CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761127Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

BLA STN 761127
Review Number: 3
Review Date: August 31, 2022

Drug Name/Dosage Form	DAXXIFY (daxibotulinumtoxinA-lanm) for injection
Strength/Potency	50 U/vial and 100 U/vial; Mouse LD50 assay
Route of Administration	Intramuscular injection
Rx/OTC dispensed	Rx
Indication	For temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients
Applicant/Sponsor	Revance Therapeutics, Inc.

Product Overview

DaxibotulinumtoxinA (DAXI; RTT150) is a purified, 150 kDa botulinum neurotoxin serotype A (BoNT/A) isolated from cultures of the Gram-positive obligate anaerobic bacterium *Clostridium botulinum*. There are no accessory proteins (haemagglutinin, non-toxin non-haemagglutinin proteins) associated with DAXI. The purified product is a two-chain polypeptide with a 100 kDa heavy chain (HC) joined by a disulfide bond [Cys430-Cys454] to a 50 kDa light chain (LC).

DAXI is an acetylcholine release inhibitor. The Mechanism of Action (MOA) of DAXI includes blocking neuromuscular transmission by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting acetylcholine release. DAXI's biological activity is determined relative to a reference standard using a lethality dose response assay in mice (Mouse LD50 assay).

DAXI drug substance and drug product are manufactured at Revance Therapeutics, Inc (Newark, CA). (b) (4) For DAXI DS, the data provided in the BLA submission support an expiration dating period of (b) (4) months when stored at (b) (4) °C.

DAXI drug product manufacturing involves (b) (4) The container closure is a 2 mL (b) (4) clear (b) (4) glass vial with a gray (b) (4) rubber stopper and aluminum seal with a plastic flip ap. Daxxify (daxibotulinumtoxinA-lanm) for injection is supplied as a sterile, preservative-free, white to off-white lyophilized powder in a single-dose vial for intramuscular use after

reconstitution. Each DP vial contains 50 Units or 100 Units of daxibotulinumtoxinA-lanm, 0.14 mg of L-histidine, 0.65 mg L-histidine-HCl monohydrate, 12 µg RTP-004 peptide, 0.1 mg polysorbate 20, and 36 mg trehalose dihydrate. The lyophilized DP is reconstituted prior to patient administration using sterile preservative-free 0.9% Sodium Chloride Injection, USP (0.6 mL for 50 U/vial or 1.2 mL for 100 U/vial, respectively). For DAXI DP, the data provided in the BLA submission support an expiration dating period of 24 months for 50 U/vial and 12 months for 100 U/vial, when stored at 20˚C to 25˚C.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Joao Pedras-Vasconcelos	DBRR III/OBP/OPQ
Drug Product	Joao Pedras-Vasconcelos	DBRR III/OBP/OPQ
Immunogenicity	Joao Pedras-Vasconcelos	DBRR III/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Virginia Carroll (DS/DP)	DBM/OPMA/OPQ
Microbiology	Reyes Candau-Chacon (DS/DP)	DBM/OPMA/OPQ
Business Process Manager	Melinda Bauerlien	RBPMB I/OPRO/OPQ
Secondary Assessor for OBP	Susan Kirshner	DBRR III/OBP/OPQ
Microbiology Team Lead	Virginia Carol (DS/DP)	DBM/OPMA/OPQ
Application Team Lead	Susan Kirshner	DBRR III/OBP/OPQ

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Kimberle Searcy	DROII/ORO/OND
Cross-disciplinary Team Lead	Snezana Trajkovic	DDD/OII/OND
Medical Officer	Tong Li-Masters	DDD/OII/OND
Pharm/Tox	Jill Merrill and Barbara Hill	DPTII/OII/OND
Clinical Pharmacology	Da Zhang and Chinmay Shukla	DIIP/OCP/OTS
Statistics	Kathy Fritsch and Mohamed Alosh	DBIII/OB/OTS

1. Names:

a. Proprietary Name: Daxxify (proposed)
b. Trade Name: Daxxify (proposed)
c. Non-Proprietary Name/USAN: DaxibotulinumtoxinA (DAXI)
d. CAS Name: 93384-43-1
e. Common Name: DaxibotulinumtoxinA (DAXI)

f. INN Name: N/A
g. Compendial Name: N/A
h. OBP systematic name: PROT P0DPI1 (BXA1_CLOBH) BOTULINUM NEUROTOXIN TYPE A [RTT150]

i. Other names: RTT150, RT002

Submissions Reviewed in current round

Sequence Number (SN)	Document Date	Review Completed	OPQ Office
SN0046 (BLA CR submission)	03/08/2022	Yes	OBP, OPMA, and OND
SN0047	03/08/2022	Yes	OBP and OPMA
SN0048	03/22/2022	Yes	OBP, OPMA
SN0049	03/31/2022	Yes	OPMA
SN0050	05/09/2022	Yes	OPMA
SN0051	05/10/2022	Yes	OBP, OND, OCP, DMEPA and OPDP
SN0052	07/22/2022	Yes	OPMA
SN00053	08/29/2022	Yes	OBP

