

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761090Orig1s000**

**PRODUCT QUALITY REVIEW(S)**



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

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**LABELS AND LABELING REVIEW**

Date of review:	July 31, 2018
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Brian Roelofs, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research II
Application:	BLA 761090
Applicant:	Dyax Corp
Submission Date:	October 31, 2017
Product:	Takhzyro (lanadelumab)
Dosage form(s):	injection
Strength and Container-Closure:	300 mg/2 mL (150 mg/mL) single-dose vials
Indication, dose, route, and frequency of administration:	prophylaxis to prevent attacks [REDACTED] (b) (4) of hereditary angioedema (HAE) in patients 12 years and older
Background and Summary Description:	The Applicant submitted an application for the prophylaxis to prevent attacks [REDACTED] (b) (4) of hereditary angioedema (HAE) in patients 12 years and older
<b>Recommendations:</b>	The container labels (submitted on June 29, 2018), carton labeling (submitted on June 1, 2018), and prescribing information, instructions for use, and patient labeling (submitted on July 30, 2018) are acceptable (see Appendix D) from an OBP labeling perspective.

<b>Materials Considered for this Label and Labeling Review</b>	
<b>Materials Reviewed</b>	<b>Appendix Section</b>
Proposed Labels and Labeling	A
Other	B (n/a)
Evaluation Tables	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

**DISCUSSION and CONCLUSION**

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations, and United States Pharmacopeia (USP) standards (see Appendix C).

The prescribing information, medication guide, patient labeling, instructions for use, 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), and USP standards.

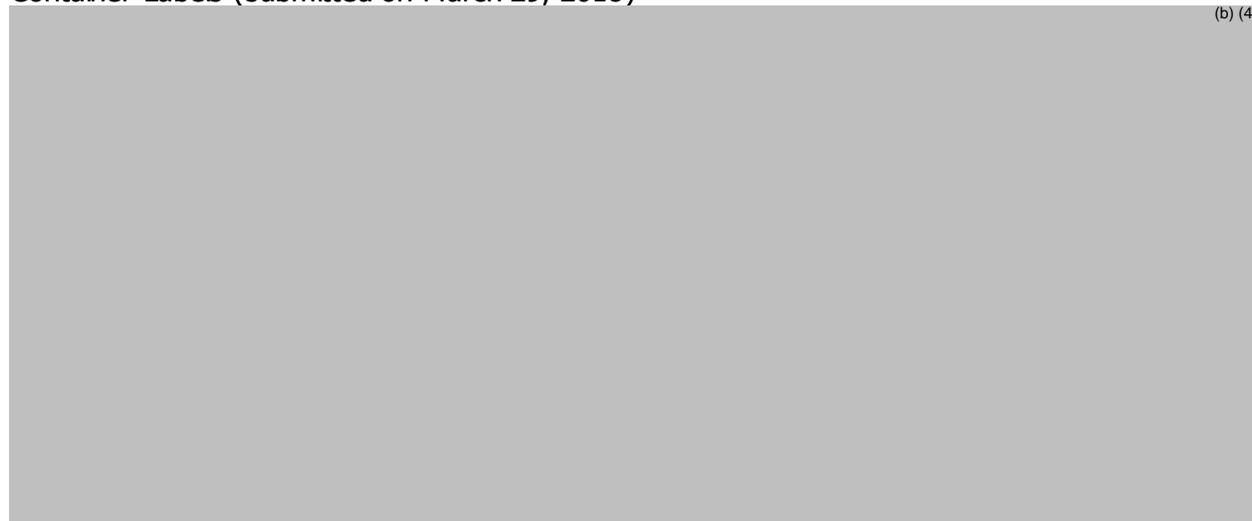
The container labels (submitted on June 29, 2018), carton labeling (submitted on June 1, 2018), and prescribing information, instructions for use, and patient labeling (submitted on July 30, 2018) are acceptable (see Appendix D) from an OBP labeling perspective.

