CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761085Orig1s000

<u>OTHER REVIEW(S)</u>

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date of review:	February 4, 2019
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Davinna Ligons, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research III
Application:	BLA 761085
Applicant:	Evolus, Inc
Submission Date:	August 2, 2018
Product:	Jeuveau (prabotulinumtoxinA-xvfs)
Dosage form(s):	for injection
Strength and Container-Closure:	100 Units/vial in a single-dose vial
Purpose of review:	The Applicant submitted a biologics license application for Agency review
Recommendations:	The prescribing information (submitted on January 30, 2019), and Medication Guide, container labels and carton labeling (submitted on January 28, 2019) were reviewed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this review

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B). The prescribing information, medication guide, container labels, and carton labeling were reviewed and found to comply with relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100, 21 CFR 208.20(a)(7), 21 CFR 208.20(a)(7)).

The prescribing information (submitted on January 30, 2019), and Medication Guide, container labels and carton labeling (submitted on January 28, 2019) were reviewed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

(b) (4)

2 Pages have been Withheld in Full as Draft Labeling Immediately Following this Page

Container[4] Label Evaluation

Proper Name *(for container of a product capable of bearing a full label)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form below the proper name):	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Ensure that the suffix is applied to the proper name. *The applicant revised as requested*	
Manufacturer name, address, and license number *(for container of a product capable of bearing a full label)*	**Acceptable**
21 CFR 610.60 (a)(2), 21 CFR 201, 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: The applicant written on Form FDA 356h is the licensed applicant, licensed manufacturer, or manufacturer. Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h. Revise the manufacturer statement as follows: Manufactured by: Evolus, Inc. Santa Barbara, California US License No. xxxx *The applicant revised as requested* Clarify the role of Daewoong Pharmaceuticals. If this is the distributor, marketer or drug product facility, then the distributor's or marketer's name and address may also be included using the appropriate clarifying phrase (e.g., "Distributed by" or "Marketed by") (see 21 CFR 610.64) or the drug product facility should appear as: at Drug Product Facility Name Address *The applicant revised as requested*	
Lot number or other lot identification *(container capable of bearing a full label shall bear)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Expiration date *(container capable of bearing a full label shall bear)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Product Strength	**Acceptable**

[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs): *Reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Multiple dose containers *(recommended individual dose)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.55	☐ Yes ☐ No ☒ N/A
Statement: "Rx only"	**Acceptable**
21 CFR 610.60, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Medication Guide	**Acceptable**
21 CFR 610.60, 21 CFR 208.24	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *see carton*	
No Package for container	**Acceptable**
21 CFR 610.60	☐ Yes ☐ No ☒ N/A
Proper Name *(for container bearing a partial label)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.10	☐ Yes ☐ No ☒ N/A
Manufacturer name, address, and license number (*for container bearing a partial label)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.10	☐ Yes ☐ No ☒ N/A
Lot number or other lot identification (*for container bearing a partial label)*	**Acceptable**
21 CFR 610.60, 21 CFR 201.10	☐ Yes ☐ No ☒ N/A
Expiration date (*for container bearing a partial label)*	**Acceptable**
21 CFR 201.17	☐ Yes ☐ No ☒ N/A
No container label	**Acceptable**

21 CFR 610.60	☐ Yes ☐ No ☒ N/A
<u>Ferrule and cap overseal</u> *<u>(for vials only)</u>*	**<u>Acceptable</u>**
Recommended labeling practices: *United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals)*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: FOR VIALS: Confirm there is no text on the ferrule and cap overseal of the vials. *Applicants response: Evolus confirms that in accordance with USP<7>, text is not included on the top surface of the ferrule or the cap over seal for JEUVEAU. USP<7> also indicates "Other statements or features including, but not limited to, identifying numbers or letters, such as code numbers, lot numbers, company names, logos, or product names, etc., may appear* ***on the side (skirt) surface*** *of the ferrule on vials containing injectable products,* ***but not on the top****" The only text included on the ferrule or cap overseal for JEUVEAU the manufacturing NO. on the side of the ferrule.* *OBP labeling finds this response acceptable.*	
<u>Visual inspection</u> *<u>(for vials only)</u>*	**<u>Acceptable</u>**
21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: FOR VIALS: Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e). *Applicant confirmed*	
<u>NDC numbers</u>	**<u>Acceptable</u>**
21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A
<u>Route of administration</u>	**<u>Acceptable</u>**
21 CFR 201.5, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: route of administration statement to appear after the strength statement on the principal display panel	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider relocating the route of administration statement to appear on the principal display panel underneath the strength statement as follows:

proper name
Proprietary name
for injection
100 units/vial
For Intramuscular Use

The applicant revised as requested

Preparation instructions	**Acceptable**
21 CFR 201.5	☐ Yes ☐ No ☒ N/A

Package type term	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. USP chapter <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The appropriate package-type term for this product is "single-dose". Include the statement "Discard unused portion." A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose.
Remove the term [redacted] (b) (4) and add the statement "Discard unused portion." to appear after the package type term "Single Dose Vial"

The applicant revised as requested

Misleading statements	**Acceptable**
21 CFR 201.6	☐ Yes ☐ No ☒ N/A
Prominence of required label statements	**Acceptable**
21 CFR 201.15	☐ Yes ☐ No ☒ N/A
Spanish-language (Drugs)	**Acceptable**
21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6	**Acceptable**
21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Phenylalanine as a component of aspartame	**Acceptable**

21 CFR 201.21	☐ Yes ☐ No ☒ N/A
Sulfites; required warning statements	**Acceptable**
21 CFR 201.22	☐ Yes ☐ No ☒ N/A
Bar code label requirements	**Acceptable**
21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	**Acceptable**
21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
Net quantity	**Acceptable**
21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Usual dosage statement	**Acceptable**
21 CFR 201.55, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Inactive ingredients	**Acceptable**
21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: see carton	
Recommended labeling practices: USP General Chapters <1091> Labeling of Inactive Ingredients	☐ Yes ☐ No ☒ N/A
Storage requirements	**Acceptable**
Recommended labeling practices: *USP General Chapters <7> Labeling* *USP General Chapters <659> Packaging and Storage Requirements*	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: see carton	
Dispensing container	**Acceptable**
21 CFR 201.100	☐ Yes ☐ No ☒ N/A

Package[5] Label Evaluation

Proper name	Acceptable
21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Ensure that the suffix is applied to the proper name. *The applicant revised as requested*	
Manufacturer name, address, and license number	**Acceptable**
21 CFR 610.61, 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: The applicant written on Form FDA 356h is the licensed applicant, licensed manufacturer, or manufacturer. Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h. Revise the manufacturer statement as follows: Manufactured by: Evolus, Inc. Santa Barbara, California US License No. xxxx *The applicant revised as requested* Clarify the role of Daewoong Pharmaceuticals. If this is the distributor, marketer or drug product facility, then the distributor's or marketer's name and address may also be included using the appropriate clarifying phrase (e.g., "Distributed by" or "Marketed by") (see 21 CFR 610.64) or the drug product facility should appear as: at Drug Product Facility Name Address *The applicant revised as requested*	
Lot number or other lot identification	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Expiration date	**Acceptable**
21 CFR 610.61, 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Preservative	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Number of containers	**Acceptable**

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

21 CFR 610.61	☐ Yes ☐ No ☒ N/A
Strength/volume	**Acceptable**
21 CFR 610.61, 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Storage temperature/requirements	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: USP General Chapters: <7> Labeling	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the storage statement [redacted] (b) (4) [redacted] (b) (4) to read as follows: "Store unopened vial refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. DO NOT FREEZE." *The applicant revised as requested*	
Handling: "Do Not Shake", "Do not Freeze" or equivalent	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: see comment for preparation instructions below	
Multiple dose containers (recommended individual dose)	**Acceptable**
21 CFR 610.61	☐ Yes ☐ No ☒ N/A
Route of administration	**Acceptable**
21 CFR 610.61, 21 CFR 201.5, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement recommended locations):	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Consider relocating the route of administration statement to appear on the principal display panel underneath the strength statement as follows: proper name Proprietary name for injection 100 units/vial For Intramuscular Use *The applicant revised as requested*	
Known sensitizing substances	**Acceptable**
21 CFR 610.61	☐ Yes

	☐ No ☒ N/A
Inactive ingredients	**Acceptable**
21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: *USP General Chapters <1091> Labeling of Inactive Ingredients* *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise (b) (4) (b) (4) to read as follows: "Each vial of Jeuveau (prabotulinumtoxinA-xvfs) contains 100 Units of botulinum toxin type A neurotoxin complex, human serum albumin (0.5 mg), and sodium chloride (0.9 mg)." for consistency with the prescribing information. *The applicant revised as requested*	
Source of the product	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *see ingredient list*	
Minimum potency of product	**Acceptable**
21 CFR 610.61	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Add the following statement to the side panel that includes the ingredient list "No U.S. standard of potency" per 21 CFR 610.61(r). *The applicant revised as requested*	
Rx only	**Acceptable**
21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Divided manufacturing	**Acceptable**
21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A
Distributor	**Acceptable**
21 CFR 610.64 (Name and address of distributor)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *see comment under manufacturer*	
Bar code	**Acceptable**
21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	**Acceptable**

21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
NDC numbers	**Acceptable**
21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A
Preparation instructions	**Acceptable**
21 CFR 201.5 *Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the reconstitution information to read as follows: "Reconstitute each vial with only sterile, preservative-free 0.9% Sodium Chloride Injection, USP by slowly injecting diluent and gently rotating the vial. Store unused reconstituted JEUVEAU refrigerated between 2° to 8°C (36°F to 46°F) in the original carton to protect from light for up to 24 hours until time of use. Do not freeze reconstituted JEUVEAU. Discard 24 hours after reconstitution." *The applicant revised as requested*	
Package type term	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. USP chapter <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Remove the term (b) (4) and add the statement "Single-Dose Vial. Discard unused portion." *The applicant revised as requested*	
Misleading statements	**Acceptable**
21 CFR 201.6	☐ Yes ☐ No ☒ N/A
Prominence of required label statements	**Acceptable**
21 CFR 201.15	✓ Yes ☐ No ☐ N/A
Spanish-language (Drugs)	**Acceptable**
21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6	**Acceptable**
21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Phenylalanine as a component of aspartame	**Acceptable**

21 CFR 201.21	☐ Yes ☐ No ☒ N/A
Sulfites; required warning statements	**Acceptable**
21 CFR 201.22	☐ Yes ☐ No ☒ N/A
Net quantity	**Acceptable**
21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Usual dosage statement	**Acceptable**
21 CFR 201.55, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Dispensing container	**Acceptable**
21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Medication Guide	**Acceptable**
21 CFR 610.60, 21 CFR 208.24	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the medication guide statement to read as follows: **"ATTENTION: Dispense the enclosed Medication Guide to each patient"** *The applicant revised as requested*	

Prescribing Information and Patient Labeling Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
DOSAGE AND ADMINISTRATION	**Acceptable**
21 CFR 201.57(a)(7)	✓ Yes ☐ No ☐ N/A
DOSAGE FORMS AND STRENGTHS	**Acceptable**
21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: *Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* *USP chapter <659> Packaging and Storage Requirements* *Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We deleted [redacted] (b) (4) since the reconstitution information is not required for this section. The reconstitution information is provided in the full prescribing information section 2 (Dosage and Administration) *The applicant revised as requested* The appropriate package-type term for this product is "single-dose". *The applicant revised as requested*	
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
21 CFR 201.57(c)(3)(iv)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We clarified the storage conditions for stability of the reconstituted drug by adding the following: "..between 2° to 8°C (36°F to 46°F) in the original carton to protect from light for up to 24 hours until time of use". *The applicant revised as requested* We relocated the statement "Do not freeze reconstituted Jeuveau" to appear with the other storage statements	

The applicant revised as requested	
Recommended labeling practices: *USP nomenclature for diluents and intravenous solutions*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised to ensure the name of the diluent aligns with USP nomenclature: "0.9% Sodium Chloride Injection, USP" *The applicant revised as requested*	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: *Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* *USP General Chapters <659>, USP General Chapters <7>*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised to the appropriate package-type term *The applicant revised as requested*	
11 DESCRIPTION	**Acceptable**
21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We added the pharmacological class per 21 CFR 201.57(c)(12) "acetylcholine release inhibitor and a neuromuscular blocking agent". *The applicant revised as requested*	
Recommended labeling practices: *USP General Chapters <1091>, USP General Chapters <7>*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We deleted [redacted] (b) (4) from the first paragraph since this paragraph discusses the drug substance. *The applicant revised as requested* We relocated the dosage form to the last paragraph for readability *The applicant revised as requested*	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised the how supplied statement to include the proper name, identifying characteristics, and dosage form per 21 CFR 201.57(c)(17). *The applicant revised as requested*	
Recommended labeling practices (placement of detailed storage conditions for reconstituted and diluted products):	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised to the appropriate package-type term.
The applicant revised as requested

We deleted [redacted] (b) (4) Only describe and list products for sale. *The applicant revised as requested*

We deleted [redacted] (b) (4) (b) (4) (b) (4). *The applicant revised as requested*

We deleted [redacted] (b) (4) (b) (4) (b) (4). *The applicant revised as requested*

MANUFACTURER INFORMATION	**Acceptable**
21 CFR 610.61, 21 CFR 610.64, 21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Per 21 CFR 610.61(b) Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h, Use the phrase "Manufactured by.", and include the license number as follows:

Applicant on Form FDA 356h
Address
US License No. xxxx

The applicant revised as requested

Recommended labeling practices:	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Clarify the role of Daewoong Pharmaceuticals. If this is the distributor or marketer, then the distributor's or marketer's name and address may also be included (e.g., "Distributed by" or "Marketed by") (see 21 CFR 610.64)
We find it acceptable that the applicant revised to appear consistent with the carton labeling as:

at
Drug Product Facility Name
Address

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices (ensure consistency with prescribing information):	☐ Yes ☐ No ☒ N/A
INGREDIENTS	**Acceptable**

Recommended labeling practices: *USP General Chapters <1091>: Labeling of inactive ingredients in alphabetical order*	✓ Yes ☐ No ☐ N/A
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 610.61, 21 CFR 610.64, 21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Per 21 CFR 610.61(b) Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h, Use the phrase "Manufactured by.", and include the license number as follows: Applicant on Form FDA 356h Address US License No. xxxx *The applicant revised as requested*	

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on January 30, 2019 \\cdsesub1\evsprod\bla761085\0049\m1\us\packageinsert.pdf)

Medication Guide (submitted on January 28,2019 \\cdsesub1\evsprod\bla761085\0047\m1\us\medicationguide.pdf)

(b) (4)

Carton Labeling (submitted on January 28, 2019)

(b) (4)

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
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Davinna Ligons

Digitally signed by Davinna Ligons
Date: 2/05/2019 09:23:32AM
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 15, 2019
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	JEUVEAU (prabotulinumtoxinA-xvfs)
Dosage Form and Route:	For injection, for intramuscular use
Application Type/Number:	BLA 761085
Applicant:	Evolus, Inc.