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Comments
(b) (4)	II		(b) (4)	3	N/A	Not reviewed. Sufficient information related to identity, purity, safety, and stability of the cell bank is provided in the BLA.
	III			2	N/A	No separate review performed. The pertinent DMF information was reviewed and found to be adequate by

						Dr. Scott Nichols on 06/26/2019. No revisions were made to the DMF since last review.
(b) (4)	III		(b) (4)	3	N/A	Not reviewed. Sufficient information related to compatibility with the product is provided in the BLA.
	III			3	N/A	

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

B. Other documents: N/A

3. Consults:

OBP requested a consult from ONDP regarding the RTP004 Synthetic Peptide Excipient used in final drug product formulation during the initial review cycle (see ONDP Quality Memo in Panorama) by Lawrence Perez. No additional ONDP consult was required during the resubmission cycle.

4. Environmental Assessment of Claim of Categorical Exclusion:

The Applicant requests a categorical exclusion from the requirement to prepare an environmental assessment under the provisions of 21 CFR 25.15(d) and 21 CFR 25.31(b). Of note, 21CFR 25.31(b) is not applicable to biological products and the Applicant should revise their claim of categorical exclusion to align with 21 CFR 25.31(c). A request to amend the categorical exclusion claim will be sent to the Applicant as an IR and the Applicant's response will be documented in an addendum to this memo.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval.

Currently, there are no product quality deficiencies or inspectional items resulting from the Pre-License Inspection that occurred July 11 to July 15, 2022, that preclude approval of this BLA.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: Revance Therapeutics, Inc., Newark, CA
- Drug Product:
  - Revance Therapeutics, Inc., Newark, CA (drug product manufacturing, release and stability testing except for osmolality, particulate matter, sterility, and container closure integrity testing)
  - (b) (4) (packaging and labeling of finished drug product)

- Fill size and dosage form – 50 or 100 Units of lyophilized powder in a single-dose vial for reconstitution

- Dating period:
  - Drug Product: 24 months for 50 U/vial; and 12 months for 100 U/vial; 20-25 °C
  - Drug Substance (b) (4) months (b) (4) °C

- Exempt from lot release
  - Daxxify is granted and exemption from the lot release requirement of 21 CFR 610.2 because the product is well characterized.

C. Benefit/Risk Considerations:

Daxxify (daxibotulinumtoxinA-lanm) is indicated for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients. The manufacturing process is sufficiently controlled to allow for safe use of the product under recommended conditions.

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

Two post-marketing commitments (PMCs) were agreed upon.

PMC 1:
To develop, validate, and implement an appropriate host cell protein (HCP) assay to monitor and control for Clostridium botulinum-derived process impurities in daxibotulinumtoxinA drug substance either as a release specification with adequate acceptance criteria or as an in-process test with appropriate rejection limits.

The current control strategy does not include HCP testing and HCP removal was not validated. Given the very low levels of drug administered this is not a safety issue. However, to better ensure manufacturing process consistency over time an enhanced HCP control strategy was agreed upon.

PMC 2:
To develop, validate, and implement an appropriate cell-based potency assay to replace the current in vivo mouse LD50 potency assay for the release and stability testing of daxibotulinumtoxinA drug substance and drug product

The current potency test requires the used of hundreds of animals for each lot. This PMC was agreed upon to promote the reduced use of animals for release testing. Cell based potency tests for botulinum toxins also have the benefit of being better controlled because, for example, cell based assays are not impacted by environmental factors such as animal feed and season.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to daxibotulinumtoxinA drug substance and drug product.

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

CQA	Risk	Origin	Control Strategy
Identity	Safety and Efficacy	Intrinsic to the molecule	(b) (4)
pH	General CQA	Formulation	

			(b) (4)
Relative Potency	Potency	Intrinsic to the molecule. Impacted by presence of high and low molecular weight species. Impacted by the DP manufacturing process, including formulation and lyophilization. Sensitive to prolonged exposure to high temperature and photo stress conditions	
(b) (4) **Content**	Potency	Entire process	
Aggregates (Product-related impurity)	Immunogenicity& Safety	Fermentation/manufacturing process	
Dimers (Product-related variant)	Immunogenicity& Safety	Fermentation/manufacturing process	
150 kDa Single Chain (Product-related impurity)	Potency	Fermentation/manufacturing process	
(b) (4) **oxidation (Product-related impurity)**	Potency	Entire process	
Deamidation (Product-related impurity)	Potency	Entire process	
N- & C-Terminal Heterogeneity (Product-related variants)	Potency	Fermentation	
Impurities: (b) (6) **(Product-related impurities)**	Potency	Fermentation	
Disulfide Confirmation	Potency, intrinsic to the molecule	Fermentation process.	