**APPENDICES**

**Appendix A:** Proposed Labeling

Prescribing Information/Patient Information Labeling/ Instructions for Use (submitted on March 29, 2018 [\\cdsesub1\evsprod\bla761090\0019\m1\us\annotated-draft-labeling-text.docx](#))

Container Labels (submitted on March 29, 2018)



**Appendix B:** Other (n/a)

**Appendix C:** Evaluation Tables (Label<sup>1,2</sup> and Labeling<sup>3</sup> Standards)

### Container<sup>4</sup> Label Evaluation

<b>Regulations, Guidance and CDER Best Labeling Practices</b>	<b>Conforms</b>
<b>Proper Name</b> (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) <i>for container of a product capable of bearing a full label</i> <b>Comment/Recommendation:</b> <i>considered a partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Manufacturer name, address, and license number</b> (21 CFR 610.60) <i>for container of a product capable of bearing a full label</i> <b>Comment/Recommendation:</b> <i>considered a partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Lot number or other lot identification</b> (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100) <b>Comment/Recommendation:</b> <i>considered a partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Expiration date</b> (21 CFR 610.60, 21 CFR 201.17) <b>Comment/Recommendation:</b> <i>considered a partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Multiple dose containers (recommended individual dose)</b> 21 CFR 610.60	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Statement: "Rx only"</b> 21 CFR 610.60 21 CFR 201.100 <b>Comment/Recommendation:</b> If space permits, add "Rx only" statement <i>The Applicant revised as requested</i>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Medication Guide</b> 21 CFR 610.60 21 CFR 208.24	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>No Package for container</b> 21 CFR 610.60	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

<sup>1</sup> Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

<sup>2</sup> Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

<sup>3</sup> Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

<sup>4</sup> 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.

<p><b>Partial label</b>  21 CFR 610.60  21 CFR 201.10  <b>Comment/Recommendation:</b></p> <p>Revise the manufacturer statement to appear. Include the license number if there is enough space on the container label:  Mfd by: Dyax Corp.  U.S. License No. XXXX  <i>The Applicant revised as requested</i></p>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><b>No container label</b>  21 CFR 610.60</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><b>Ferrule and cap overseal</b></p> <p><b>Comment/Recommendation:</b></p> <p>FOR VIALS: Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: &lt;7&gt; Labeling (Ferrules and Cap Overseals).</p> <p><i>Applicant's response: The Applicant confirms that there is no text on the top surface of the ferrule and cap overseal of the vials in compliance with USP &lt;1&gt;. The lot number is printed on the skirt of the cap overseal following the USP guidance.</i></p> <p><i>FDA response: We find the Applicant's response acceptable per General Chapters: &lt;7&gt; Labeling (Ferrules and Cap Overseals), 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 (circle) surface of the ferrule or cap overseal.</i></p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><b>Visual inspection</b>  21 CFR 610.60</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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).

*The Applicant confirmed and we find this response acceptable*



<b><u>NDC numbers</u></b> 21 CFR 201.2 21 CFR 207.35 <b>Comment/Recommendation:</b> <i>Not required for partial labels</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b><u>Route of administration</u></b> 21 CFR 201.5 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<b><u>Preparation instructions</u></b> 21 CFR 201.5	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b><u>Package type term</u></b> 21 CFR 201.5	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Comment/Recommendation:</b> <i>partial label</i>	
<b><u>Drugs</u></b> <b><u>Misleading statements</u></b> 21 CFR 201.6	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b><u>Strength</u></b> 21 CFR 201.10 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<b><u>Drugs</u></b> <b><u>Prominence of required label statements</u></b> 21 CFR 201.15	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b><u>Spanish-language (Drugs)</u></b> 21 CFR 201.16	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b><u>FD&amp;C Yellow No. 5 and/or FD&amp;C Yellow No. 6</u></b> 21 CFR 201.20	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