1 INTRODUCTION

On August 2, 2018, Evolus, Inc., re-submitted for the Agency's review an original New Drug Application (NDA) for JEUVEAU (prabotulinumtoxinA-xvfs), for injection, for intramuscular use, for the proposed indication of the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on August 8, 2018 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for JEUVEAU (prabotulinumtoxinA-xvfs), for injection, for intramuscular use.

2 MATERIAL REVIEWED

- Draft JEUVEAU (prabotulinumtoxinA-xvfs) MG received on August 2, 2018 and received by DMPP and OPDP on January 7, 2019.
- Draft JEUVEAU (prabotulinumtoxinA-xvfs) Prescribing Information (PI) received on August 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 7, 2019.

3 REVIEW METHODS

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
01/15/2019 01:27:53 PM

LAURIE J BUONACCORSI
01/15/2019 01:45:19 PM

LASHAWN M GRIFFITHS
01/15/2019 01:48:30 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 14, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761085
Product Name and Strength:	Jeuveau (prabotulinumtoxinA-xvfs) For Injection 100 Units/vial
Applicant/Sponsor Name:	Evolus, Inc.
FDA Received Date:	January 9, 2019
OSE RCM #:	2017-1159-2
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader (acting):	Teresa McMillan, PharmD

1 PURPOSE OF MEMORANDUM

Division of Dermatology and Dental Products (DDDP) requested that we review the revised container label, carton labeling, Prescribing Information (PI), and Medication Guide (MG) for Jeuveau (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label, carton labeling, PI, and MG for Jeuveau is acceptable from a medication error perspective. We have no further recommendations at this time.

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[a] Patel M. Label and Labeling Review for JEUVEAU (prabotulinumtoxinA-xvfs) (BLA 761085). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 17. RCM No.: 2017-1159-1.

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/s/

MADHURI R PATEL
01/14/2019 03:17:08 PM

TERESA S MCMILLAN
01/14/2019 03:20:38 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date:	January 9, 2019
To:	Gary Chiang, M.D., Clinical Reviewer, Division of Dermatology and Dental Products (DDDP) Matthew White, Regulatory Project Manager, (DDDP) Barbara Gould, Regulatory Project Manager, (DDDP) Nancy Xu, Associate Director for Labeling, (DDDP)
From:	Laurie Buonaccorsi, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)
CC:	Matthew Falter, Team Leader, OPDP
Subject:	OPDP Labeling Comments for JEUVEAU (prabotulinumtoxinA-xvfs) for injection, for intramuscular use
BLA:	761085

In response to DDDP's consult request dated August 8, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for JEUVEAU (prabotulinumtoxinA-xvfs) for injection, for intramuscular use (Jeuveau).

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDDP on January 7, 2019, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DDDP on January 8, 2019, and our comments are provided below and on the attached label.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

Carton and Container Labeling Comments

Per 21 CFR 201.10(a), the established name should be together with the proprietary name, without any intervening matter. The proposed carton label contains significant whitespace between the established and proprietary names, which gives the appearance of separation. Also, the graphic symbol placement between the two names is intervening matter. We recommend reducing the whitespace between the established and proprietary names. We also recommend placing the graphic symbol after the proprietary name so that it does not separate the established and proprietary names. Please also apply these comments to the vial label.

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/s/

LAURIE J BUONACCORSI
01/09/2019 02:35:46 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 17, 2018
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761085
Product Name and Strength:	Jeuveau (prabotulinumtoxinA-xvfs) For Injection 100 Units/vial
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Evolus Inc.
FDA Received Date:	August 2, 2018 and November 21, 2018
OSE RCM #:	2017-1159-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader (acting):	Teresa McMillan, PharmD

1 PURPOSE OF REVIEW

This review evaluates the proposed labels and labeling for Jeuveau (prabotulinumtoxinA-xvfs) for injection (BLA 761085) to identify areas of vulnerability that may lead to medication errors. The Division of Dermatology and Dental Products (DDDP) requested this review as part of their evaluation of the 351(a) application for Jeuveau submitted by Evolus Inc on August 2, 2018 and updated container label and carton labeling on November 21, 2018.

2 REGULATORY HISTORY

We previously reviewed the labels and labeling for BLA 761085[a]. However, BLA 761085 received a Complete Response (CR) letter on May 15, 2018[b]. Thus, Evolus submitted a Class 2 Resubmission on August 2, 2018.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted labels and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

---

[a] Mena-Grillasca C. Label Labeling and Packaging Review for Jeuveau (prabotulinumtoxinA-xxxx). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 22. RCM No.: 2017-1159.

[b] Beitz, J. Complete Response (BLA 761085). Silver Spring (MD): FDA, CDER, OND, DDDP (US); 2018 MAY 15.

Table 2: Identified Issues and Recommendations for Division of Dermatology and Dental Products (DDDP)

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			
1.	The nonproprietary name, prabotulinumtoxinA-xvfs, was found conditionally acceptable, but is not reflected in the labels and labeling.	The labels and labeling should contain the correct nonproprietary name for identification of the product and to minimize wrong drug errors.	Revise the nonproprietary name to read 'prabotulinumtoxinA-xvfs on all labels and labeling.
Highlights of Prescribing Information			
1.	Under "Dosage Forms and Strengths", we note the use of the term (b) (4). However, we note the carton labeling and container label uses the term (b) (4).	Inclusion of consistent and correct package type term helps to minimize the risk of wrong administration technique errors.	We defer to the Office of Pharmaceutical Quality (OPQ), for the final determination of the package type term.
Full Prescribing Information			
1.	Under "Dosage and Administration", "Dosage Forms and Strengths", and "How Supplied" sections, we note the use of the term (b) (4). However, we note the carton labeling and container label uses the term (b) (4)	Inclusion of consistent and correct package type term helps to minimize the risk of wrong administration technique errors.	We defer to the Office of Pharmaceutical Quality (OPQ), for the final determination of the package type term.

Table 3: Identified Issues and Recommendations for Evolus, Inc. (entire table to be conveyed to Applicant)

Container Labels			
1.	Dosage information states [redacted] (b) (4) [redacted] (b) (4)	The term [redacted] (b) (4) could lead to confusion since the document is titled as “Prescribing Information”.	Revise the statement [redacted] (b) (4) [redacted] (b) (4) to “See Prescribing Information”.
Carton Labeling			
1.	The nonproprietary name lacks prominence commensurate with the proprietary name.	According to 21 CFR 610.62, the point size and typeface of the proper name is at least as prominent as the point size and type face of the proprietary name.	Ensure that the point size and typeface of the proper name is at least as prominent as the point size and type face of the proprietary name (see 21 CFR 610.62). You can achieve this by either increasing the size of the proper name or reducing the size of the proprietary name. Consider relocating the nonproprietary name directly above the proprietary name, and deleting, reducing the size of, or relocating the graphic ‘⌘’ in order to implement this recommendation effectively.
2.	The route of administration is missing from the principal display panel (PDP).	The route of administration is important as medication errors could occur involving the wrong route of administration.	Relocate the route of administration to the PDP mitigate medication errors involving the wrong route of administration.
3.	As currently presented the net quantity of contents is not included on your proposed carton labeling.	The net quantity is required per 21 CFR 201.51.	Add the net quantity of 1 vial in accordance with 21 CFR 201.51 to the carton labeling. Consider adding it to the PDP as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April

			2013[c]. For example, "1 single-dose vial". Additionally, ensure there is sufficient space between the net quantity and strength statements as post-marketing experience has shown risk of numerical confusion between the strength and net quantity when the net quantity statement is located in close proximity to the strength statement.
4.	We note the statement "Discard Unused Portion" has not been included following the package type.	We note there is a possibility that less than the full contents of the vial may be administered to the patient and the remaining contents would need to be discarded.	Add the statement "Discard unused portion", on a single line below the package type.
5.	Diluent name does not conform to proper USP nomenclature.	Use of proper USP nomenclature can help minimize the risk of wrong administration technique errors.	Revise the statement 'Reconstitute with non-preserved saline' to read 'ONLY reconstitute each vial with preservative-free 0.9% Sodium Chloride Injection, USP'.
6.	As currently presented the storage statement font is not bolded.	Improper storage, if the storage information is overlooked could lead to degradation of the product. Additionally, adding the units of measurement following all numbers in the temperature range, providing the Fahrenheit range, and replacing the	Bold the storage statement to increase the prominence of this important information. For example, "Store unopened vial in a refrigerator (2°C to 8°C (36°F to 46°F)."

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

		hyphens with the intended meaning "to" would provide for clarity.	
7.	Dosage information states (b) (4) (b) (4)	The term (b) (4) could lead to confusion since the document is titled as "Prescribing Information".	Revise the statement (b) (4) (b) (4) to "See Prescribing Information".

5 CONCLUSION

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Evolus Inc. so that recommendations are implemented prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Jeuveau that Evolus Inc. submitted on August 2, 2018.

Table 4. Relevant Product Information for Jeuveau	
Initial Approval Date	N/A
Active Ingredient	prabotulinumtoxinA-xvfs
Indication	temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients
Route of Administration	intramuscular
Dosage Form	for injection
Strength	100 Units/vial
Dose and Frequency	0.1 mL (4 Units) by intramuscular injection into each of five sites, for a total dose of 20 Units no more than every 3 months
How Supplied	100 Units/vial in single-dose vials
Storage	refrigerated 2° to 8°C (36° to 46° F)
Container Closure	vacuum-dried powder in a single dose vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 3, 2018, we searched the L:drive and AIMS using the terms, ‘prabotulinum’ to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 1 previous relevant labeling review[d], and we note that the review was completed in the previous review cycle prior to the Complete Response letter.

We reviewed our previous recommendations for Jeuveau BLA 761085 to ensure our recommendations are consistent with our previous recommendations.

Table 5. Summary of Previous DMEPA Reviews for Jeuveau

OSE RCM #	Review Date	Summary of Recommendations
2017-1159	November 22, 2017	<u>General</u> • Revised the proprietary name to the conditionally acceptable name, Jeuveau. • Revise the nonproprietary name presentation for prominence. <u>Container Label</u> • Consider deleting or reducing the size of the company logo ‘e’. • Relocate ‘Single Patient Use’ below the route of administration. • Add ‘Discard unused portion’ below ‘Single Patient Use’. <u>Carton Labeling</u> • Add ‘Discard unused portion’ below ‘Single Patient Use’. • Revise the statement [redacted] (b) (4) (b) (4) to read ‘ONLY reconstitute with preservative-free 0.9% Sodium Chloride Injection, USP’.

[d] Mena-Grillasca C. Label Labeling and Packaging Review for Jeuveau (prabotulinumtoxinA-xxxx). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 22. RCM No.: 2017-1159.

APPEARS THIS WAY ON ORIGINAL

APPENDIX C. ISMP NEWSLETTERS – N/A

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX E. OTHER – N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Jeuveau labels and labeling submitted by Evolus Inc. on August 2, 2018 and November 21, 2018.

- Container label received on November 21, 2018
- Carton labeling received on November 21, 2018
- Medication Guide (Image not shown) received on August 2, 2018
- Prescribing Information (Image not shown) received on August 2, 2018

F.2 Label and Labeling Images

Container Label

(b) (4)

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

(b) (4)

[redacted]

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/s/

MADHURI R PATEL
12/17/2018

TERESA S MCMILLAN
12/17/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	May 9, 2018
To:	Kendall Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	Botulinum toxin Type A
Dosage Form and Route:	Injection, for subcutaneous use
Application Type/Number:	BLA 761085
Applicant:	Evolus, Inc.

1 INTRODUCTION

On May 13, 2017, Evolus, Inc., submitted for the Agency's review a Biologics Licensing Application (BLA) for botulinum toxin Type A, injection, for subcutaneous use, for the proposed indication of the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. On June 14, 2017, the Division of Dermatology and Dental Products (DDDP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for Botulinum toxin Type A.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for Botulinum toxin Type A.

2 CONCLUSIONS

Due to outstanding deficiencies, DDDP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHAWNA L HUTCHINS
05/09/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: April 13, 2018

To: Strother D. Dixon
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Jina Kwak, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, PharmD
Team Leader
OPDP

Subject: **BLA 761085**
OPDP labeling comments for Botulinum Toxin Type A injection

This memo is in response to DDDP labeling consult request dated June 14, 2017. Due to outstanding deficiencies, DDDP plans to issue a Complete Response letter. Therefore, OPDP defers comments on the proposed labeling at this time and request that DDDP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Jina Kwak at (301) 796-4809 or jina.kwak@fda.hhs.gov

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/s/

JINA KWAK
04/13/2018

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Pharmaceutical Quality
Office of Biotechnology Products/Division III
10903 New Hampshire Avenue
Silver Spring, MD 20993

Memorandum of Review for Immunogenicity Assays

Original BLA: 761085

Primary reviewer: Davinna L. Ligons, Ph.D.
Secondary Reviewer: Frances Namuswe, Ph.D.
Tertiary Reviewer: Susan Kirshner, Ph.D.

Product: DWP-450 (Botulinum toxin, Type A)

Indication: Treatment of moderate to severe glabellar lines

Route of Admin: Intramuscular injection
Dose Regimen: 20 Units/dose

Sponsor: Evolus, Inc
Clinical Division: ODEIII/DDDP

Received Date: May 15, 2017
Target Date: December 26, 2017
PDUFA Date: May 15, 2018

Recommendation: From an immunogenicity assay perspective, this BLA is recommended for approval. The Sponsor did a suboptimal job in some aspects of assay validation. Specifically, they used fewer than the recommended number of samples for establishing the cut point, and they did not robustly assess assay precision. However, we do not recommend repeating the validation exercise because the assay showed adequate sensitivity, 60 ng/ml, the in-study false positive rate was ranged from 4.6% - 11.3%, which is consistent with the FDA recommendation of at least 5%, and the low positive control was 200 ng/ml, which is within the FDA recommended sensitivity of ADA assays.

Review

Immunogenicity Clinical Trials Summary

DWP-450 (Botulinum toxin, type A) is manufactured by Daewoong Pharmaceutical Co., Ltd. located in South Korea for the treatment of moderate to severe glabellar lines. Five clinical trials shown in Table 1 were conducted to study DWP-450 and each patient received a dose of 20 U of drug product. Immunogenicity was assessed in all clinical trials except EVB-003.