		No change is expected during DS storage through expiry	(b) (4)

B. Drug Substance [DaxibotulinumtoxinA] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

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

CQA	Risk	Origin	Control Strategy
Appearance	Immunogenicity & Safety	Entire process	(b) (4)
(b) (4) **(Process-related impurities)**	Immunogenicity & Safety	Fermentation process. No change is expected during DS storage through expiry	
(b) (4) **(Process-related impurities)**	Immunogenicity & Safety	Fermentation process. No change is expected during DS storage through expiry	
HCP (Process-related impurity)	Immunogenicity, Safety, and Purity (degradation or modification of the product by contaminating proteases)	Fermentation process. No change is expected during DS storage through expiry	

			(b) (4)
DNA (Process-related impurities)	Immunogenicity & Safety	Fermentation process. No change is expected during DS storage through expiry	
(b) (4) **(Process- mpurity)**	Immunogenicity & Safety	Process aid (b) (4)	
(b) (6) **(Process-related impurity)**	Immunogenicity & Safety	Process aid (b) (4)	
(b) (4) **(Process-related impurity)**	Immunogenicity & Safety	Process aid (b) (4)	

DAXI DS Concentration	Potency	Fermentation, step yields of unit operation	(b) (4)
Spores	Immunogenicity & Safety	Potentially sourced from the production strain	
Vegetative *Clostridium* bacteria	Immunogenicity& Safety	Sourced from the production strain	
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden introduced from raw materials and throughout the manufacturing process	
Endotoxin	Immunogenicity & Safety	Endotoxin introduced from raw materials and throughout the manufacturing process	

- Description:
  The active pharmaceutical ingredient (API) in Daxxify (daxibotulintoxinA/DAXI) is a purified type A neurotoxin with a molecular weight of 150 kDa and is produced by the anaerobic fermentation of the bacterium *Clostridium botulinum* type A. The neurotoxin is a dimeric molecule linked by disulfide bonds. The neurotoxin moiety is a 1296 amino acid dimer molecule consisting of a heavy chain (HC) and a light chain (LC) linked by a disulfide bond.

- Mechanism of Action (MoA):
  Daxxify is an acetylcholine release inhibitor. Daxxify 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 HC and LC chains. The HC mediates neuron-specific binding, up- take by receptor-mediated endocytosis and transport of 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 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 IM at therapeutic doses, Daxxify induces partial physico-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 Assay:
  The mouse lethal dose assay is used to assess product potency. The assay is conducted by administration of pre-established dilutions of daxibotulinumtoxinA into groups of female CD-1 mice. The number of deaths that occur at each dilution is measured over a 72 hr observation period. 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 can be wide inter-laboratory variability, precluding standardization of LD50 units between products. If this product is approved, a post marketing commitment for development and implementation of the cell-based potency assay will be issued.

- Reference Materials:
  The current DAXI DS reference material system is a two-tier system consisting of primary and working reference materials. (b) (4) .

(b) (4)

(b) (4)

- Critical starting materials or intermediates:
  The Applicant currently uses a two-tiered cell banking system consisting of a Master (MCB) and Working (WCB) cell banks. (b) (4)

- Manufacturing process summary:
  (b) (4)

- Container closure:
  The drug substance primary container closure system consists of (b) (4)

- Dating period and storage conditions:
  The data support an expiration dating period of (b) (4) months when stored at (b) (4) °C.

C. Drug Product [Daxxify] Quality Summary:

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

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

CQA	Risk	Origin	Control Strategy (b) (4)
Appearance	Immunogenicity & Safety	Entire process	
DAXI DP Concentration	Potency	DAXI DS content, DP formulation process	
Reconstitution Time	Immunogenicity, Safety, and Potency	Entire manufacturing process, including the lyophilization step	
Fill Volume	Safety, Potency	Filling process	
Moisture Content	Potency, product stability	Lyophilization, CCS	
Osmolality	General CQA (excipient)	Formulation	
Particulate Matter	General CQA (excipient)	Manufacturing process, CCS, and product on stability	
RTP004 concentration, purity	General CQA	Formulation	

			(b) (4)
and impurities (novel excipient)	(excipient)		
Polysorbate 20 Concentration	General CQA (excipient)	Formulation	
Trehalose Concentration	General CQA (excipient)	Formulation	
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden introduced from raw materials and throughout the manufacturing process	
Endotoxin	Immunogenicity, Safety, and Purity	Endotoxin introduced from raw materials and throughout the manufacturing process	
Sterility	Safety (infection), efficacy (degradation or modification of the product)	Contamination may be introduced throughout the DP manufacturing process, container closure failure	
Sterility/Container Closure Integrity	Safety (loss of sterility), efficacy (change in product strength due to evaporation or leakage)	Container closure breaches during manufacture and storage	

- Potency and Strength:
  Daxxify is supplied as 50 U or 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. For DP, potency is reported relative to the DP reference standard. The potency assay is the same as described in the DS section of this review memo.