<p><b>Phenylalanine as a component of aspartame</b> 21 CFR 201.21</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><b>Sulfites; required warning statements</b> 21 CFR 201.22</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><b>Bar code label requirements</b> 21 CFR 201.25 21 CFR 610.67</p>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><b>Comment/Recommendation:</b> Ensure the linear bar code appears on the label per 21 CFR 610.67.</p>	
<p><i>Applicant's response:</i></p>	
<div style="background-color: #cccccc; height: 200px; width: 100%;"></div> <p style="text-align: right;">(b) (4)</p>	
<p><i>FDA response: We find the response unacceptable and do not concur. Per 21 CFR 201.25(c)(2), the barcode must appear on the drug's label as defined by section 201(k) of the Federal Food, Drug, and Cosmetic Act. See 21 CFR 201.25(d) for the mechanism to request exemption from the bar code requirement: Can a drug be exempted from the bar code requirement? (1) On our own initiative, or in response to a written request from a manufacturer, repacker, relabeler or private label distributor, we may exempt a drug product from the bar code label requirements set forth in this section. The exemption request must document why:</i></p> <p style="padding-left: 40px;"><i>(i) compliance with the bar code requirement would adversely affect the safety, effectiveness, purity or potency of the drug or not be technologically feasible, and the concerns underlying the request could not reasonably be addressed by measures such as package redesign or use of overwraps; or</i></p> <p style="padding-left: 40px;"><i>(ii) an alternative regulatory program or method of product use renders the bar code unnecessary for patient safety.</i></p> <p><i>(2) Requests for an exemption should be sent to the Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993-0002 (requests involving a drug product or biological product regulated by the Center for Drug Evaluation and Research) or to the Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., Bldg. 71, Rm. G112, Silver Spring, MD 20993-0002 (requests involving a biological product regulated by the Center for Biologics Evaluation and Research).</i></p> <p>The applicant revised as requested</p>	

<b>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</b> 21 CFR 610.68 21 CFR 201.26	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Net quantity</b> 21 CFR 201.51  <b>Comment/Recommendation:</b> <i>partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Usual dosage statement</b> 21 CFR 201.55 21 CFR 201.100 <b>Comment/Recommendation:</b> <i>partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Inactive ingredients</b> 21 CFR 201.100  <b>Comment/Recommendation:</b> <i>partial label</i>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Storage requirements</b>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Dispensing container</b> 21 CFR 201.100	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

### **Package Label<sup>5</sup> Evaluation**

<b>Regulations, Guidance, and USP</b>	<b>Conforms</b>
<b>Proper name</b> (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Manufacturer name, address, and license number</b> 21 CFR 610.61  <b>Comment/Recommendation:</b> Ensure that the licensed manufacturer, address (as the Applicant listed on the submitted Form FDA 356h), and US license number appear on the carton labeling per 21 CFR 610.61(b) as follows: Manufactured by: Dyax Corp Lexington, MA 02421 U.S. License No. XXXX  <i>The Applicant revised as requested</i>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Lot number or other lot identification</b> 21 CFR 610.61	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes

<sup>5</sup> 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.