Table 1. Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
US Pivotal Phase III	EV-001	5.3.5.1	Safety and Efficacy	• multicenter • randomized (3:1) • double blind • placebo controlled	Single treatment of 20 U DWP-450 or 0.5mL saline (Placebo)	330 • 246 DWP-450 • 84 Placebo	Healthy adults (≥18 years) who had moderate to severe glabellar lines (GLS score ≥2) at maximum frown, as independently agreed by both IA and SA	150 days duration	Complete; Full
US Pivotal Phase III	EV-002	5.3.5.1	Safety and Efficacy	• multicenter • randomized (3:1) • double blind • placebo controlled	Single treatment of 20 U DWP-450 or 0.5mL saline (Placebo)	324 • 246 DWP-450 • 78 Placebo	Healthy adults (≥18 years) who had moderate to severe glabellar lines (GLS score ≥2) at maximum frown, as independently agreed by both IA and SA	150 days duration	Complete; Full
EU Pivotal Phase III	EVB-003	5.3.5.1	Safety and Efficacy	• multicenter • randomized (5:5:1) • double blind • placebo and active controlled	Single treatment of 20 U DWP-450 or 20 U BOTOX® or 0.5mL saline (Placebo)	540 • 245 DWP-450 • 246 BOTOX • 49 Placebo	Healthy adults (≥18 years) who had moderate to severe glabellar lines (GLS score ≥2) at maximum frown by IA only **AND** who felt that their glabellar lines had an important psychological impact	150 days duration	Complete; Full
US Phase II	EV-004	5.3.5.2	Long-term Safety	• multicenter • non-randomized • open label	20 U DWP-450 per treatment, maximum 4 treatments	352 treated with DWP-450 • 33 received 1 treatment • 57 received 2 treatments • 108 received 3 treatments • 154 received 4 treatments	Healthy adults (≥18 years) who had moderate to severe glabellar lines (GLS score ≥2) at maximum frown by IA only	365 days duration	Complete; Full
US Phase II	EV-006	5.3.5.2	Long-term Safety	• multicenter • non-randomized • open label	20 U DWP-450 per treatment, maximum 4 treatments	570 treated with DWP-450 • 46 received 1 treatment • 93 received 2 treatments • 217 received 3 treatments • 214 received 4 treatments	Healthy adults (≥18 years) who had moderate to severe glabellar lines (GLS score ≥2) at maximum frown, as independently agreed by both IA and SA	365 days duration	Complete; Full

Anti-botulinum antibodies were detected in a total of four patients. One patient in the single dose study, EV-001, had anti-botulinum antibodies at all time points tested including baseline. This patient recently had a prior exposure to botulinum during an injection in the forehead. One patient had anti-botulinum toxin antibodies at baseline in the EV-006 clinical trial and the titer was 50. However, the patient tested negative for ADAs at subsequent time points. The patient was previously exposed to botulinum toxin, type A. Two patients in the multi-dose clinical trial EV-004 had treatment emergent ADAs (2/352, 0.6%) with titers of 50 at a single time point during the study. Clinical trial EV-004 used the [redacted] (b) (4) formulation which contains a [redacted] (b) (4) overage. The other four clinical trials used the vacuum dried formulation for DWP-450 which has a [redacted] (b) (4) overage. No patient receiving the vacuum dried DWP-450 developed treatment emergent anti-drug antibodies. The table below summarizes the process used for lyophilization of drug product used in each clinical trial.

Clinical Study	Toxin Batch	DP Lot No.	Process
EV-001	076091	076540	Vacuum-dried
EV-002	076091	076540	Vacuum-dried
EV-004	974285	975952	(b) (4)
EV-006	076091	076540	Vacuum-dried
EVB-003	076091	076540	Vacuum-dried

Table 33 below summarizes the anti-drug antibody results for pooled single dose treatment studies (EV-001 and EV-002) and pooled multiple dose treatment studies (EV-004 and EV-006).

Table 33. Clinical Laboratory Findings – Positive for Antibotulinum Toxin Antibodies – Safety Population

	Control		DWP-450					
	Pooled Placebo (N=162)		Pooled Single Dose (N=492)		Pooled Multiple Dose (N=922)		Pooled All (N=1414)	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Single and Multiple Dose Studies								
Initial Treatment								
Day 0	0/158	(0.0)	1/478	(0.2)	1/920	(0.1)	2/1398	(0.1)
Day 30	0/155	(0.0)	1/470	(0.2)	0/886	(0.0)	1/1356	(<0.1)
Day 90	0/150	(0.0)	1/454	(0.2)	0/700	(0.0)	1/1154	(<0.1)
EOS (Day 150)/ET for single dose studies only	0/155	(0.0)	1/465	(0.2)	---	---	1/465	(0.2)
Multiple Dose Studies Only								
Repeat Treatment 1								
Day 0	---	---	---	---	0/831	(0.0)	0/831	(0.0)
Day 30	---	---	---	---	1/786	(0.1)	1/786	(0.1)
Day 90	---	---	---	---	0/148	(0.0)	0/148	(0.0)
Repeat Treatment 2								
Day 0	---	---	---	---	0/683	(0.0)	0/683	(0.0)
Day 30	---	---	---	---	0/587	(0.0)	0/587	(0.0)
Day 90	---	---	---	---	0/122	(0.0)	0/122	(0.0)
Repeat Treatment 3								
Day 0	---	---	---	---	0/353	(0.0)	0/353	(0.0)
Day 30	---	---	---	---	0/276	(0.0)	0/276	(0.0)
Day 90	---	---	---	---	0/2	(0.0)	0/2	(0.0)
EOS (Day 365)/ET	---	---	---	---	1/794	(0.1)	1/794	(0.1)
Single and Multiple Dose Studies								
Any Post-Baseline Visit [a]	0/160	(0.0)	1/480	(0.2)	2/901	(0.2)	3/1381	(0.2)
Excluding Subjects with Antibodies at Baseline [b]	0/160	(0.0)	0/479	(0.0)	2/900	(0.2)	2/1379	(0.1)

Note: For individual visits, percentages were calculated with number of subjects with non-missing values at the respective visit as the denominator. Laboratory tests were not collected in the EVB-003 study, therefore the Pooled Placebo and Pooled Single Dose DWP-450 groups are pooled from the EV-001 and EV-002 studies only.

a Percentages were calculated with number of subjects with non-missing post-baseline values as denominator. A subject was regarded as "Negative" only if all available post-baseline values were negative; otherwise, the subject was regarded as "Positive."

b Percentages were calculated with number of subjects with no antibodies present at baseline and non-missing post-baseline values as denominator. A subject was regarded as "Negative" only if all available post-baseline values were negative; otherwise, the subject was regarded as "Positive."

Source: Integrated Summary of Safety Table 70

Reviewer comment:
The vacuum dried formulation for the DWP-450 will be used for commercial distributions and patients receiving this formulation did not develop anti-drug antibodies. However, it remains possible that patients receiving DWP-450 will develop antibodies to botulinum toxin, type A. A neutralizing assay was not developed to characterize ADA

positive serum samples. For assessment of the impact of ADA on efficacy, we defer to OND.

Validation of the Immunogenicity Assays

Immunogenicity testing and assay validation were conducted at [redacted] (b) (4). The Sponsor provided the validation reports for the screening and confirmatory assays. A neutralizing assay was not developed which is acceptable because the literature indicates that anti-drug antibodies to botulinum toxin can be neutralizing by preventing cellular uptake which would affect efficacy and not pose a safety issue.

<u>1. Screening Assay (Validation Report 14H0044R-A04)</u>

(b) (4)

[redacted]

(b) (4)

Positive and Negative Control
The positive control antibody, polyclonal rabbit anti-botulinum toxin type A, is diluted in pooled naïve human serum (PNHS) to a final concentration of 0.2 µg/mL. The negative control is PNHS of a different lot than what was used to dilute the positive control antibody.

Reviewer comment:
The concentration of the positive control antibody is less than the sensitivity of the assay of (b) (4) *µg/mL which was reported in the original submission. An IR was sent to the Sponsor to clarify the concentration of the positive control antibody used in the assay and its discrepancy with the sensitivity of the assay,* (b) (4) *µg/mL. In response to the IR, the Sponsor stated that after factoring in the 50 fold dilution, the sensitivity of the assay is 60 ng/mL (refer to Sensitivity section of this review for details). The Sponsor confirmed that the concentration of the positive control antibody used in the assay is 0.2 µg/mL. This is acceptable because the concentration of the positive control (200 ng/mL) is higher than the sensitivity of the assay (60 ng/mL).*

Minimal required dilution (MRD)
The MRD of a 1:50 dilution was determined during development using 20 individual NHS samples. During validation, the MRD was tested with PNHS samples diluted 50 fold. The acceptance criterion for the MRD is the mean A450 absorbance is less than 0.5.

Sample	Wells	A450	Mean A450	Standard Deviation	CV%
PNHS	C1	0.110	0.114	0.007	6.2
	C2	0.127			
	C3	0.117			
	D1	0.108			
	D2	0.110			
	D3	0.113			

Reviewer comment:
This MRD for this assay is within the FDA guidance recommendations that the samples not be diluted more than 100 fold.

Sensitivity
The sensitivity of the assay was tested by diluting the positive control antibody in PNHS. The table below shows the results for determining the sensitivity. The cut point for this plate was 0.127 for mean A450. The sensitivity of the assay provided in the original BLA is 3µg/mL. In response to an IR, the Sponsor made a correction to the sensitivity of the assay and stated that the assay sensitivity is 60 ng/mL because the positive control antibody concentrations listed in table below are diluted 50 fold. See the IR response below.

Sample	Mean A450	Standard Deviation	CV%	Result
50 µg/mL	0.687	0.016	2.3	Positive
25 µg/mL	0.390	0.006	1.5	Positive
10 µg/mL	0.217	0.003	1.2	Positive
6 µg/mL	0.175	0.003	1.5	Positive
3 µg/mL	0.146	0.002	1.1	Positive
1 µg/mL	0.126	0.007	5.6	Negative

Reviewer comment:
The FDA recommends the sensitivity of screening assays to be 0.1 ug/mL or less. The sensitivity of (b)(4) *ug/mL reported in the original BLA is not acceptable especially when the concentration of the positive control antibody used in the assay is 0.2 ug/mL. An IR was sent to the Sponsor to provide evidence that the assay can detect low antibody levels as suggested by the concentration of the positive control antibody. In response to the IR, the Sponsor stated that the concentration of the positive control antibody used to determine sensitivity is diluted 50 fold. Thus, the* (b)(4) *µg/mL is diluted 50 fold yielding the concentration of 60 ng/mL and that the sensitivity of the assay is 60 ng/mL. The revised sensitivity of the assay is within the FDA recommended sensitivity and is therefore acceptable.*

Selectivity

Reviewer comment:

The FDA recommends that the selectivity of the assay is tested by spiking different concentrations of positive control antibody in sample matrix, human sera, and determine percent recovery compared to dilution in buffer alone. The selectivity of the assay was not tested. The absence of directly demonstrating the selectivity of the assay is acceptable in this case, because the sensitivity of the assay is reasonable. The specificity of the assay is supported by the results that a positive signal is generated by the positive control antibody in the presence of human sera, the sample matrix.

Specificity

To determine the specificity of the assay, the positive control antibody was incubated on plates not coated with the toxin. The mean A450 for the positive control was like that of the negative control which demonstrates that a positive signal in the assay is specific to binding to botulinum toxin, type A.

Sample	Mean A450	Standard Deviation	CV%
PNHS	0.094	0.002	1.7
PC	0.095	0.002	2.3
NC	0.098	0.005	4.8

Reviewer comment:

In the absence of toxin on the plate, the result is negative for the positive control antibody. This demonstrates a positive signal is only generated when the toxin is present in the assay. The specificity of the assay is acceptable. Per FDA guidance the preferred way to demonstrate specificity is by specific competition, which was done for establishing the confirmatory cut point (see section 2). No further studies are needed.

Screening Assay Cut Point

A floating screening cut point is generated for each plate to identify positive serum samples. The screening cut point (SCP) for each plate is determined by multiplying the screening cut point factor (SCPF) determined for a given lot of PNHS by the mean A450 for the PNHS on each plate.

During assay validation, the SCPF and SCP were determined using 20 individual NHS and PNHS lot BRH332321 diluted 50 times. Samples were run in triplicate by two analysts on three separate days. The acceptance criteria were %CV ≤ 25% for the replicates and all results met these acceptance criteria. The SCPF was determined to be 1.048 based on a 5% false positive rate.

The SCPF determined during validation is specific to PNHS lot BRH332321. If a new lot of PNHS is required when testing patient samples, a new SCPF will be determined by performing a partial validation with the new lot of PNHS.

During clinical sample testing, an in-study validation was performed with twenty naïve pre-dose patient samples and PNHS lot BRH 882321. The SCPF was determined to be 1.204. The SCPF is multiplied with the average absorbance 450 of the PNHS on each plate during the clinical trial to determine the cut point.

Reviewer comment:
A floating cut point factor is acceptable to determine plate specific cut points in cases where plate to plate variability is observed. Because a different lot of PNHS was used when testing clinical samples, an in-study partial validation was done to determine the SCPF for the clinical trial samples.

According the assay validation report, it appears that the data were log transformed to determine the cut point factor; however, the report did not mention that a test for normality was performed. An IR was sent to the Sponsor to clarify whether the data were log transformed. In response to the IR, the Sponsor stated that the data were not log transformed and the A450 values were compared to the cut point directly.

The guidance for validating immunogenicity assays recommends using 50 human serum samples to determine the cut point. However, the Sponsor used 20 normal human serum samples for assay validation and 20 naïve pre-dose patient serum samples for the in-study partial validation. An IR was sent to the Sponsor to justify using less than 50 samples to calculate the cut point factor. In response to the IR, the Sponsor explained that this assay was validated prior to the publication of the April 2016 FDA draft guidance for Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. This is not a credible rationale for using fewer than recommended samples because the 2009 FDA draft guidance for assay validation was available and also recommends using 50 serum samples. The Sponsor justified the use of 20 samples by arguing that for full assay validation, a target patient population, which consist primarily of women was selected. For the in-study validation, the pre-dose patient sample was used to establish the cut point for the clinical study. Because the cut point was calculated using the in-study pre-dose samples it is acceptable to use 20 serum samples to validate the assay. Additionally, the cut point between the two populations is not similar 1.048 determined for the normal serum samples and 1.204 determined for the in-study sample which further justifies the need for the in-study SCPF. The variance for both studies is %CV < 25%. It is acceptable to use 20 in-study pre-dose samples because the cut point is representative of the clinical population and thus, fewer samples are acceptable.

Precision

Reviewer comment:
The validation report stated that the %CV was less than 25% for the twenty normal human samples ran on 3 plates although the exact precision of the assay was not reported in the validation report. An IR was sent to the Sponsor to provide inter-assay and intra-assay precision for the assay. In response to the IR, the Sponsor stated that the assay was validated prior to the April 2016 draft guidance for validating immunogenicity assays. This is not a credible rationale for not properly establishing precision because

the 2009 FDA draft guidance for assay validation was available and discusses assay precision assessment. The Sponsor argues that the purpose of validating assay precision is to demonstrate that the variability of the assay does not interfere with the ability to detect low positive samples as positive. The 20 validation samples were tested 3 times by two analysts and 2 of the 60 samples were positive yielding a 3.3% false positive rate. The Sponsor further proposes that the assay is precise because one baseline positive sample in the clinical trial was positive at all subsequent time points demonstrating consistency in detecting anti-botulinum toxin antibody. The Sponsor's response suggests their ability to consistently detect antibody the positive patient sample at different time points.

The Agency accepts that the assay because low variability between plates and samples is observed when reviewing the data of the 20 normal serum samples provided in the report. Additionally, the precision of the positive control antibody during routine assay performance should be %CV < 20%. Overall, the precision of the assay seems acceptable.