- Summary of Product Design:
  Daxxify (daxibotulinumtoxinA-lanm) for injection is supplied as a sterile, preservative-free, white to off-white lyophilized powder in a single-dose vial for intramuscular use after reconstitution. The DP is supplied at two strengths; 50 U/vial and 100 U/vial. Each DP vial contains 50 Units or 100 Units of daxibotulinumtoxinA-lanm, 0.14 mg of L-histidine, 0.65 mg L-histidine-HCl monohydrate, 12 µg RTP-004 peptide, 36 mg trehalose dihydrate, and 0.1 mg polysorbate 20.

- List of Excipients:

Excipients include L-histidine, L-histidine-HCl monohydrate, RTP004 peptide, trehalose dihydrate, and polysorbate 20.

Novel Excipients:
The drug product is formulated with a novel 35-amino acid synthetic polypeptide, RTP004, that functions as a stabilizer in DAXI for injection. (b) (4)

- Reference Materials:
The DP reference standard system is a single-tier system (b) (4)

(b) (4)

- Manufacturing process summary:

(b) (4)

(b) (4)

- Container closure:
  The primary container closure for Daxxify consists of a single-dose, clear, 2-mL (b) (4) glass vial (b) (4) with a 13-mm Gray (b) (4) rubber (b) (4)) and aluminum seal with a plastic (b) (4)) flip-off cap (b) (4)

- Dating period and storage conditions:
  The dating period for Daxxify DP is 24 months for 50 U/vial and 12 months for 100 U/vial, when stored at 20˚C to 25˚C, protected from light.

D. Novel Approaches/Precedents: None.

E. Any Special Product Quality Labeling Recommendations:

Store unopened vials at room temperature 20°C to 25°C (68°F to 77°F) or 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 sterile Sodium Chloride 0.9% Injection USP (0.6 mL for 50 U/vial, 1.2 mL for 100 U/vial). 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 72 hours until the time of use and discard any remaining solution after administration. Do not freeze reconstituted product.

The label should be updated to include the following: Section 3.2.P.2.6 Compatibility states that the reconstituted solution in syringe must be stored at 2-8°C and used within (b) (4) hours post reconstitution. However, Section 2.3 Reconstitution of the current label does not specify a storage period for the filled syringe, and should be revised accordingly.

F. Establishment Information:

Overall Recommendation: Approval. The Agency conducted a second pre-approval inspection of Revance Therapeutics, Inc. located in Newark, CA (FEI 3007772056) from 07/11/2022 to 07/15/2022. Facility status was deemed VAI, with final recommendation of approval for the BLA					
DRUG SUBSTANCE					
Function	**Site Information**	**DUNS/FEI Number**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**

Manufacturer	Revance Therapeutics, Inc. 7555 Gateway Blvd. Newark, CA, USA, 94560	FEI 3007772056	Needs PLI	Yes	Approve
Tester	Revance Therapeutics, Inc. Bldg 261, Room 144 Moffett Boulevard, Moffett Field, CA 94035 (b) (4)	FEI Number: 3019604545	Needs PLI	No	Approve

DRUG PRODUCT

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacturer	Revance Therapeutics, Inc. 7555 Gateway Blvd. Newark, CA, USA, 94560	FEI 3007772056	Needs PLI	Yes	Approve
Tester	Revance Therapeutics, Inc. Bldg 261, Room 144 Moffett Boulevard, Moffett Field, CA 94035 (b) (4)	FEI Number: 3019604545	Needs PLI	No	Approve
Tester	(b) (4)		Approval based on previous history	N/A	Approve
Tester			Approval based on previous history	N/A	Approve
Tester			Approval based on previous history	N/A	Approve

Tester	(b) (4)		Approval based on previous history	N/A	Approve
Secondary Packaging			Approval based on previous history	N/A	Approve

G. Facilities:

Recommendation is Approval. The conducted a second pre-license inspection of the drug substance and drug product manufacturing facility, Revance Therapeutics, Inc., located in Newark, CA (FEI 3007772056).

The compliance recommendations for the other facilities described in section F, above, which are not inspected within scope of this BLA, are for approval.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols :
   1. Post-approval DS stability protocol
   2. MCB qualification protocol
   3. WCB qualification protocol
   4. RS qualification protocol

ii. Outstanding review issues/residual risk: Post marketing commitments were made to update the Host Cell Protein assay and to develop a cell-based potency assay.

iii. Future inspection points to consider: None.

b. Drug Product

i. Protocols:
   1. Post-approval DP stability protocol
   2. DP stability protocol for the extension of shelf-live

ii. Outstanding review issues/residual risk: A post-marketing commitment was made to develop a cell-based potency assay.
iii. Future inspection points to consider: None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUSAN L KIRSHNER
09/02/2022 05:51:25 PM

Recommendation: Pending

BLA STN 761127
Review Number: 1
Review Date: July 14, 2020

Drug Name/Dosage Form	DAXXIFY (daxibotulinumtoxinA-lanm)/for injection
Strength/Potency	50 U/vial and 100 U/vial; Mouse LD50 assay
Route of Administration	Intramuscular injection
Rx/OTC dispensed	Rx
Indication	For temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients
Applicant/Sponsor	Revance Therapeutics, Inc.

