 3012333115)
Product: DWP-450 (Botulinum toxin, Type A)
Dosage: Powder for solution, 100U
Indication: For the treatment of moderate to severe glabellar lines
Due Date: 5/15/18

Recommendation: The proposed manufacturing and testing site is recommended for approval from a facilities assessment standpoint for the 11/08/17 to 11/17/17 inspection of the Daewoong Pharmaceutical Co., Ltd. site (FEI 3012333115).

SUMMARY

The subject BLA proposes manufacture of Botulinum toxin Type A Drug Substance and Drug Product at the following facility.

Daewoong Pharmaceutical Co., Ltd. in the Republic of Korea (FEI 3012333115) is responsible for DS and DP manufacturing. A PLI was conducted from 11/08/17 to 11/17/17. This inspection was a system-based covered Quality, Laboratory, Raw Materials, Facilities and Equipment, and Production Systems. A 10-item Form FDA 483, Inspectional Observations was issued to the firm at the end of the inspection for the following: inadequate investigations, inadequate test procedures, inadequate environmental monitoring, inadequate cleaning and disinfecting, inadequate procedures for microbiological contamination control, production operations not conducted in manner to prevent contamination, deviations from procedures not justified and inadequate training. The initial recommendation was withhold/OAI. *The facility and inspection EIR review recommendation is approve. Proposed corrective actions appear adequate.*

The facility descriptions submitted in this BLA have been reviewed and are approved. Facility and inspection EIR review determined site is adequate to support the manufacture of Botulinum toxin Type A Drug Substance and Drug Product.

ASSESSMENT

DRUG SUBSTANCE

3.2.S.2.1 Manufacturers

The proposed Botulinum toxin Type A DS manufacturing, storage, release testing, and stability testing sites are listed below in Table 1.

Table 1. Botulinum toxin Type A Drug Substance Facility

Site Name	Address	FEI	Responsibilities
Daewoong Pharmaceutical Co., Ltd.	35-14, Jeyakgongdan 4-Gil, Hyangnam-Eup Hwaseong-Si, Gyeonggi-Do Republic of Korea	3012333115	Master Cell Bank storage Working Cell Bank production and storage Drug substance manufacturing

Review comment: The facility for the manufacturing, storage, release testing, and stability testing for the Botulinum toxin Type A drug substance is adequately described.

—Satisfactory—

Facility Inspection:

Prior Inspection History

There is no inspectional history available for Daewoong Pharmaceutical Co., Ltd. in the Republic of Korea (FEI 3012333115). A PLI was requested. The inspection occurred on from 11/08/17 to 11/17/17. The inspection covered CBI. The initial recommendation is withhold. *The facility and inspection EIR review recommendation is approve. Proposed corrective actions appear adequate.*

Current PLI Outcome

Daewoong Pharmaceutical Co., Ltd. (FEI #3012333115) was inspected from 11/08/17 to 11/17/17 under FACTS assignment # 11768960 with an initial recommendation of Withhold. *The facility and inspection EIR review recommendation is approve. Proposed corrective actions appear adequate.*

Review comment: The compliance status of the facility associated with the manufacture of Botulinum toxin Type A drug substance is approve.

—Satisfactory—

3.2.A.1 Facilities and Equipment

DRUG PRODUCT**3.2.P.2.1 Manufacturers**

The manufacturing, storage, release testing, and stability testing for the Botulinum toxin Type A drug product is shown in Table 2.

Table 2. Botulinum toxin Type A Drug Product Facility

Site Name	Address	FEI	Responsibilities
Daewoong Pharmaceutical Co., Ltd.	35-14, Jeyakgongdan 4-Gil, Hyangnam-Eup Hwaseong-Si, Gyeonggi-Do Republic of Korea	3012333115	Drug product manufacturing, storage, release testing and stability testing

Review comment: *The provided information regarding the identity of the facility utilized for manufacturing, storage, release testing, and stability testing for Botulinum toxin Type A drug product is adequate. The site for drug product manufacture is the same site as for drug substance manufacturing.*

—Satisfactory—

Prior Inspection History

There is no inspectional history available for Daewoong Pharmaceutical Co., Ltd. in the Republic of Korea (FEI 3012333115). A PLI was requested. The inspection occurred from 11/08/17 to 11/17/17. The inspection covered SVL. The initial recommendation is Withhold. *The facility and inspection EIR review recommendation is approve. Proposed corrective actions appear adequate.*

Current PLI Outcome

Daewoong Pharmaceutical Co., Ltd. (FEI #3012333115) was inspected from 11/08/17 to 11/17/17 under FACTS assignment #11768960 with an initial recommendation of Withhold/OAI. *The facility and inspection EIR review recommendation is approve. Proposed corrective actions appear adequate.*

Review comment: The compliance status of the facility associated with the manufacture of Botulinum toxin Type A drug product is approve.

—*Satisfactory*—

3.2.A.1 Facilities and Equipment



Conclusion:

Adequate description was provided for the following site proposed for Botulinum toxin Type A DS and DP manufacture:

Daewoong Pharmaceutical Co., Ltd. Gyeonggi-Do, Republic of Korea (FEI: 3012333115)

The proposed manufacturing and testing site is recommended for approval from a facilities assessment standpoint for the 11/08/17 to 11/17/17 inspection of the Daewoong Pharmaceutical Co., Ltd. site (FEI 3012333115).

Viviana Matta -A

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Viviana Matta
Consumer Safety Officer
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -
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Zhihao (Peter) Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1