Drug tolerance

Reviewer comment:

Drug tolerance studies were not performed for this assay. The following information was provided in the Summary of Biopharmaceutic Studies in section 2.7.1 of the BLA. Approximately 20 units of drug which is approximately (b) (4) *of drug substance is given in each dose of drug product. The expected concentration of drug in the plasma is* (b) (4) *ng/mL which is* (b) (4) *below the level of sensitivity of most assays used to detect botulinum in the serum. Based on this information, the reviewer agrees that it is acceptable to not study drug tolerance because the non-detectable levels of the drug in the serum should not affect the assay.*

Robustness

There are two critical incubation steps in the assay: sample incubation on the plate and SureBlue TMB microwell peroxidase substrate incubation. The standard incubation times for samples and the positive control antibody is one hour, and 25 minutes for TMB incubation. To test robustness of these steps, different incubation times were tested. For all conditions tested, the positive control antibody yielded a positive signal and the negative control was negative. The protocol was updated to show the range of incubation times tested during validation.

Reviewer comment:

The assay was shown to be robust for the critical incubation times in the assay.

Sample stability

The serum samples and positive and negative controls are stored at -60 - -80°C and expire within three years of preparation. The positive control antibody and negative control samples were tested for sample stability following repeated freeze-thaw cycles. Samples were tested after one to four freeze thaw cycles. For all conditions tested, the positive control antibody and the negative control samples were stable and yield positive and negative results, respectively.

Reviewer comment:
These results show that the positive control antibody and negative control can undergo 4 freeze/thaw cycles. The long-term stability of the controls will be tested at 1, 3, 6 and 12 months.

2. <u>Confirmation Assay (Validation Report 15G0023S-A01)</u>

Principal of the assay
The confirmatory bridging ELISA assay uses the same platform as the screening assay.

(b) (4)

[redacted]

Confirmatory Cut Point Determination
Each clinical sample was run in two sets of triplicates. The first set of triplicates is incubation without the inhibitor DWP-450 and the second set of triples is incubated with the inhibitor.

The cut point for the confirmatory assay is the same as that for the screening assay. The mean A450 value of PNHS on each plate will be multiplied by the cut point factor to generate the plate specific cut point. If the average A450 value of samples not incubated with the inhibitor DWP-450 is greater than the cut point, then the sample will be screened positive. Samples incubated with the inhibitor DWP-450 that have a mean A450 value below the cut point are confirmed positive. Additionally, if the mean A450 value of samples incubated with the inhibitor DWP-450 is 30% less than the mean A450 of the same sample not incubated with the inhibitor the sample is confirmed positive.

<u>Acceptance criteria for the assay</u>
The variance (%CV) between triplicate samples must be < 20%. If %CV is not less than 20%, a Q-test is used to identify outliers. The positive control signal must be above the cut point and the negative control must be below the cut point. If these criteria are not met the plate is failed and samples must be run again.

Reviewer comment:
The concentration of the inhibitory DWP-450 was not provided in the submission. An IR was sent to the Sponsor requesting how much DWP-450 was added to the assay. In response to the IR, the Sponsor stated that the confirmatory assay used 250ng DWP-450 per well with a final concentration of 2 µg/mL. The amount of inhibitory drug is in excess and acceptable because a negative signal is observed with positive control antibody.

The Sponsor established two outcomes that will deem a sample positive. First, the floating screening cut point is used to confirm positive samples. In this case, confirmed positive samples are those samples that are positive in the screening assay and yield a signal below the cut point in the confirmatory assay. The second method to confirm positive samples is a 30% reduction in the signal when comparing the same sample incubated with and without the inhibitor, DWP-450. In the validation report, it was not clear why the 30% inhibition in signal was selected as an inhibitory cut point. The Sponsor was asked to justify the 30% inhibitory cut point and to provide the false positive rate associated with the inhibitory cut point. In response to the IR, the Sponsor explained that the 30% inhibition criterion was based on the variability of the assay and was added because the criteria of confirming a sample positive if the signal drops below the cut point alone may not be sufficient to detect low true positive samples due to variability. The Agency accepts the use of the 30% cut point because it will increase the likelihood of confirming additional positive samples as opposed to eliminating potentially true positive samples in cases where the sample is not below the cut point in the confirmatory assay. Regarding the false positive rate, the Sponsor stated that the false positive rate across 4 clinical trials was between 4.6% and 11.3% and the confirmed or 'true positive' rate was between 0% and 0.3%. The false positive rate reported for the clinical study is acceptable because it is around the expected false positive rate of 5% for the screening assay.

Specificity
The positive control antibody was incubated on the plate followed by the addition of a non-related protein, ovalbumin, to demonstrate specificity of the confirmatory assay. DWP-450 was also added to samples to show a reduction in the signal. The acceptance criteria were that the signal of the positive control alone or in the presence of ovalbumin should be above the cut point and the addition of DWP-450 should reduce the signal by 30% or below the cut point.

Table 1. Specificity Results

Validation Sample	Average A450	Pass / Fail
Plate Cutpoint	0.108	Pass
PC triplicate	0.165	
DWP-450 triplicate	0.099	
Ovalbumin triplicate	0.166	

Reviewer comment:
There is a 30% reduction in the positive control signal when the inhibitor DWP-450 is used in the assay. However, there is no reduction in the signal when the non-specific protein ovalbumin was used in the assay. These data show that the confirmatory assay is specific to DWP-450.

Precision
Three independent runs were performed by two analysts on two different days. The criteria for reproducibility is that positive control signal should be above the cut point and the signal following incubation with the inhibitor should be 30% reduced or below the cut point. The table below shows the results for precision.

Table 2. Reproducibility Results

Run #	Plate Cutpoint	PC triplicate	DWP-450 triplicate	Pass / Fail
1	0.108	0.165	0.099	Pass
2	0.114	0.160	0.104	Pass
3	0.169	0.238	0.160	Pass

Reviewer comment:
The data provided shows that variability between analysts and day the assay is performed does not affect the results. In all three runs, the addition of the inhibitory drug generates a positive signal.

Robustness
The length of incubation with the inhibitor, DWP-450 was tested. Incubation times 5, 10 and 15 minutes were tested. The acceptance criteria were that the %CV should be less than 25%. The positive control signal should be above the cut point and the incubation with DWP-450 should be below the cut point or 30% reduced. All three incubation conditions with the inhibitor met the acceptance criteria.

Reviewer comment:
The incubation time with inhibitor between 5 – 15 minutes is robust.

3. <u>Titer Assay</u>

Reviewer comment:

The clinical immunogenicity test results include determination of titers for the ADA positive clinical serum samples. However, the assay validation reports do not provide information for validating the titer assay. An IR was sent to the Sponsor to provide the validation results for the titration assay, including the cut point used for the assay, the false positive rate used to determine the titer cut point, and the precision of the titer measurements. In response to the IR, the Sponsor stated that the titer assay is performed by diluting samples 3 fold and using the same platform and cut point which is based on a 5% false positive rate as the screening assay. Although this is suboptimal the Sponsor won't be asked to perform these studies because the main impact of ADA for this product is loss of efficacy rather than safety. Given the low safety risk for this product and the very low immunogenicity rate observed, understanding antibody titers is not important for assessing the safety and efficacy of this product. Therefore, no further action is needed.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: December 18, 2017 **Date Consulted:** June 27, 2017

From: Jane Liedtka, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Gary Chang, M.D., Medical Officer,
Division of Dermatology and Dental Products (DDDP)

Drug: DWP-450 (a Botulinum Toxin Type A (BTTA) product)[1]

BLA: 761085

Subject: Pregnancy and Lactation Labeling

Proposed Indication:
DWP-450 is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

Applicant: Evolus, Inc.

[1] In this document, we generally refer to Evolus' proposed product by the Evolus descriptor "DWP-450," which was the name used to refer to this product during development. The nonproprietary name for this botulinum type A product has not yet been determined.

Materials Reviewed:

- Applicant's background package for BLA 761085 submitted as Supporting Document (SD)#1 on May 15, 2017.
- Applicant's revised label, literature review and summary of pharmacovigilance database submitted as SD#5 on July 7, 2017.

Consult Question:

The Division requests assistance with the review of the PLLR labeling.

INTRODUCTION

On June 27, 2017, DDDP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of DWP-450 labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

- On May 15, 2017, Evolus, Inc. submitted a new BLA 761085 for DWP-450.
- DWP-450, a BTTA product, is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.
- On June 29, 2017, the Agency sent the Applicant an information request (IR) requesting that they submit a review and summary of the available published literature and a summary of the Applicant's pharmacovigilance database regarding DWP-450 use in pregnant and lactating women and effect on fertility.
- On July 7, 2017, the Applicant submitted the revised labeling and the requested supporting information which was adequate.

BACKGROUND

Botulinum Toxin Type A and Drug Characteristics[2]

- DWP-450 is a sterile, vacuum-dried, botulinum toxin type A (BTTA), produced from fermentation of *Clostridium botulinum*, intended for intramuscular use.
- Molecular weight ≈ 900 kilodaltons.
- DWP-450 blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25[3], a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, DWP-450produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition,

[2] Proposed labeling, DWP-450.
[3] SNAP-25: synaptosomal-associated protein 25

the muscle may atrophy, axonal sprouting may occur, and extra-junctional acetylcholine receptors may develop. There is evidence that re-innervation of the muscle may occur, thus slowly reversing muscle denervation produced by DWP-450.

- The percent protein bound and the half-life for DWP-450 are not known.
- Using currently available analytical technology, it is not possible to detect DWP-450 in the peripheral blood following intramuscular injection at the recommended doses.
- The most common adverse reactions seen in clinical studies of DWP-450 were headache (9.3%) and eyelid ptosis (b) (4) 0%).

REVIEW

Pregnancy

Nonclinical experience

An embryofetal developmental study conducted with DWP-450 in pregnant rats revealed no treatment-related effects to the developing fetus when DWP-450 was administered intramuscularly during organogenesis at doses up to 12 times the maximum recommended human dose (MRHD).

For further details, the reader is directed to the Nonclinical Review by Jianyong Wang, PhD.

Applicant's Review of Literature

The Applicant searched the medical literature to identify articles related to exposure to botulinum toxin type A products and pregnancy. No details were provided regarding the time period covered or which databases were searched. Multiple articles were identified, which are included in Table 1 below under the section of this review entitled "DPMH's Review of Literature".

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed using the search terms "botulinum toxin type A and pregnancy," "botulinum toxin type A and pregnant women," "botulinum toxin type A and pregnancy and birth defects," "botulinum toxin type A and pregnancy and congenital malformations," "botulinum toxin type A and pregnancy and stillbirth," "botulinum toxin type A and spontaneous abortion" and "botulinum toxin type A and pregnancy and miscarriage." No reports of adequate and well-controlled studies of botulinum toxin type A use in pregnant women were found. Multiple case reports including those cited by the Applicant were identified and are included in Table 1 below. The results reported from a survey of physicians using botulinum toxin type A reported by Morgan,[4] *et al* (2006) are also included in Table 1; however, the article was not relied upon to inform labeling. In addition, an article summarizing the pregnancy outcomes from Allergan's Botox and Botox Cosmetic pharmacovigilance database was identified, which was reported by Brin,[5] *et al* (2016). DPMH's summary of the article by Brin,[5] *et al* (2016) and an analysis of the publication's quality [by the Office of Surveillance and

[4] Morgan JC *et al*. Botulinum toxin A during pregnancy: a survey of treating physicians. J Neurol Neurosurg Psychiatry. 2006;77(1):117-9.
[5] Brin MF *et al*. Pregnancy outcomes following exposure to onabotulinumtoxinA. Pharmacoepidemiology and drug safety 2016; 25: 179–187.

Epidemiology (OSE)] are presented following the summary. A separate table of case reports of outcomes for pregnant patients with botulism is provided in Table 2.

Table 1: Pregnancies in Patients Exposed to Botulinum Toxin Type A Products (see below)

Source: Reviewer's Table

Pregnancy #/ Author/ Year	Maternal Age (yrs.)	Fetal Age at Exposure (weeks)/ Pregnancy #	Dose of the Botulinum Toxin Type A Product (units)	Specific BTTA used	Condition/ Diagnosis (Dx)	Maternal/ Fetal Outcomes
#1, 2, 3, 4 (same woman) Newman[6] *et al* 2004	26 29 31 33	1st-? a few weeks (wks), 15 wks, 21 wks, 32 wks 2nd- no details on estimated gestational age (EGA) 3rd- no details on EGA 4th- no details on EGA	300, 200, 100, 300 300, 300 300, 300 300, 300	Botox	Idiopathic cervical dystonia (ICD)	Healthy child for all 4 pregnancies, no complications, follow-up to age 5 for 1st baby
#5, 6 (different women) Bodkin[7] *et al* 2005	38 39	2 wks (other meds-alprazolam) 4 wks (twin pregnancy, maternal history of miscarriage, other meds-benztropine, clonazepam, fluoxetine)	200 500	Botox	ICD ICD	Healthy term baby by C-section Fetal demise- no fetal heartbeats at 10 wks via US
#7,8 (different women) De Oliveira Monteiro[8] 2006	34 37	6 wks 5 wks	54 65	Not reported	Periorbital lines Facial lines	Healthy term baby by caesarian section in both cases, Apgars - 9,10 for both
#9-27 (16 women with 19 pregnancies, one-twins, one-three separate singleton pregnancies) Morgan[9] *et al* 2006	Not stated	12 women-1st TM 1 woman-2nd TM 1 woman-3Rd TM 1-woman-unknown EGA	1.25-300	Not reported	ICD (9) Strabismus (2) Blepharospasm (2) Limb (1) and Oromandibular (1) dystonia Spasmodic dysphonia (1)	Spontaneous abortion (SAB)-1 (maternal history of SAB) Therapeutic abortion- 1 Term deliveries without complications -17
#28 Kuczkowski[10] KM 2007	46	1st TM	Unknown	Not reported	Facial lines	Unknown
#29 Wataganara[11] *et al*. 2009	39	33 wks	80	Botox	Esophageal achalasia	1800-gram female via C-section at 36 wks, no signs of neuromuscular (NM) blockade
#30 Li Yim and Weir[12] 2010	17	? a few wks	Unknown	Botox	Left convergent squint	Healthy baby

[6] Newman WJ *et al*. Botulinum toxin type A therapy during pregnancy. Mov Disord. 2004;19(11):1384-5.
[7] Bodkin *et al*. Botulinum toxin type A therapy during pregnancy. Mov Disord. 2005;20(8):1081-2.
[8] De Oliveira Monteiro E. Botulinum toxin and pregnancy. Skinmed. 2006;5(6):308.
[9] Morgan *et al*. Botulism toxin A during pregnancy: a survey of treating physicians. J Neurol Neurosurg Psychiatry 2006;77(1):117-9.
[10] Kuczkowski KM. Anesthetic implications of botulinum toxin type A (Botox) injections for the treatment of 'the aging face' in the parturient. Acta Anaesthesiol Scand. 2007;51(4):515-6.
[11] Wataganara *et al.* Treatment of severe achalasia during pregnancy with esophagoscopic injection of botulinum toxin A: a case report. J Perinatol 2009;29(9):637-9.
[12] Li Yim JFT and Weir CR. Botulinum toxin and pregnancy—a cautionary tale. Strabismus 2010;18(2):65-6.