Product Overview

DaxibotulinumtoxinA (DAXI; RTT150) is a purified, 150 kDa botulinum neurotoxin serotype A (BoNT/A) isolated from cultures of the Gram-positive obligate anaerobic bacterium *Clostridium botulinum*. There are no accessory proteins (haemagglutinin, non-toxin non-haemagglutinin proteins) associated with DAXI. The purified product is a two-chain polypeptide with a 100 kDa heavy chain (HC) joined by a disulfide bond [Cys430-Cys454] to a 50 kDa light chain (LC).

DAXI is an acetylcholine release inhibitor. The Mechanism of Action (MOA) of DAXI includes blocking neuromuscular transmission by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting acetylcholine release. DAXI's biological activity is determined relative to a reference standard using a lethality dose response assay in mice (Mouse LD50 assay).

DAXI drug substance and drug product are manufactured at Revance Therapeutics, Inc (Newark, CA). (b) (4) . For DAXI DS, the data provided in the BLA submission support an expiration dating period of (b) (4) months when stored at (b) (4) °C.

DAXI drug product manufacturing involves (b) (4) The container closure is a 2 mL (b) (4) clear (b) (4) glass vial with a gray (b) (4) rubber stopper and aluminum seal with a plastic flip-off cap. Daxxify (daxibotulinumtoxinA-lanm) for injection is supplied as a sterile, preservative-free, white to off-white lyophilized powder in a single-dose vial for intramuscular use after

reconstitution. Each DP vial contains 50 Units or 100 Units of daxibotulinumtoxinA-lanm, 0.14 mg of L-histidine, 0.65 mg L-histidine-HCl monohydrate, 12 µg RTP-004 peptide, 0.1 mg polysorbate 20, and 36 mg trehalose dihydrate. The lyophilized DP is reconstituted prior to patient administration using sterile preservative-free 0.9% Sodium Chloride Injection, USP (0.6 mL for 50 U/vial or 1.2 mL for 100 U/vial, respectively). For DAXI DP, the data provided in the BLA submission support an expiration dating period of 24 months for 50 U/vial and (b) (4) months for 100 U/vial, when stored at 20˚C to 25˚C.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Joao Pedras-Vasconcelos	DBRR III/OBP/OPQ
Drug Product	Joao Pedras-Vasconcelos	DBRR III/OBP/OPQ
Immunogenicity	Joao Pedras-Vasconcelos	DBRR III/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
Facility	Viviana Matta (DS) and Virginia Carroll (DP)	DBM/OPMA/OPQ
Microbiology (DS)	Viviana Matta	DBM/OPMA/OPQ
Microbiology (DP)	Virginia Carroll	DBM/OPMA/OPQ
Novel Excipient (RTP004 peptide)	Lawrence Perez	ONDP/OPQ
Business Process Manager	Melinda Bauerlien	RBPMB I/OPRO/OPQ
Team Lead for OBP	Ramesh Potla	DBRR III/OBP/OPQ
Tertiary Reviewer for OBP	Susan Kirshner	DBRR III/OBP/OPQ
Microbiology Team Lead (DS)	Maxwell Van Tassell	DBM/OPMA/OPQ
Microbiology Team Lead (DP)	Reyes Candau-Chacon	DBM/OPMA/OPQ
Application Team Lead	Ramesh Potla	DBRR III/OBP/OPQ

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Kimberle Searcy	DROII/ORO/OND
Cross-disciplinary Team Lead	Snezana Trajkovic	DDD/OII/OND
Medical Officer	Tong Li-Masters	DDD/OII/OND
Pharm/Tox	Jill Merrill and Barbara Hill	DPTII/OII/OND
Clinical Pharmacology	Da Zhang and Chinmay Shukla	DIIP/OCP/OTS
Statistics	Kathy Fritsch and Mohamed Alosh	DBIII/OB/OTS

1. Names:

a. Proprietary Name: Daxxify (proposed)
b. Trade Name: Daxxify (proposed)
c. Non-Proprietary Name/USAN: DaxibotulinumtoxinA (DAXI)
d. CAS Name: 93384-43-1

e. Common Name: DaxibotulinumtoxinA (DAXI)

f. INN Name: N/A
g. Compendial Name: N/A
h. OBP systematic name: PROT P0DPI1 (BXA1_CLOBH) BOTULINUM NEUROTOXIN TYPE A [RTT150]
i. Other names: RTT150, RT002