<p><b>Comment/Recommendation:</b> Ensure lot number appears on the label per 21 CFR 610.61 (c).  <i>The Applicant revised as requested</i></p>	<input type="checkbox"/> N/A
<p><b>Expiration date</b>  21 CFR 610.61  21 CFR 201.17  <b>Comment/Recommendation:</b> Ensure the expiration date appears on the label per 21 CFR 610.61 (d).  <i>The Applicant revised as requested</i></p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><b>Preservative</b>  21 CFR 610.61  <b>Comment/Recommendation:</b> If no preservative, ensure "No preservative" appears on the labeling per 21 CFR 610.61 (e).  <i>The Applicant revised as requested</i></p>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><b>Number of containers</b>  21 CFR 610.61</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><b>Strength/volume</b>  21 CFR 610.61  21 CFR 201.10  21 CFR 201.100</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><b>Storage temperature/requirements</b>  21 CFR 610.61</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><b>Handling: "Do Not Shake", "Do not Freeze" or equivalent</b>  (21 CFR 610.61)  <b>Comment/Recommendation:</b> Add the handling instruction "Do Not Shake"  <i>The Applicant revised as requested</i></p>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><b>Multiple dose containers (recommended individual dose)</b>  21 CFR 610.61</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><b>Route of administration</b>  21CFR 610.61  21 CFR 201.5  21 CFR 201.100</p>	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<p><b>Known sensitizing substances</b>  21CFR 610.61</p>	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<p><b>Inactive ingredients</b>  21 CFR 610.61  21 CFR 201.100  <b>Comment/Recommendation:</b> Include the list of active and inactive ingredients as follows:  Each mL of solution contains 150 mg lanadelumab, citric acid monohydrate (4.1.mg), L-histidine (7.8.mg), polysorbate 80 (0.1 mg), sodium chloride (5.3 mg), sodium phosphate dibasic</p>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A

dihydrate (5.3 mg), and Water for Injection, USP.

*The Applicant revised as requested*

<b>Source of the product</b> 21 CFR 610.61	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Minimum potency of product</b> 21 CFR 610.61	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> Ensure that if there is no US standard of potency that the words "No U.S. standard of potency" appear on the carton labeling per 21CFR 610.61 (r) <i>The Applicant revised as requested</i>	
<b>Rx only</b> 21CFR 610.61 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Divided manufacturing</b> 21 CFR 610.63	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Distributor</b> 21 CFR 610.64	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Bar code</b> 21 CFR 610.67 21 CFR 201.25	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)</b> 21 CFR 610.68 21 CFR 201.26	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>NDC numbers</b> 21 CFR 201.2 21 CFR 207.35	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Preparation instructions</b> 21 CFR 201.5	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Package type term</b> 21 CFR 201.5	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> Revise to the appropriate package type term for this product, "single-dose vial" <i>The Applicant revised as requested</i>	
<b>Drugs</b> <b>Misleading statements</b> 21 CFR 201.6	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Drugs</b> <b>Prominence of required label statements</b> 21 CFR 201.15	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Spanish-language (Drugs)</b> 21 CFR 201.16	<input type="checkbox"/> No <input type="checkbox"/> Yes

	<input checked="" type="checkbox"/> N/A
<b>FD&amp;C Yellow No. 5 and/or FD&amp;C Yellow No. 6</b> 21 CFR 201.20	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Phenylalanine as a component of aspartame</b> 21 CFR 201.21	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Sulfites; required warning statements</b> 21 CFR 201.22	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Net quantity</b> 21 CFR 201.51	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> Add the net quantity statement (b) (4) 2 mL as appropriate) to carton labeling. Ensure the net quantity appears on the PDP less prominent and away from the strength statement. <i>The Applicant revised as requested</i>	
<b>Usual dosage statement</b> 21 CFR 201.55 21 CFR 201.100	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Dispensing container</b> 21 CFR 201.100	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A
<b>Medication Guide</b> 21 CFR 610.60 21 CFR 208.24	<input type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> N/A

### **Prescribing Information and Patient Labeling Evaluation**

<b>Regulations</b>	<b>Conforms</b>
<b>PRESCRIBING INFORMATION</b>	
<b>Highlights of prescribing information</b>	
<b>PRODUCT TITLE</b> 21 CFR 201.57(a)(2)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> the proper name, dosage form, and route of administration in the product title should appear in lower case letters per <a href="https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm592850.pdf">https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm592850.pdf</a> <i>The Applicant revised as requested</i>	
<b>DOSAGE AND ADMINISTRATION</b> 21 CFR 201.57(a)(7)	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>DOSAGE FORMS AND STRENGTHS</b> 21 CFR 201.57(a)(8)	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> N/A
<b>Comment/Recommendation:</b> we revised the dosage form to "injection" and revised the strength presentation according to USP General Chapters <7> Labeling, the primary expression	

of strength is the strength per total volume (total drug content supplied in container) followed in close proximity by a parenthetical that includes the strength/mL