#31 Aranda[13] *et al.* 2012	41	2nd TM, 3rd TM	250, 250	Not reported	ICD	Healthy 3400-gram boy at 40 wks, Apgars-7,10 Followed till 7 months
#32 Tan[14] *et al.* 2013	Not stated	?1st TM	62	Not reported	Facial lines	Unknown
#33 Robinson and Grogan[15] 2014	Not stated	18 wks	Unknown	Not reported	Migraine Headache	Healthy term girl Followed till 6.5 years' old
#34 Hooft[16] *et al.* 2015	23	14 wks	199	Not reported	Achalasia	Healthy term girl
#35, 36, 37 (3 pregnancies, 2 different women) Krug[17] *et al.* 2015	38 39	1st pregnancy-8 wks 2nd pregnancy-16 wks, 29 wks 2 wks, 16 wks	200 200, 200 170, 100	Unknown; article not available	ICD Segmental dystonia	Miscarriage at 10 weeks (inherent anembryonic pregnancy) 4570-gram boy via C-section at 38 wks, Apgars-10,10 Normal child at 37 wks via C-section, Apgars-6,7,8
#38 Holliday and Baker[18] 2016	17	31+3 wks	unknown	Unknown; article not available	Esophageal achalasia	Mild intrauterine growth restriction (IUGR) diagnosed at 31+3 wks, Mild preeclampsia at 37 wks, 2240-gram female at 37+4 wks, Apgars-9,9
#39 Figueiredo[19] *et al.* 2017	34	18 wks	unknown	Unknown; article not available	Esophageal achalasia	"Successful" vaginal delivery at 39 wks

[13] Aranda MA *et al*. Botulinum toxin A during pregnancy, still a debate. Eur J Neurol. 2012; 19: e81–82.
[14] Tan M *et al*. Botulinum toxin type A in pregnancy. Motherisk Update. Canadian Family Physician. 2013; 59:1183-4.
[15] Robinson AY and Grogan PM. OnabotulinumtoxinA successfully used as migraine prophylaxis during pregnancy: A case report. Mil Med 2014;179: e703–4.
[16] Hooft N *et al*. Achalasia in pregnancy: Botulinum toxin A injection of lower esophageal sphincter. Case Rep Surg 2015
[17] Krug H *et al*. Safe Administration of Botulinum Toxin Type A Injections During Pregnancy: A Report of Two Cases. Movement Disorders Clinical Practice. 2015; pg187-9.
[18] Holliday N and Baker S. Intra-sphincteric botulinum toxin injections to treat achalasia diagnosed during pregnancy a case report. J Reprod Med. 2016;61(6):615-617.
[19] Figueiredo S *et al*. Successful treatment of achalasia in pregnancy with botulinum toxin A: A case presentation. Maternal Medicine Poster Abstracts. BJOG. 2017; pg 88-89.

Table 2: Cases of Botulism in Pregnant Women

Pregnancy #/ Author/ Year	Maternal Age (years)	Fetal Age at Exposure (weeks)	Maternal Condition/ Diagnosis (Dx)	Fetal/ Maternal Outcomes
#1 O'Brien[20] *et al*. 1973	32	32	Botulism, likely foodborne, + toxin in maternal serum	Precipitous delivery (PD) of a 3 lb 6 oz boy with respiratory difficulty, seizures and ↑bilirubin, no signs of botulism in infant, maternal death on day 13 of hospitalization
#2 St. Clair[21] *et al* 1975	32	34	Botulism, + toxin in maternal serum	Possible partial placental abruption, PD of a 1538-gram boy with respiratory difficulty, Infant had subsequent aspiration pneumonia, anemia, seizures and probable intraventricular hemorrhage (IVH) felt to be the result of hypoxia, PD and IVH, no botulinum toxin in infant's serum 4 hours after birth
#3 MMWR[22] 1995	30	≈27	Heroin addict, skin popping, multiple leg abscesses-wound botulism, + toxin in maternal tissue and serum	Baby delivered by C-section at 34 weeks, infant still in ICU ≈ 4 weeks later, no other details available
#4, Robin[23] et al 1996	24	16	Botulism, likely foodborne, + *C. botulinum* in maternal stool	4300-gram healthy boy delivered at 42 weeks
#5 Polo[24] et al 1996	37	23	Botulism, likely foodborne	Mother completely paralyzed (fetal movements were the only visible motion), required intubation and respiratory support for 2 months, normal delivery of healthy baby at term
#6 Morrison[25] et al. 2006	23	36	Heroin addict, hepatitis C +, left thigh abscess -wound botulism, + mouse inoculation testing, Concomitant meds-iron, methadone and heroin	Emergency C-section due to maternal respiratory deterioration, 2270-gram female admitted to ICU for respiratory tract infection and drug withdrawal
#7 Magri[26] et al 2006	Not stated	2nd trimester	Unknown	Unknown

Source: Reviewer's Table

[20] O'Brien M *et al.* Centers for Disease Control and Prevention. Type A botulism-Oregon. MMWR 1973;22(26):218-23.
[21] St. Clair EH *et al.* Observations of an infant born to a mother with botulism [Letter]. J Pediatr 1975;87(4):658.
[22] Centers for Disease Control and Prevention. Wound botulism—California, 1995. MMWR Morb Mortal Wkly Rep 1995;44(48):889-92.
[23] Robin L *et al*. Botulism in a pregnant woman. N Engl J Med 1996;335(11):823-4.
[24] Polo JM *et al*. Botulism and pregnancy. Lancet 1996;348(9021):195.
[25] Morrison GA *et al*. Botulism in a pregnant intravenous drug abuser. Anaesthesia 2006;61(1):57-60.
[26] Magri K *et al*. Botulisme et grossesse. J Gynecol Obstet Biol Reprod (Paris) 2006;35(6):624-6.

Allergan's Pharmacovigilance Database Summary[5]

Brin, [5] *et al* (2016) reported a review of the Allergan Global Safety Database from January, 1990 to December, 2013. The authors identified 232 pregnancies of maternal onabotulinum toxin A exposure with known outcomes.

- 137 were considered prospective cases (reported before the pregnancy outcome was known) with 139 fetuses (2 sets of twins).
- 95 were considered retrospective cases (reported after the pregnancy outcome was known) with 98 fetuses (3 sets of twins).
- The majority of fetal exposures to the drug (96%) occurred either during the first trimester of pregnancy or up to 3 months prior to the estimated date of conception.
- 174 live births, with 7 abnormalities
- In the prospective pregnancies, the prevalence rate of major fetal defects was 0.9%, and the prevalence rate of overall fetal defects was 2.7%, similar to background rates in the general population.

See Table 3 below for the summary of fetal defects reported in this publication[5] on page 184.

Table 3: Summary of fetal defects in cases of live births and abortions

Adverse event	Outcome	BOTOX indication	Time of exposure	BOTOX dose	Maternal age
Prospective fetal defects in live births					
Major fetal defects ($n = 1$)					
Ventricular septal defect	C-section; asymptomatic, no intervention required	Axillary hyperhidrosis	37 days pre-conception	100U	28 years
Minor fetal malformations ($n = 2$)					
Metatarsus adductus	Induced vaginal delivery (decreased fetal movement); no other abnormalities	Chronic migraine	15 days post-conception	155U	19 years
Innocent asymptomatic cardiac murmur*	Family history of cardiac murmur	Blepharospasm	Trimesters 1, 2, 3	8U, 12U, 14U	23 years
Birth complication ($n = 1$)					
Horner syndrome	C-section, placenta previa, and uterine varicosities; no abnormalities reported 11 months later	Axillary hyperhidrosis	"Few days" before conception	100U (50U each axilla)	Unknown
Prospective fetal defect in abortions					
Genetic abnormalities ($n = 1$)					
Down syndrome	Miscarriage at gestation month 5	Skin wrinkling (glabella)	40 days post-conception	12U	38 years
Retrospective fetal defects in live births					
Major fetal defects ($n = 1$)					
Tracheoesophageal fistula, esophagealatresia	Pre-term labor at ~33 weeks resulting in C-section; surgical repair successful	Facial wrinkles	3 days post-conception	36U	30 years
Minor fetal malformations ($n = 1$)					
Laryngomalacia	Planned C-section at 38 weeks; settled spontaneously over several months	Facial wrinkles	1 week pre-conception and 2 weeks post-conception	Not reported	38 years
Significant adverse event ($n = 1$)					
Brain tumor (unspecified)†	Successful surgical resection	Cervical dystonia	Within 1 week before conception	100U	25 years
Retrospective fetal defects in abortions					
Genetic abnormality ($n = 1$)					
Down syndrome	Elective abortion at week 20	Skin wrinkling (glabella)	"Immediately after injection"	25U	40 years

*Diagnosed at 7 days.
†Diagnosed at 13 months.

DPMH consulted Division of Epidemiology (DEPI) regarding the Brin, *et al* (2016) article and asked for their input as to whether the data regarding another botulinum toxin type A product (onabotulinumtoxinA) was relevant to DWP-450 and of sufficient quality to include in labeling. The preliminary opinion provided by the DEPI reviewer is provided below:

> It appears that the article by Brin,[5] *et al*. is non-informative for estimating the prevalence of or risk of pregnancy outcomes in women exposed to botulinum toxin for the following reasons:

1. The data are collected as part of Allergan's adverse event reporting system so it more closely resembles FAERS data than more rigorous observational study designs. There is no true denominator for a true prevalence estimate. Therefore, it is not as robust as we would like it to be for labeling.
2. Since the data are essentially a case series, the analysis does not give any information on risk.
3. In addition to the type of data, major limitations of the study include the potential reporting bias (as we only have information on the woman and events that get reported to Allergan) and missing data on (or lack of) complete medical information.

Due to the limitations of the study, DEPI recommends providing, in the product label, a qualitative summary of the post-marketing report (PMR) study along with a statement about the unknown causal relationship between BOTOX exposure and fetal loss and abnormal birth outcomes.

The labeling language proposed by DEPI is provided below:

8.1 Pregnancy
Data
Pregnancy Exposure in Human Data from the Allergan Global Safety Database was searched from 1/1/90 to 12/31/13 to identify woman with onabotulinum toxin A exposure ≤ 3 months before conception or during pregnancy. Among the live births, the majority were normal. Although there were four cases of abnormal birth outcomes (1 major fetal defect, 2 minor fetal malformations, 1 birth complication) and fetal loss reported, exposure data were insufficient to determine if these outcomes were more common or the same as background rates among unexposed pregnancies. The data were not sufficient to allow estimation of a prevalence rate of BOTOX-induced fetal loss or fetal defects. In addition, a causal relationship between these outcomes and BOTOX exposure cannot be determined due to limitations of the data source.

Reviewer's Comments
Given the relatively poor quality of the data in the Brin, et al.[5] article, this reviewer does not recommend including the results in the labeling for DWP-450. Accordingly, it is unnecessary to provide comments on the labeling language proposed by DEPI. (It should be noted, however, that the source of the database search results described in the proposed labeling language is published literature.) The only additional information available are the case reports presented in Table 1. Case reports are not customarily included in Section 8.1 of labeling unless they reveal a unique worrisome finding.

Applicant's Pharmacovigilance Database Summary

According to the Applicant, there were eight pregnancies that occurred during the clinical development program for DWP-450. Seven of these pregnancies resulted in a healthy term infant with no congenital malformations or complications. Subject (b) (6) a 43-year-old woman, had a spontaneous abortion (SAB) that occurred 114 days after treatment with DWP-450. This was assessed as an adverse event and deemed “not related” by the investigator.

Reviewer’s Comments
This reviewer agrees with the investigator that given the inability to measure any systemic exposure to DWP-450 in the plasma after treatment with the product and the long lag time between any potential exposure and the SAB, it is unlikely that DWP-450 caused the event.

Summary

Limited human pregnancy exposure outcome data for use of botulinum toxin type A products in the published literature failed to identify a consistent pattern of malformation or increased incidence of adverse maternal or fetal outcomes. The findings in animal studies conducted by Evolus did not demonstrate any findings indicative of risk to the fetus. The inability to measure systemic levels of botulinum toxin in the plasma after treatment for any of the botulinum toxin type A products, the high molecular weight of the product and the lack of adverse events seen in infants born to women with botulism suggest placental transfer in significant amounts is unlikely.

Additionally, although it is too early to recommend use of botulinum toxin type A for facial line indications during pregnancy, the accumulating information does not suggest a substantial risk to the fetus with inadvertent maternal exposure of botulinum toxin type A during pregnancy. The risk versus benefits for a pregnant woman with facial line indications for treatment (for which Evolus, is seeking licensure) should be made on an individual basis. See DPMH proposed labeling below for details.

Lactation

Nonclinical Experience

No lactation studies with DWP-450 have been conducted in animals.

Applicant’s Review of Literature

The Applicant searched the medical literature to identify articles related to botulinum toxin and lactation. No details were provided regarding the time-period covered or which databases were searched. A single article was identified which is summarized below.

- Middaugh[27] (1978) reported on a 24-year-old breastfeeding woman severely poisoned by foodborne botulism toxin who continued to breastfeed her 8-month-old daughter throughout the illness. Type A botulism toxin was identified in the pre-treatment specimens of serum and stool obtained from the mother at the time of hospitalization. Four hours after treatment with trivalent botulism anti-toxin on the same day of her admission, the woman’s milk was tested and was free of botulinum toxin or *C. botulinum* bacteria, although she was still severely ill. The woman required tracheostomy and respiratory support for two weeks before eventually recovering. The infant showed no

[27] Middaugh J. Botulism and breast milk. NEJM. 1978; 298(6): 343.

symptoms of poisoning. No botulism toxin was detected in specimens of the infants' serum and stool (obtained on the day of admission).

DPMH's Review of Literature

DPMH conducted a search of Dr. Hale's *Medications and Mother's Milk*[28], the Drugs and Lactation Database (LactMed)[29], Micromedex[30], and of published literature in PubMed and EMBASE using the search terms "botulinumtoxin type A and lactation" and "botulinumtoxin type A and breastfeeding." No relevant publications aside from the article identified by the Applicant were found.

In *Medications and Mother's Milk*[15], Thomas Hale, a breastfeeding expert, states the following regarding botulinum toxin type A and lactation:

> No Data, Probably Compatible…When injected properly, and directly into the muscle, the toxin does not enter the systemic circulation. Thus, levels in maternal plasma, and milk are very unlikely. Waiting a few hours for dissipation of any toxin would all but eliminate any risk to the infant.

Hale goes on to summarize the case reported by Middaugh[5] (1978) discussed above.

Botulinum toxin type A is referenced in LactMed[16]. The summary of use during lactation states:

> No data exist on the medical use of botulin A (botulinum toxin) during breastfeeding. However, one infant was safely breastfed during maternal botulism and no botulinum toxin was detectable in the mother's milk or infant[5]. Since the doses used medically are far lower than those that cause botulism, amounts ingested by the infant, if any, are expected to be small and not cause any adverse effects in breastfed infants[31]. No special precautions are required.

Botulinum toxin type A is referenced in Micromedex. The Lactation Rating states:

> Infant risk cannot be ruled out…Exercise caution when administering to a lactating woman. Weigh the benefits of breastfeeding with the mother's clinical need for treatment with onabotulinum toxin A and the potential for adverse effects on the breastfed infant or from the mother's underlying clinical diagnosis or condition.