Submissions Reviewed

Sequence Number (SN)	Document Date	Review Completed	OPQ Office
SN0001 (original BLA submission)	11/25/2019	Yes	OBP, OPMA, and ONDP
SN0002	12/20/2019	Yes	OBP and OPMA
SN0003	01/13/2020	Yes	OPMA
SN0004	01/16/2020	Yes	OPMA
SN0005	01/24/2020	Yes	OPMA
SN0008	02/20/2020	Yes	OPMA
SN0009	02/21/2020	Yes	OBP and OPMA
SN00012	05/01/2020	Yes	OPMA
SN00013	05/11/2020	Yes	OPMA
SN00015	06/10/2020	Yes	OPMA
SN00016	06/22/2020	Yes	OPMA
SN00017	07/08/2020	Yes	OPMA

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Comments
(b) (4)	II		(b) (4)	3	N/A	Not reviewed. Sufficient information related to identity, purity, safety, and stability of the cell bank is

						provided in the BLA.
(b) (4)	III		(b) (4)	2	N/A	No separate review performed. The pertinent DMF information was reviewed and found to be adequate by Dr. Scott Nichols on 06/26/2019. No revisions were made to the DMF since last review.
	III			3	N/A	Not reviewed. Sufficient information related to compatibility with the product is provided in the BLA.
	III			3	N/A	

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

B. Other documents: N/A

3. Consults: OBP requested a consult from ONDP regarding the RTP004 Synthetic Peptide Excipient used in final drug product formulation. See ONDP Quality Memo in Panorama by Lawrence Perez.

4. Environmental Assessment of Claim of Categorical Exclusion:
The Applicant requests a categorical exclusion from the requirement to prepare an environmental assessment under the provisions of 21 CFR 25.15(d) and 21 CFR 25.31(b). Of note, 21CFR 25.31(b) is not applicable to biological products and the Applicant should revise their claim of categorical exclusion to align with 21 CFR 25.31(c). A request to amend the categorical exclusion claim will be

sent to the Applicant as an IR and the Applicant's response will be documented in an addendum to this memo.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Pending.

Currently, there are no product quality deficiencies precluding approval of this BLA. However, a final recommendation regarding product quality is currently pending and will be made in an addendum to this report after satisfactory resolution of the following outstanding items:

1. A pre-license inspection of Revance Therapeutics, Inc., the drug substance and drug product manufacturing facility (Newark, CA; FEI: 3007772056), is required to verify that the firm's manufacturing operations are in compliance with cGMPs and that the product quality data submitted to the daxibotulinumtoxinA BLA are accurate, reliable, and complete. This facility has never been inspected by the FDA before.

2. Applicant responses to all outstanding information requests (IRs). The Applicant is expected to provide a response to the following IR comments by the end of September 2020:

(b) (4)

Additional Information Requests (IR) will be sent to the Applicant to address pending review issues and an assessment of Applicant's IR response will be documented in the addendum to this report once all outstanding information has been reviewed.

3. Updates to the BLA reflecting all changes made in response to FDA product quality information requests.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: Revance Therapeutics, Inc., Newark, CA
- Drug Product:
  - Revance Therapeutics, Inc., Newark, CA (drug product manufacturing, release and stability testing except for osmolality, particulate matter, sterility, and container closure integrity testing)
  - (b) (4) (packaging and labeling of finished drug product)

- Fill size and dosage form – 50 or 100 Units of lyophilized powder in a single-dose vial for reconstitution

- Dating period:
  - Drug Product: 24 months for 50 U/vial; and (b) (4) months for 100 U/vial; 20-25 °C
  - Drug Substance: (b) (4) months; ≤ (b) (4) °C

- Exempt from lot release
  - No, Daxxify is a non-specified biological product and should be on lot release per 21 CFR 610.2. An IR will be sent to the Applicant to submit a request for exemption from lot release.

C. Benefit/Risk Considerations:

Daxxify (daxibotulinumtoxinA-lanm) is indicated for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients.

A review of benefit-risk assessment will be documented in the addendum to this report once all outstanding information has been reviewed.

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

Potential post marketing commitments/requirements will be documented in the addendum to this report once all outstanding information has been reviewed.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and their control strategies that are relevant to daxibotulinumtoxinA drug substance and drug product.

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

CQA	Risk	Origin	Control Strategy
Identity	Safety and Efficacy	Intrinsic to the molecule	(b) (4)
pH	General CQA	Formulation	
Relative Potency	Potency	Intrinsic to the molecule. Impacted by presence of high and low molecular weight species. Impacted by the DP manufacturing process, including formulation and lyophilization. Sensitive to prolonged exposure to high temperature and photo stress conditions	
(b) (4) **Content**	Potency	Entire process	
Aggregates (Product-related impurity)	Immunogenicity& Safety	Fermentation/manufacturing process	
Dimers (Product-related variant)	Immunogenicity& Safety	Fermentation/manufacturing process	
150 kDa Single Chain (Product-related impurity)	Potency	Fermentation/manufacturing process	
(b) (4)	Potency	Entire process	

oxidation (Product-related impurity)			(b) (4)
Deamidation (Product-related impurity)	Potency	Entire process	
N- & C-Terminal Heterogeneity (Product-related variants)	Potency	Fermentation	
Impurities: (b) (4) **(Product-related impurities)**	Potency	Fermentation	
Disulfide Confirmation	Potency, intrinsic to the molecule	Fermentation process. No change is expected during DS storage through expiry	