In *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*[32],

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[28] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing

[29] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[30] Truven Health Analytics information, http://www.micromedexsolutions.com/.

[31] Lee KC, Korgavkar K, Dufresne RGJ et al. Safety of cosmetic dermatologic procedures during pregnancy. Dermatol Surg. 2013; 39:1573-86.

[32] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

the author notes: “No human data, probably compatible”. The author goes on to state:

> Because the toxin is not expected to appear in the systemic circulation, it would not be available for excretion into breast milk. Therefore, the risk to the nursing infant is probably nil.

Summary

No lactation studies with DWP-450 have been conducted in animals. In a single publication that described a lactating patient with foodborne botulism, there was no measurable botulinum toxin in the mother’s milk and no adverse effects seen in the infant; however, antitoxin had been administered to the mother four hours before the milk sample was taken. Given the high molecular weight of botulinum toxin and the lack of evidence for systemic absorption when approved doses are used, the risk to the infant appears to be low. DPMH recommends that the breastfeeding risk/benefit statement is included in section 8.2 of labeling. See DPMH proposed labeling below for further details.

Females and Males of Reproductive Potential

Nonclinical Experience

Animal studies have not been conducted to evaluate the carcinogenic, mutagenic or impairment of fertility potential of DWP-450.

For further details, see the review by Jianyong Wang, Ph.D.

Applicant’s Review of Literature

The Applicant searched the medical literature to identify articles related to botulinum toxin and effects on fertility. No details were provided regarding the time-period covered or which databases were searched. A single article was identified which involved intra-detrusor botulinum toxin injection leading to localized pharmacologically mediated effects on fertility[33]. Since these effects would not be relevant to the intramuscular injection of the face for the indication of “temporary improvement in the appearance of moderate to severe glabellar lines” this article is not discussed in further detail in this review.

DPMH’s Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding botulinum toxin type A and its effects on fertility and found no relevant clinical articles.

[33] Caremel R *et al*. Side effects of intra-detrusor botulinum toxin injections on ejaculation and fertility in men with spinal cord injury: preliminary findings. BJU Int. 2012 Jun;109(11):1698-702.

Summary

Animal studies have not been conducted to evaluate the carcinogenic, mutagenic or impairment of fertility potential of DWP-450. Given the lack of findings in humans exposed to botulinum toxin type A in clinical studies, DPMH recommends that subsection 8.3 be omitted from labeling.

CONCLUSION

The Pregnancy and Lactation, sections of DWP-450 labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of DWP-450 labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of DWP-450 labeling was formatted in the PLLR format to include the "Risk Summary" section.

RECOMMENDATIONS

DPMH participated in a labeling meeting with DDDP on 11/29/17. DPMH revised sections 8.1 and 8.2 of DWP-450 labeling for compliance with the PLLR. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Botulinum Toxin Type A Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data on the use of JEUVEAU in pregnant women are insufficient to inform a drug-associated risk for adverse developmental outcomes. An embryofetal developmental study conducted with JEUVEAU in pregnant rats revealed no treatment-related effects to the developing fetus when JEUVEAU was administered intramuscularly during organogenesis at doses up to 12 times the maximum recommended human dose (MRHD) *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryofetal developmental study, intramuscular doses up to 4 unit/kg JEUVEAU were administered to pregnant rats once daily during organogenesis (gestation days 6 to 16). No maternal or embryofetal toxicities were observed at doses up to 4 unit/kg (12 times the MRHD of 20 units, based on unit/kg comparison).

8.2 Lactation

Risk Summary

There is no information regarding the presence of BTTA in human or animal milk, its effects on the breastfed infant or on milk production. However, in a case report, an eight-month-old infant was breastfed during maternal botulism (which leads to measurable serum levels unlike medical use), and no botulinum toxin was detectable in the mother's milk and no adverse effects were noted in the infant. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for JEUVEAU and any potential adverse effects on the breastfed infant from JEUVEAU or from the underlying maternal condition.

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/s/

JANE E LIEDTKA
12/18/2017

MIRIAM C DINATALE
12/19/2017

LYNNE P YAO
12/20/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Single Published Study

Date:	December 12, 2017
Reviewer:	Michelle R. Iannacone, PhD Division of Epidemiology I
Team Leader:	Patricia L. Bright, MSPH, PhD Division of Epidemiology I
Division Deputy Director:	Sukhminder Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	Review of published manuscript entitled "Pregnancy outcomes following exposure to onabotulinumtoxinA"
Drug Name(s):	Botox and Botox Cosmetic (onabotulinumtoxinA)
Application Type/Number:	BLA 761085
OSE RCM #:	2017-2196

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EXECUTIVE SUMMARY

On October 26, 2017, the Division of Pediatric and Maternal Health (DPMH) consulted the Division of Epidemiology I (DEPI-I) to review the published article entitled: "Pregnancy outcomes following exposure to onabotulinumtoxinA" [1]. DPMH requested that DEPI-I assess the quality of the data described and whether the method of assessment is a reasonable one. Also, DPMH requested that DEPI-I comment on the strengths and weaknesses (beyond the obvious small number of patients) and provide input on what findings should be included (if any) in labeling.

Brin et al. conducted a retrospective case[a] series to evaluate pregnancy outcomes following onabotulinumtoxinA exposure using the Allergan Global Safety Database. The database contains reports of onabotulinumtoxinA administered before and/or during pregnancy including both prospective [b](pregnancy case reported before outcome was known) and retrospective (outcome already known) cases. The database was searched from January 1, 1990, to December 31, 2013, for eligible cases whose treatment occurred during pregnancy or ≤3 months before conception.

Overall, 574 pregnancy cases with maternal onabotulinumtoxinA exposure were retrieved from the Allergan Global Safety Database for the specified time period. Collectively, there were 232 pregnancies (237 fetuses) identified in the case reports that met the inclusion criteria (i.e. patient exposed to onabotulinumtoxinA injection occurring during pregnancy or up to 3 months prior to the estimated date of conception) and had known pregnancy outcomes. Among 190 patients with available indication data, onabotulinumtoxinA was received most frequently for cosmetic indications (51%), movement disorders (17%), and pain disorders (14%). Among 146 cases with known maternal age, 48% were ≥35 years. Most (96.0%) fetal exposures occurred during or before the first trimester and received a dose <50U (40%).

Of the 237 fetuses, 174 (73%) resulted in live birth and 63 (27%) resulted in fetal loss. In total, there were 7 (4% of 174) live births classified as abnormal and 50 (79% of 63) fetal losses classified as spontaneous. Of the 137 prospective cases (139 fetuses), 110 (79.1%) were live births; with four abnormal birth outcomes (1 major fetal defect, 2 minor fetal malformations, 1 birth complication). According to the authors, there was a 2.7% (3/110; 95% CI, 0.6–8.0%) prevalence rate for overall fetal defects.

DEPI-I concludes the study by Brin et al. has several limitations making the results non-informative for estimating the prevalence of or risk of pregnancy outcomes in women exposed to onabotulinumtoxinA. The number of pregnant women exposed is unknown so the prevalence of fetal defects among exposed women cannot be determined. The data does not clarify the risk to the fetus from exposure during pregnancy and there are major limitations due to reporting bias. (For a detailed description, see Section 4 of the review.)

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[a] Brin et al. do not directly state the study design. This reviewer's understanding is that a retrospective case series was conducted to fulfill the study aim.

[b] The data presented in the study by Brin et al. was queried retrospectively; however, a proportion of the women included in the study who were exposed to onabotulinumtoxinA during the qualified time period, reported their pregnancy before the outcome was known.

Section 6 of this review includes recommendations to DPMH and Section 7 includes DEPI-I's recommended labeling language based on the Brin et al. study.

1 INTRODUCTION

This DEPI-I review provides a critical evaluation of an observational study of pregnancy outcomes following onabotulinumtoixA exposure, published by Brin et al. in Pharmacoepidemiology and Drug Safety in 2016, to assist DPMH in evaluating the data's quality for potential inclusion in the BOTOX Cosmetic label.

1.1 BACKGROUND

OnabotulinumtoxinA (BOTOX, BOTOX Cosmetic) is a purified neurotoxin complex produced from fermentation of Hall strain *Clostridium botulinum* type A. The neurotoxin blocks neuromuscular transmission by binding to receptor sites on motor nerve terminals, entering the nerve terminals and inhibiting the release of acetycholine. When injected intramuscularly at therapeutic doses, BOTOX Cosmetic produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity.[c]

The FDA approved onabotulinumtoxinA in 1989, under the trade name Botox, for the treatment of strabismus and blepharospasm associated with dystonia, and in 2000 for the treatment of cervical dystonia. In 2002, the FDA approved the use of onabotulinumtoxinA for a cosmetic indication under the trade name BOTOX Cosmetic in U.S. adults. However, when used for treatment of blepharospasm and strasmus, onabotulinumtoxinA is indicated for patients who are ≥12 years of age.

There are no adequate and well controlled studies in pregnant women; onabotulinumtoxinA should only be used during pregnancy if the benefits outweigh the risks. While women who are pregnant, nursing or planning a pregnancy are excluded from clinical trials on botulinum toxin (BoNT), many women are being treated with onabotulinumtoxinA (e.g. chronic migraine, axillary hyperhidrosis and cosmetic use) and are of reproductive age. Several of the indications for which onabotulinumtoxinA is approved are more prevalent in women and therefore, the overall use is greater in women. In addition, there is high frequency of use among women of fertile age [1].

On October, 27, 2017, DPMH consulted DEPI-I and requested the following: "We would like your assessment of the quality of the data described [in Brin et al.'s article entitled "Pregnancy outcomes following exposure to onabotulinumtoxinA"] and whether the method of assessment is a reasonable one. We are considering including the findings of this article in the human data section of 8.1 for this new botulinum toxin. Please comment on strengths and weaknesses (beyond the obvious small number of patients) and provide your input on what findings (if any) should be included in labeling."

1.2 REGULATORY HISTORY

Botulinum toxin type A was first approved for use in the United States by the FDA in December 1989 for the treatment of blepharospasm associated with dystonia and for the treatment of strabismus (marketed under the trade name Botox). In April 2002, the FDA approved the supplement to the BLA for Botulinum Toxin Type A. Under that approval, Botulinum Toxin

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[c] BOTOX Cosmetic Label; Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/botuall041202LB.pdf on November 20, 2017.

Type A was marketed and labeled as BOTOX COSMETIC indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age. Table 1* lists currently approved indications, approval dates, and recommended doses for Botox and Botox Cosmetic.

Table 1. FDA-Approved Indications and Recommended Doses for Botox and Botox Cosmetic*

Product	Approval Date	Indication	Recommended Total Treatment Dose[a] and Route
Botox	December 1989	Treatment of blepharospasm associated with dystonia in patients ≥12 years of age	3.75-7.5 units intramuscular
Botox	December 1989	Treatment of strabismus in patients ≥12 years of age	1.25-5 units intramuscular
Botox	December 2000	Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain	50 units per site intramuscular
Botox Cosmetic	April 2002	Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients	20 units intramuscular
Botox	July 2004	Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients	50 units per axilla intradermal
Botox	March 2010	Treatment of upper limb spasticity in adult patients	Site dependent; ranges from 12.5-50 units per site intramuscular
Botox	October 2010	Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer)	155 units intramuscular
Botox	August 2011	Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication	200 units intradetrusor
Botox	January 2013	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication	100 units intradetrusor
Botox Cosmetic	September 2013	Temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients	24 units intramuscular
Botox	April 2015	Treatment of spasticity of the thumb flexors (adductor pollicis and flexor pollicis longus)	20 units intramuscular
[a]In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 units (Botox) or 360 units (Botox Cosmetic) in a 3-month interval			

*Adapted from FDA Pharmacovigilance Review of Botox (onabotulinumtoxinA) and Myocardial Infarction and Arrhythmia; Reviewer: Jessica Weintraub, Pharm D, BCPS; BLA 103000; November 20, 2015; Reference ID: 3849779

1.3 PRODUCT LABELING

At the time of this current review, the label for BLA 761085 has not been finalized.

2 REVIEW METHODS AND MATERIALS

This is a review of the Brin et al. publication, titled "Pregnancy outcomes following exposure to onabotulinumtoxinA" published in Pharmacoepidemiology and Drug Safety on December 4, 2016 [1]. On October, 27, 2017, DPMH consulted DEPI-I and requested the following: "We would like your assessment of the quality of the data described and whether the method of assessment is a reasonable one. We are considering including the findings of this article in the human data section of 8.1 for this new botulinum toxin. Please comment on strengths and weaknesses (beyond the obvious small number of patients) and provide your input on what findings (if any) should be included in labeling."

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

Brin et al. conducted a retrospective case[d] series to evaluate pregnancy outcomes following onabotulinumtoxinA exposure using the Allergan Global Safety Database. This database contains individual case safety reports received from pre-and post-approval sources, including Allergan-sponsored and partner-sponsored clinical trials (serious adverse events and pregnancies), spontaneous sources (serious and non-serious events reported by consumers and healthcare providers), post-authorization studies, health authorities, and published literature. In particular, the database contains reports of onabotulinumtoxinA administered before and/or during pregnancy including both prospective (reported before outcome) and retrospective (outcome already known) cases. The database was searched from January 1, 1990, to December, 31 2013, for eligible cases whose treatment occurred during pregnancy or ≤3 months before conception.

Overall, 574 pregnancy cases with maternal onabotulinumtoxinA exposure were retrieved from the Allergan Global Safety Database for the specified time period. Collectively, there were 232 pregnancies (237 fetuses) that were eligible with known outcomes. Among 190 patients with available indication data, onabotulinumtoxinA was received most frequently for cosmetic indications (51%), movement disorders (17%), and pain disorders (14%). Among 146 cases with known maternal age, 48% were ≥35 years. Most (96.0%) fetal exposures occurred during or before the first trimester and received a dose <50U (40%).

Of the 237 fetuses, 174 (73%) resulted in live birth and 63 (27%) resulted in fetal loss. In total, there were 7 (4% of 174) live births classified as abnormal and 50 (79% of 63) fetal losses classified as spontaneous. Of the 137 prospective cases (139 fetuses), 110 (79.1%) were live births; with four abnormal birth outcomes (1 major fetal defect, 2 minor fetal malformations, 1 birth complication). According to the authors, there was a 2.7% (3/110; 95% CI, 0.6–8.0%) prevalence rate for overall fetal defects.

3.2 STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

[d] Brin et al. do not directly state the study design. This reviewer's understanding is that a retrospective case series was conducted to fulfill the study aim. For a fuller description of the data sources screened to identify the cases, see section 3.3.1.2.

Brin et al. conducted the analysis to evaluate pregnancy outcomes following onabotulinumtoxinA or BoNT type A (manufacturer unspecified) exposure captured in the Allergan Global Safety Database.