B. Drug Substance [DaxibotulinumtoxinA] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

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

CQA	Risk	Origin	Control Strategy
Appearance	Immunogenicity & Safety	Entire process	(b) (4)
(b) (4) **(Process-related impurities)**	Immunogenicity & Safety	Fermentation process. No change is expected during DS storage through expiry	

(b) (4) **(Process-related impurities)**	Immunogenicity & Safety	Fermentation process. No change is expected during DS storage through expiry
HCP (Process-related impurity)	Immunogenicity, Safety, and Purity (degradation or modification of the product by contaminating proteases)	Fermentation process. No change is expected during DS storage through expiry
DNA (Process-related impurities)	Immunogenicity & Safety	Fermentation process. No change is expected during DS storage through expiry
(b) (4) **(Process-related impurity)**	Immunogenicity & Safety	Process aid (b) (4)
(b) (4) **(Process-related impurity)**	Immunogenicity & Safety	Process aid (b) (4)

(b) (4)

(b) (4) **(Process-related impurity)**	Immunogenicity & Safety	Process aid (b) (4)
DAXI DS Concentration	Potency	Fermentation, step yields of unit operation
Spores	Immunogenicity & Safety	Potentially sourced from the production strain
Vegetative *Clostridium* bacteria	Immunogenicity& Safety	Sourced from the production strain
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden introduced from raw materials and throughout the manufacturing process
Endotoxin	Immunogenicity & Safety	Endotoxin introduced from raw materials and throughout the manufacturing process

(b) (4)

- Description:
  The active pharmaceutical ingredient (API) in Daxxify (daxibotulintoxinA/DAXI) is a purified type A neurotoxin with a molecular weight of 150 kDa and is produced by the anaerobic fermentation of the bacterium *Clostridium botulinum* type A. The neurotoxin is a dimeric molecule linked by disulfide bonds. The neurotoxin moiety is a 1296 amino acid dimer molecule consisting of a heavy chain (HC) and a light chain (LC) linked by a disulfide bond.

- Mechanism of Action (MoA):
  Daxxify is an acetylcholine release inhibitor. Daxxify 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 HC and LC chains. The HC mediates neuron-specific binding, up- take by receptor-mediated endocytosis and transport of 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 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 IM at therapeutic doses, Daxxify induces partial physico-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 Assay:
  The mouse lethal dose assay is used to assess product potency. The assay is conducted by administration of pre-established dilutions of daxibotulinumtoxinA into groups of female CD-1 mice. The number of deaths that occur at each dilution is measured over a 72 hr observation period. 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 can be wide inter-laboratory variability, precluding standardization of LD50 units between products. If this product is approved, a post marketing commitment for development and implementation of the cell-based potency assay will be issued.

- Reference Materials:
  The current DAXI DS reference material system is a two-tier system consisting of primary and working reference materials. (b) (4)

  (b) (4)

- Critical starting materials or intermediates:
  The Applicant currently uses a two-tiered cell banking system consisting of a Master (MCB) and Working (WCB) cell banks. (b) (4)

- Manufacturing process summary:

  (b) (4)

(b) (4)

- Container closure:
  The drug substance primary container closure system consists of (b) (4)

- Dating period and storage conditions:
  The data support an expiration dating period of (b) (4) months when stored at (b) (4) °C.

C. Drug Product [Daxxify] Quality Summary:

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

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

CQA	Risk	Origin	Control Strategy
Appearance	Immunogenicity & Safety	Entire process	(b) (4)
DAXI DP Concentration	Potency	DAXI DS content, DP formulation process	
Reconstitution Time	Immunogenicity, Safety, and Potency	Entire manufacturing process, including the lyophilization step	

			compliance with USP <631>, Ph. Eur. 2.2.1, Ph. Eur. 2.2.2.
Fill Volume	Safety, Potency	Filling process	(b) (4)
Moisture Content	Potency, product stability	Lyophilization, CCS	
Osmolality	General CQA (excipient)	Formulation	
Particulate Matter	General CQA (excipient)	Manufacturing process, CCS, and product on stability	
RTP004 concentration, purity and impurities (novel excipient)	General CQA (excipient)	Formulation	
Polysorbate 20 Concentration	General CQA (excipient)	Formulation	
Trehalose Concentration	General CQA (excipient)	Formulation	
Bioburden	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden introduced from raw materials and throughout the manufacturing process	
Endotoxin	Immunogenicity, Safety, and Purity	Endotoxin introduced from raw materials and throughout the manufacturing process	
Sterility	Safety (infection), efficacy (degradation or modification of the product)	Contamination may be introduced throughout the DP manufacturing process, container closure failure	
Sterility/Container Closure Integrity	Safety (loss of sterility), efficacy (change in product strength due to evaporation or leakage)	Container closure breaches during manufacture and storage	