3.3 Study Methods

3.3.1 Design & Setting

3.3.1.1 Study Type

Retrospective case-series[d]

3.3.1.2 Data Source

The Allergan Global Safety Database contains individual case safety reports received from pre- and post-approval sources, including Allergan-sponsored and partner-sponsored clinical trials (serious adverse events and pregnancies), spontaneous sources (serious and non-serious events reported by consumers and healthcare providers), post-authorization studies, health authorities, and published literature. The database includes cases with pregnancy outcomes that are prospectively (pregnancy case reported before outcome was known) or retrospectively (outcome known when pregnancy case was reported) collected.

3.3.1.3 Population & Time Period

The Allergan Global Safety Database was used to create a case series of women exposed to onabotulinumtoxinA from January 1, 1990, through December 31, 2013.

3.3.1.4 Selection, Inclusion, and Exclusion Criteria

The case report was *included* if it had:

- an identifiable patient exposed to onabotulinumtoxinA or BoNT type A who was confirmed pregnant
- a patient with unknown age or was under the age of 65 years
- exposure to onabotulinumtoxinA injection occurring during pregnancy or up to 3 months prior to the estimated date of conception[e] (the approximate duration of action of the drug in striated muscle)

The case report was *excluded* if it:

- concerned accidental topical exposure to onabotulinumtoxinA

3.3.2 Exposure & Outcome

3.3.2.1 Exposure

The exposure of interest was onabotulinumtoxinA or BoNT type A (manufacturer unspecified) injection. OnabotulinumtoxinA is not expected to be present in peripheral blood at measurable levels following intramuscular or intradermal injection at the recommended doses and is predicted to be completely eliminated from the systemic circulation within 48-hours post-injection. Therefore, only cases in which onabotulinumtoxinA injection occurred during

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[e] The authors did not include information on their methods for calculating the estimated date of conception.

pregnancy or up to 3 months prior to the estimated date of conception were considered eligible pregnancies for the purpose of this analysis.

3.3.2.2 Outcome

The main outcome of interest was fetal outcomes, in particular, fetal defects and fetal loss.

All cases were reviewed by a medical safety physician, who determined if the outcome was a fetal loss (which included both spontaneous and elective abortions, as well as other cases of fetal loss) or a normal live birth; in which case, whether there were any fetal defects. It is not clear to DEPI what else would be included under "fetal loss".

Fetal defects were assigned to the following categories:

- **major**: which have serious medical and/or social implications and often require surgical repair
- **minor**: which are of mostly cosmetic significance and are rarely medically significant or require surgical repair
- **birth complication**: which results from the birthing process
- **genetic abnormality**: which results from a genetic disorder
- **significant adverse event**: which is another event considered to be significant by the reviewer.

3.3.3 Covariates

Additional evaluated variables were maternal age, timing of exposure, indication, and dose.

3.3.4 Sample Size/Power

Not discussed.

3.3.5 Statistical Analyses

Consistent with FDA guidance, only prospective pregnancy cases were used to estimate prevalence rates of abnormal pregnancy outcomes, along with 95% confidence intervals, based on a Poisson distribution.

3.4 STUDY RESULTS

Overall, 574 pregnancy cases were retrieved from the Allergan Global Safety Database for the time period of January 1, 1990, through December 31, 2013. Figure 1 presents the distribution of pregnancy cases and fetal outcomes. Of the *prospective* fetuses (n=110) that resulted in live birth, four were abnormal birth outcomes (see Table 3 below). Of the *retrospective* fetuses (n=98) that resulted in live birth, three were abnormal birth outcomes (see Table 3 below).

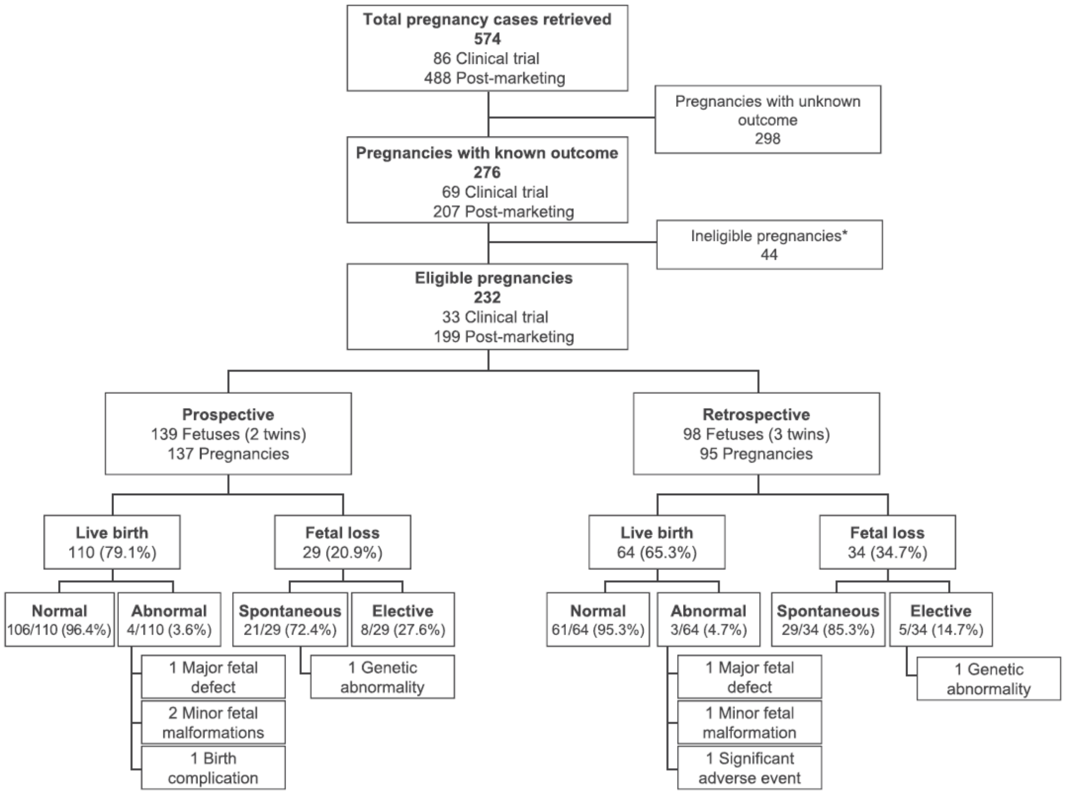

Figure 1. Distribution of pregnancy cases (figure verbatim from Brin et al.). *Pregnancies in which onabotulinumtoxinA injection occurred >3months before the estimated date of conception.

Maternal characteristics are described in Table 2 below (data is expressed among those with known information; therefore, it does not match to the n (%) represented in Figure 1 above). Most women were of advanced maternal age (≥35 years) (47.9%). The most commonly reported condition for which patients received onabotulinumtoxinA injection was cosmetic use (50.5%), followed by movement disorders (16.8%) and pain disorders (14.2%). The majority of fetal exposures occurred during the first trimester (82.6%) and the most common dose of onabotulinumtoxinA was <50U (40.1%).

Table 2: Characteristics of prospective and retrospective pregnancy cases with known outcome (table verbatim from Brin et al.).*

	Prospective pregnancies ($n = 137$)	Retrospective pregnancies ($n = 95$)	Total ($N = 232$)
Maternal age			
Age known, *n*	97	49	146
<35 years	56 (57.7)	20 (40.8)	76 (52.1)
≥35 years	41 (42.3)	29 (59.2)	70 (47.9)
BOTOX indication			
MedDRA preferred term			
Indication known, *n*	128	62	190
Cosmetic	70 (54.7)	26 (41.9)	96 (50.5)
Skin cosmetic procedure	1	0	1
Skin wrinkling	69	26	95
Gastrointestinal disorders	1 (0.8)	2 (3.2)	3 (1.6)
Anal fissure	1	0	1
Esophageal achalasia	0	2	2
Hyperhidrosis	12 (9.4)	10 (16.1)	22 (11.6)
Hyperhidrosis	12 (9.4)	10 (16.1)	22 (11.6)
Movement disorders	15 (11.7)	17 (27.4)	32 (16.8)
Blepharospasm	1	0	1
Dystonia	4	0	4
Hemiparesis	1	0	1
Muscle contracture	0	1	1
Spasmodic dysphonia	1	2	3
Strabismus	0	1	1
Torticollis	8	13	21
Pain disorders	22 (17.2)	5 (8.1)	27 (14.2)
Headache	2	0	2
Migraine	17	5	22
Muscle spasms	2	0	2
Pelvic pain	1	0	1
Spasticity	3 (2.3)	1 (1.6)	4 (2.1)
Muscle spasticity	3	1	4
Urological disorders	5 (3.9)	1 (1.6)	6 (3.2)
Cystitis interstitial	1	0	1
Hypertonic bladder	1	0	1
Neurogenic bladder	3	1	4
Timing of exposure			
Timing known, *n*	124	77	201
Prior to conception			
>2–3 months	2 (1.6)	1 (1.3)	3 (1.5)
>1–2 months	7 (5.6)	2 (2.6)	9 (4.5)
0–1 month	12 (9.7)	3 (3.9)	15 (7.5)
First trimester	98 (79.0)	68 (88.3)	166 (82.6)
Second trimester	5 (4.0)	1 (1.3)	6 (3.0)
Third trimester	0 (0)	2 (2.6)	2 (1.0)
BOTOX dose			
Dose known, n	95	42	137
<50U	40 (42.1)	15 (35.7)	55 (40.1)
50U to <100U	13 (13.7)	7 (16.7)	20 (14.6)
100U to <150U	17 (17.9)	9 (21.4)	26 (19.0)
150U to <200U	10 (10.5)	2 (4.8)	12 (8.8)
200U to <250U	6 (6.3)	3 (7.1)	9 (6.6)
250U to <300U	1 (1.1)	0 (0)	1 (0.7)
300U to <350U	6 (6.3)	1 (2.4)	7 (5.1)
350U to <400U	2 (2.1)	0 (0)	2 (1.5)
>400U	0 (0)	5 (11.9)	5 (3.6)

MedDRA = Medical Dictionary for Regulatory Activities.
*Data are expressed as *n* or *n* (% among those with known information).

Among all the live births (n=174), there were a total of seven abnormalities (Table 3). Two fetal cases were categorized as a major malformation: ventricular septal defect, which was prospective, asymptomatic, and did not require medical intervention, and tracheoesophageal fistula/esophageal atresia, a retrospective case that was successfully surgically repaired. The single prospective case of major malformation gave a 0.9% (1/110; 95% CI: 0.02-5.1%) prevalence rate of major fetal defect. Table 3 below summarizing the fetal defects observed, by outcome, BOTOX indication, time of exposure, BOTOX dose and maternal age, in the prospective and retrospective cases of live births and abortions.

Table 3: Summary of fetal defects in prospective and retrospective cases of live births and abortions (table verbatim from Brin et al.).

Adverse event	Outcome	BOTOX indication	Time of exposure	BOTOX dose	Maternal age
Prospective fetal defects in live births					
Major fetal defects ($n = 1$)					
Ventricular septal defect	C-section; asymptomatic, no intervention required	Axillary hyperhidrosis	37 days pre-conception	100U	28 years
Minor fetal malformations ($n = 2$)					
Metatarsus adductus	Induced vaginal delivery (decreased fetal movement); no other abnormalities	Chronic migraine	15 days post-conception	155U	19 years
Innocent asymptomatic cardiac murmur*	Family history of cardiac murmur	Blepharospasm	Trimesters 1, 2, 3	8U, 12U, 14U	23 years
Birth complication ($n = 1$)					
Horner syndrome	C-section, placenta previa, and uterine varicosities; no abnormalities reported 11 months later	Axillary hyperhidrosis	"Few days" before conception	100U (50U each axilla)	Unknown
Prospective fetal defect in abortions					
Genetic abnormalities ($n = 1$)					
Down syndrome	Miscarriage at gestation month 5	Skin wrinkling (glabella)	40 days post-conception	12U	38 years
Retrospective fetal defects in live births					
Major fetal defects ($n = 1$)					
Tracheoesophageal fistula, esophagealatresia	Pre-term labor at ~33 weeks resulting in C-section; surgical repair successful	Facial wrinkles	3 days post-conception	36U	30 years
Minor fetal malformations ($n = 1$)					
Laryngomalacia	Planned C-section at 38 weeks; settled spontaneously over several months	Facial wrinkles	1 week pre-conception and 2 weeks post-conception	Not reported	38 years
Significant adverse event ($n = 1$)					
Brain tumor (unspecified)†	Successful surgical resection	Cervical dystonia	Within 1 week before conception	100U	25 years
Retrospective fetal defects in abortions					
Genetic abnormality ($n = 1$)					
Down syndrome	Elective abortion at week 20	Skin wrinkling (glabella)	"Immediately after injection"	25U	40 years

*Diagnosed at 7 days.
†Diagnosed at 13 months.

Table 4 below compares the characteristics between prospective pregnancy cases with live births and spontaneous abortions (data is expressed among those with known information; therefore, it does not match to the n (%) represented in Figure 1 above). Of note is that the timing of exposure (i.e. prior to conception versus first/second trimester) to onabotulinumtoxinA was comparable in both the spontaneous abortions and live birth cases.

Table 4: Comparison of characteristics between prospective pregnancy cases with live births and spontaneous abortions (table verbatim from Brin et al.).*

Characteristic	Pregnancies with live births (n=109)	Pregnancies with spontaneous abortions (n=20)	p-values
Maternal age			
Age known, n	16	16	
<35 years	46 (60.5)	15 (31.3)	
≥35 years	30 (39.5)	11 (68.8)	0.032
BOTOX indication			
Indication known, n	103	19	
Cosmetic	52 (50.5)	17 (89.5)	
Therapeutic	51 (49.5)	2 (10.5)	0.002
Timing of exposure			
Timing known, n	99	17	
Prior to conception	18 (18.82)	2 (11.8)	
First/Second trimester	81 (81.8)	15 (88.2)	0.518
BOTOX dose			
Dose known, n	80	12	
<50U	32 (40.4)	8 (66.7)	
50U to <100U	11 (13.8)	2 (16.7)	
≥100U	37 (46.3)	2 (16.7)	0.141

Pregnancy cases with unknown maternal age, BOTOX indication, and timing of exposure or BOTOX dose were not included in the individual analyses.

*Data are expressed as n or n (% among those with known information).

3.5 STUDY CONCLUSIONS

Brin et al. concluded that based on a 24-year retrospective review of the Allergan safety database, the prevalence of abnormal pregnancy outcomes in mothers exposed to onabotulinumtoxinA prior to or during pregnancy is consistent with background rates in the general population. No consistent types of malformation by organ were observed, and no new safety concerns were identified.

4 DISCUSSION

The study by Brin et al. describes retrospective data on pregnancy outcomes in women exposed to onabotulinumtoxinA. However, the study has several limitations that need to be considered. The study findings should be interpreted with caution and have the potential to be misleading.

The Brin et al. study limitations include:

1) The data are collected as part of Allergan's adverse event reporting system and more closely resemble FAERS data or a case series than more rigorous observational study designs. There is no true denominator; only a select group of pregnant women reported their exposure to onabotulinumtoxinA to the Allergan safety database. Therefore, a true

prevalence estimate cannot be estimated. As a result, the study findings are not as robust as may be needed for labeling.

2) Since the data is essentially a case series,
   a. the analysis does not give any information on risk
   b. even for healthy live births, adverse events that manifest as differences in the infant/child's development would likely be missed because the infant/child is not followed over time
   c. reports may not include full data on factors such as dose, duration, and timing of exposure (i.e. high level of missing data), which limits detailed analysis on risk factors in this population. Missing data on the timing of the exposure during pregnancy prevents assessing whether exposure risk differs by stage of fetal development.
   d. reporting bias is inherent for the retrospective cases because reporting the exposure may be influenced by the outcome itself

3) The 2008 update of the CDC's morbidity and mortality weekly report (MMWR) was referenced to compare the study's fetal defect prevalence rate. This comparison has several limitations, including:
   a. the MMWR report includes findings from childbearing women in Atlanta, Georgia who may not be generalizable to other populations
   b. the specific defect inclusion and exclusion criteria (i.e. case definitions) may differ
   c. the report does not include prenatal defects diagnosed among pregnancies electively terminated before 20 weeks' gestation or outside a hospital setting
   d. the report does not include complete data on maternal age or sex, birthweight or gestational age of offspring

5 CONCLUSION

1) The article by Brin et al. is non-informative for estimating the prevalence of or risk of pregnancy outcomes in women exposed to onabotulinumtoxinA. The number of pregnant women exposed is unknown so the prevalence of fetal defects among exposed women cannot be determined. The cases do not clarify the risk to the fetus from exposure during pregnancy, and there are major limitations due to reporting bias. (For a detailed description, see Section 4 of the review.)

Thus, the totality of evidence remains inconclusive about the relationship between onabotulinumtoxinA exposure among women preconception or during pregnancy and abnormal fetal outcomes.

6 RECOMMENDATIONS TO DPMH

Due to the limitations of the study, DEPI-I recommends providing in the product label a qualitative summary of the Brin et al. study along with a statement about the unknown causal relationship between BOTOX cosmetic exposure and fetal loss and abnormal birth outcomes.

Section 7 includes DEPI-I's recommended labeling language based on the Brin et al. study.

7 DEPI-I RECOMMENDED LABELING

DEPI-I proposes the following draft language for DPMH consideration[f].

8.1 Pregnancy

Data

Pregnancy Exposure in Human

Data from the Allergan Global Safety Database was searched from 1/1/90 to 12/31/13 to identify woman with onabotulinumtoxinA exposure ≤3 months before conception or during pregnancy. Among the live births, the majority were normal. Although there were four cases of abnormal birth outcomes (1 major fetal defect, 2 minor fetal malformations, 1 birth complication) and fetal loss reported, exposure data were insufficient to determine if these outcomes were more common or the same as background rates among unexposed pregnancies. The data were not sufficient to allow estimation of a prevalence rate of BOTOX-induced fetal loss or fetal defects. In addition, a causal relationship between these outcomes and BOTOX exposure cannot be determined due to limitations of the data source.

8 REFERENCES

[1] Brin MF, Kirby RS, Slavotinek A, Miller-Messana MA, Parker L, Yushmanova I, Yang H. Pregnancy outcomes following exposure to onabotulinumtoxinA. Pharmacoepidemiol Drug Saf. 2016 Feb;25(2):179-87.

[f] The Division of Dermatology and Dental Products (DDDP), with consultation from DPMH, will ultimately decide on the language for inclusion (or not) in the product labeling.

CC:

Iannacone MR, Sandhu SK, Bright PL, Weissfeld J, Pinheiro SP, Calloway P / DEPI-1 / OSE

Bui Nguyen T / OSE

Liedtka J, Bacho M, Dinatale M / DPMH / ODE IV / OND

White M, Chiang G, Kettl D, Oussova T, Marcus K, Lindstrom J / DDDP / OND

Dixon, SD / ODEIII / OND

APPENDICES

Table 1 – Design Summary

	Study
1 1 Objectives/Aims/Scope	To evaluate pregnancy outcomes following onabotulinumtoxinA (US FDA pregnancy category C product) or BoNT type A (manufacturer unspecified) exposure using the Allergan Global Safety Database.
1 2.1 Design	
1.2.1.1 Type	Retrospective case-series
1.2.1.2 Data Source	Allergan Global Safety Database
1.2.1.3 Time Period	January 1, 1990 – December 31, 2013
1.2.1.4 Criterion (Selection) Standards	The case report was *included* if it had: • an identifiable patient exposed to onabotulinumtoxinA or BoNT type A who was con-firmed pregnant • a patient with unknown age or was under the age of 65 years • exposure to onabotulinumtoxinA injection occurring during pregnancy or up to 3 months prior to the estimated date of conception* (the approximate duration of action of the drug in striated muscle) The case report was *excluded* if it: • concerned accidental topical exposure to onabotulinumtoxinA
1 2.2 Setting	Allergan Global Safety Database
1 2.3 Exposure/Intervention	OnabotulinumtoxinA (BOTOX Cosmetic)
1 2.4 Outcome(s)	Pregnancy outcomes
1 2.5 Covariates	Maternal age, timing of exposure, indication, dose and disorders.
1 2.6 Sample Size	232 eligible pregnancies
1 2.7 Statistical Analyses	Prevalence estimates of abnormal pregnancy outcomes and their 95% confidence intervals based on a Poisson distribution.
1 2.8 Study Results	Overall, 574 pregnancies cases with maternal onabotulinumtoxinA exposure were retrieved from the

	Allergan Global Safety Database for the specified time period. Collectively, there were 232 pregnancies (237 fetuses) that were eligible with known outcomes. Among 190 patients with available indication data, onabotulinumtoxinA was received most frequently for cosmetic indications (51%), movement disorders (17%), and pain disorders (14%). Among 146 cases with known maternal age, 48% were ≥35 years. Most (96.0%) fetal exposures occurred during or before the first trimester and received a dose <50U (40%). Of the 237 fetuses, 174 (73%) resulted in live birth and 63 (27%) resulted in fetal loss. In total, there were 7 (4%) live births classified as abnormal and 50 (79%) fetal losses classified as spontaneous. Of the 137 prospective cases (139 fetuses), 110 (79.1%) were live births; with four abnormal birth outcomes (1 major fetal defect, 2 minor fetal malformations, 1 birth complication). According to the authors there was a 2.7% (3/110; 95% CI, 0.6–8.0%) prevalence rate for overall fetal defects.

*The authors did not include information on their methods for calculating the estimated date of conception.

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/s/

MICHELLE R IANNACONE
12/12/2017

PATRICIA L BRIGHT
12/12/2017

SUKHMINDER K SANDHU
12/12/2017

Clinical Inspection Summary

Date	December 1, 2017
From	Bei Yu, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Strother D. Dixon, Regulatory Project Manager Gary Chiang, Clinical Reviewer David Kettl, Clinical Team Leader Division of Dermatology and Dental Products (DDDP)
BLA #	761085
Applicant	Evolus, Inc.
Drug	DWP-450 (Botulinum toxin, Type A) Injection
NME	No
Review Priority	Standard Review
Proposed Indication	Treatment of Moderate to Severe Glabellar Lines
Consultation Request Date	March 30, 2017
Summary Goal Date	December 18, 2017
Action Goal Date	May 01, 2018
PDUFA Date	May 15, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Jones and Lorenc were inspected in support of this BLA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The preliminary classification of the inspection of Dr. Jones' site was No Action Indicated (NAI). The final classification of the inspection of Dr. Lorenc's site was NAI.

2. BACKGROUND

The Applicant submitted this BLA to support the use of DWP-450 (Botulinum toxin, Type A) for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

Inspections were requested for the following two identical protocols in support of this application:

Protocols EVLCLIN001and **EVLCLIN002**, both entitled "A phase III, multi-center, randomized, double blind, placebo controlled, single dose trial to demonstrate safety and efficacy of DWP-450 in adults for treatment of moderate-to-severe glabellar lines".

Study 001 was conducted at 10 U.S. sites between January and September 2015. A total of 330 subjects were enrolled.

Study 002 was conducted at 10 U.S. sites between January and September 2015. A total of 324 subjects were enrolled.

These two identical Phase 3 studies were multicenter, randomized, double-blind, placebo-controlled trials. Following a screening visit, eligible subjects were randomly assigned in a 3:1 ratio to receive a single dose of DWP-450 at 20 Units or placebo (0.9% saline). Following initial treatment, the subjects were followed for 150 days of safety and efficacy monitoring.

The primary efficacy endpoint was the proportion of subjects who were classified as responders on Day 30. The primary efficacy measure was a composite endpoint. Using the four-point Global Line Scale (GLS) (0=none, 1=mild, 2=moderate, 3=severe), investigators and subjects assessed the glabellar lines at maximum frown on Day 0 and Day 30. A subject was a responder only if both the investigator and subject independently agreed that a ≥ 2 point improvement in the GLS had occurred from Day 0 to Day 30.

Rationale for Site Selection
Dr. Jones's and Lorenc's sites were selected for inspection due to a high enrollment, a high site efficacy effect, and the fact that these investigators had no prior history of GCP inspections.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol # / # of Subjects Enrolled	Inspection Dates	Classification
Site #107 Jones, Derek 9201 West Sunset Boulevard Suite 602 Los Angeles, CA 90069	EVLCLIN001 Subjects: 36	16 - 19 Oct. 2017	NAI*
Site# 204 Lorenc, Z. Paul 983 Park Avenue New York, NY 10028	EVLCLIN002 Subjects: 35	29 Sept.- 05 Oct. 2017	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.

*Pending = Preliminary classification based on preliminary communication with the field; EIR has not been received from the field, or complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Derek H. Jones, M.D.

At this site for Protocol EVLCLIN001, a total of 36 subjects were screened and 36 subjects were enrolled, 34 of whom completed the study.

The records of all subjects enrolled into the trial were reviewed. The records reviewed for these subjects included, but were not limited to, informed consent forms (ICF), inclusion/exclusion criteria, demographics, medical history, physical exam, vital signs, toxin antibody test, results of laboratory tests, ECGs, concomitant medications and treatments, investigational product administration and accountability, investigator and subject assessments for Glabellar Line Scale (GLS) at maximum frown and rest, and adverse events reports. Source documents and electronic case report forms (eCRFs) were compared with the data line listings provided with the inspection assignment.

The primary endpoint data were verifiable. There was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. However, at the close-out of the inspection, one item was discussed with Dr. Jones, specifically that one ECG tracing was not on file in two subject's clinical research charts. The firm obtained the ECG tracings from the sponsor during this inspection and promised voluntary corrections within the next 30 days to prevent this from occurring in the future.

2. Z. Paul Lorenc, M.D.

At this site for Protocol EVLCLIN002, 39 subjects were screened and 35 subjects were enrolled, all of whom completed the study.

ICFs for all 39 screened subjects were reviewed to ensure that subjects were properly consented. For verification of the primary and secondary efficacy endpoints, source document data for all 35 enrolled subjects were verified against the data line listings provided with the inspection assignment. No discrepancies were noted. In addition, there was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. However, at the close-out of the inspection, two items were discussed with Dr. Lorenc and the study coordinator, specifically (1) regarding the incorrect practice of filling in dates on behalf of patients on ICFs and (2) that one eligible subject (Subject (b) (6)) was not enrolled into the study but there was no documentation in the study file to explain why.

In response to the discussion items, the study coordinator stated that in current studies at the site, ICFs are both signed and dated by the subjects. In addition, she explained that Subject (b) (6) was a traveling nurse who decided to withdraw from the study and acknowledged that proper documentation should be included in the study file.

{See appended electronic signature page}

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OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Bei Yu
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague

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/s/

BEI YU
12/04/2017

PHILLIP D KRONSTEIN
12/04/2017

KASSA AYALEW
12/04/2017

LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 22, 2017
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761085
Product Name and Strength:	Jeuveau (prabotulinumtoxinA-xxxx) For Injection 100 Units/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Evolus Inc.
Submission Date:	May 15, 2017
OSE RCM #:	2017-1159
DMEPA Safety Evaluator:	Carlos M Mena-Grillasca, BS Pharm
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, and Prescribing Information (PI), for Jeuveau (prabotulinumtoxinA-xxxx) for injection (BLA 761085), in response to a consult from the Division of Dermatology and Dental Products (DDDP). The Applicant submitted BLA 761085, a 351(a) application, on March 15, 2017 for a single-use vial containing Jeuveau (prabotulinumtoxinA-xxxx) for injection.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing to market Jeuveau in 100 mg per vial. We note the vial size is the same as Botox Cosmetic, another botulinumtoxinA product that share the same indication and dosing as Jeuveau; therefore, we find the proposed vial size adequate.

We reviewed the container labels and carton labeling and noted that the established name is not at least ½ the size of the proprietary name and does not meet 21 CFR 201.10(g)(2). In order to prevent medication errors, we recommend including the statement 'Discard Unused Portion' on the container and carton labeling and 'ONLY reconstitute with preservative-free 0 9% Sodium Chloride Injection, USP' on the carton labeling.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed 100 mg per vial packaging configuration acceptable. We recommend the following label and labeling revision be implemented prior to approval of this BLA.

4.1 RECOMMENDATIONS FOR EVOLUS INC.

A. General Recommendations (All labels and labeling).

1. Your proposed proprietary name, Jeuveau, was found conditionally acceptable. Therefore, revise the proprietary name from 'Evolus' to read 'Jeuveau'.
2. Revise the presentation of the nonproprietary name to ensure that it is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). You can achieve this by either increasing the size of the nonproprietary name or reducing the size of the proprietary name.

B. Container label

1. Consider deleting or reducing the size of the company logo 'e' in order to implement recommendation A.2. effectively.

2. Relocate the statement 'Single Patient Use' to right panel, below the route of administration statement 'For Intramuscular Use Only'.

3. Add the statement 'Discard Unused Portion' on the right panel, on a single line below the statement 'Single Patient Use'.

C. Carton labeling

1. Add the statement 'Discard Unused Portion', on a single line below the statement 'Single Patient Use'.

2. Revise the statement [redacted] (b) (4) to read '**ONLY reconstitute with preservative-free 0.9% Sodium Chloride Injection, USP'**.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Jeuveau that Evolus Inc. submitted on May 15, 2017.

Table 2. Relevant Product Information for Jeuveau	
Initial Approval Date	N/A
Active Ingredient	prabotulinumtoxinA-xxxx
Indication	Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.
Route of Administration	Intramuscular
Dosage Form	For Injection
Strength	100 Units/vial
Dose and Frequency	0.1 mL (4 Units) into each of five sites, for a total dose of 20 Units
How Supplied	100 Units/vial in single-use vials
Storage	Refrigerated at 2° to 8°C (36° to 46°F)
Container Closure	n/a

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 22, 2017, we searched DMEPA's previous reviews using the terms, Jeuveau. Our search did not identify any previous reviews.

APPENDIX C. HUMAN FACTORS STUDY

N/A

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER SOURCES

N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Jeuveau labels and labeling submitted by Evolus Inc. on May 15, 2017.

- Container label
- Carton labeling

G.2 Label and Labeling Images

Container Label (not to scale)

(b) (4)

[redacted]

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling (not to scale)

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARLOS M MENA-GRILLASCA
11/22/2017

SARAH K VEE
11/22/2017