- Potency and Strength:

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

- Summary of Product Design:
  Daxxify (daxibotulinumtoxinA-lanm) for injection is supplied as a sterile, preservative-free, white to off-white lyophilized powder in a single-dose vial for intramuscular use after reconstitution. The DP is supplied at two strengths; 50 U/vial and 100 U/vial. Each DP vial contains 50 Units or 100 Units of daxibotulinumtoxinA-lanm, 0.14 mg of L-histidine, 0.65 mg L-histidine-HCl monohydrate, 12 µg RTP-004 peptide, 36 mg trehalose dihydrate, and 0.1 mg polysorbate 20.

- List of Excipients:
  Excipients include L-histidine, L-histidine-HCl monohydrate, RTP004 peptide, trehalose dihydrate, and polysorbate 20.

  Novel Excipients:
  The drug product is formulated with a novel 35-amino acid synthetic polypeptide, RTP004, that functions as a stabilizer in DAXI for injection. (b) (4)

- Reference Materials:
  The DP reference standard system is a single-tier system (b) (4) .

(b) (4)

(b) (4)

- Manufacturing process summary:

(b) (4)

- Container closure:
  The primary container closure for Daxxify consists of a single-dose, clear, 2-mL (b) (4) glass vial with (b) (4) coating (b) (4) with a 13-mm Gray (b) (4) rubber (b) (4) and aluminum seal with a plastic (b) (4) flip-off cap (b) (4)

- Dating period and storage conditions:
  The dating period for Daxxify DP is 24 months for 50 U/vial and (b) (4) months for 100 U/vial, when stored at 20˚C to 25˚C, protected from light.

D. Novel Approaches/Precedents: None.

E. Any Special Product Quality Labeling Recommendations:

Store unopened vials at room temperature 20°C to 25°C (68°F to 77°F) or 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 sterile Sodium Chloride 0.9% Injection USP (0.6 mL for 50 U/vial, 1.2 mL for 100 U/vial). 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 72 hours until the time of use and discard any remaining solution after administration. Do not freeze reconstituted product.

The label should be updated to include the following: Section 3.2.P.2.6 Compatibility states that the reconstituted solution in syringe must be stored at 2-8°C and used within (b) (4) hours post reconstitution. However, Section 2.3 Reconstitution of the current label does not specify a storage period for the filled syringe, and should be revised accordingly.

F. Establishment Information:

Overall Recommendation: Pending. The Agency was unable to conduct a pre-approval inspection of Revance Therapeutics, Inc. located in Newark, CA (FEI 3007772056) prior to the User Fee date (11/25/2020) due to extenuating circumstances, i.e. travel restrictions.

DRUG SUBSTANCE

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacturer	Revance Therapeutics, Inc. 7555 Gateway Blvd. Newark, CA, USA, 94560	FEI 3007772056	Needs PLI	N/A	Pending PLI

DRUG PRODUCT

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacturer	Revance Therapeutics, Inc. 7555 Gateway Blvd. Newark, CA, USA, 94560	FEI 3007772056	Needs PLI	N/A	Pending PLI
Tester	(b) (4)		Approval based on previous history	N/A	Approve
Tester			Approval based on previous history	N/A	Approve
Tester			Approval based on previous history	N/A	Approve
Tester			Approval based on previous history	N/A	Approve

	(b) (4)				
Secondary Packaging		(b) (4)	Approval based on previous history	N/A	Approve

G. Facilities:

Recommendation is pending. The Agency was unable to conduct a pre-license inspection of the drug substance and drug product manufacturing facility, Revance Therapeutics, Inc., located in Newark, CA (FEI 3007772056), due to travel restrictions.

The compliance recommendations for the other facilities described in section F, above, which are not inspected within scope of this BLA, are for approval.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols :
   1. Post-approval DS stability protocol

ii. Outstanding review issues/residual risk: See "Recommendation" section for outstanding review issues.

iii. Future inspection points to consider: A pre-license inspection of Revance Therapeutics, Inc., the manufacturing facility for doxibotulinumtoxinA drug substance and drug product, is required before the application can be approved as the FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to COVID-19 related U.S. Government and Agency-wide travel restrictions, we will be unable to conduct an inspection of the Revance facility until the restriction is lifted.

b. Drug Product

i. Protocols:
   1. Post-approval DP stability protocol

ii. Outstanding review issues/residual risk: See "Recommendation" section for outstanding review issues.

iii. Future inspection points to consider: See the inspectional issues listed under "Drug Substance" section above.

Ramesh Potla

Digitally signed by Ramesh Potla
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Susan Kirshner

Digitally signed by Susan Kirshner
Date: 7/19/2020 12:53:48PM
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