*The Applicant revised as requested*

**Full Prescribing Information**

**2 DOSAGE AND ADMINISTRATION**

21 CFR 201.57(c)(3)

- No
- Yes
- N/A

**3 DOSAGE FORMS AND STRENGTHS**

21 CFR 201.57(c)(4)

- No
- Yes
- N/A

**Comment/Recommendation:** We added the identifying characteristics of the dosage form and the dosage form per 21 CFR 201.57(c)(4).

*The Applicant revised as requested*

We removed non-required information for this section.

*The Applicant revised as requested*

Ensure that the package type term is consistent throughout all labels and labeling as "single-dose"

*The Applicant revised as requested*

We revised according to USP General Chapter <7> Labeling, the primary expression of strength is the strength per total volume (total drug content supplied in container) followed in close proximity by a parenthetical that includes the strength/mL.

*The Applicant revised as requested*

**6.2 IMMUNOGENICITY**

Draft Guidance for Industry: Labeling for Biosimilar Products

- No
- Yes
- N/A

**Comment/Recommendation:** we revised to the standard statement per Draft Guidance for Industry: Labeling for Biosimilar Products

*The Applicant revised as requested*

**11 DESCRIPTION**

(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))

- No
- Yes
- N/A

**Comment/Recommendation:** We deleted the (b) (4) since this 1st paragraph discusses the drug substance.

*The Applicant revised as requested*

We added the dosage form and route of administration per 21 CFR 201.57(c)(12)

*The Applicant revised as requested*

We revised the inactive ingredient list to appear in alphabetical order (see USP General Chapters <1091> Labeling of inactive ingredients)

*The Applicant revised as requested*

**16 HOW SUPPLIED/ STORAGE AND HANDLING**

21 CFR 201.57(c)(17)

- No
- Yes
- N/A

Comment/Recommendation: We added the identifying characteristics of the dosage form and the dosage form per 21 CFR 201.57(c)(17).

*The Applicant revised as requested*

We deleted as (b) (4) is not required information for this section

*The Applicant revised as requested*

We added "do not shake"

*The Applicant revised as requested*

We deleted the (b) (4) instructions since supportive data has not been submitted to the BLA.

*Applicant's response:* (b) (4)

(b) (4)

**MANUFACTURER INFORMATION**

21 CFR 610.61, 21 CFR 610.64

- No  
 Yes  
 N/A

**Comment/Recommendation:**

Ensure that the licensed manufacturer, address (as the Applicant listed on the submitted Form FDA 356h), and US license number appear here per 21 CFR 610.61(b)

*The Applicant revised as requested*

**INSTRUCTIONS FOR USE AND PATIENT INFORMATION**

**TITLE (NAMES AND DOSAGE FORM)**

- No  
 Yes  
 N/A

**Comment/Recommendation:** For patient information labeling: we revised added the dosage form by revising the route of administration statement

*The Applicant revised as requested*

**STORAGE AND HANDLING**

- No  
 Yes  
 N/A

**Comment/Recommendation:** For patient information labeling: We deleted the (b) (4) instructions since supportive data has not been submitted to the BLA

*The Applicant revised as requested*

**INGREDIENTS**

- No  
 Yes  
 N/A

**MANUFACTURER INFORMATION**

21 CFR 610.61, 21 CFR 610.64

- No  
 Yes  
 N/A

**Comment/Recommendation:** For patient information labeling: Ensure that the licensed manufacturer, address (as the Applicant listed on the submitted Form FDA 356h), and US license number appear here per 21 CFR 610.61(b)

*The Applicant revised as requested*

For IFU: revised the statement “(b) (4)” to “manufactured by”

*The Applicant revised as requested*

#### **APPENDIX D. Acceptable Labels and Labeling**

- Prescribing Information (submitted on July 30, 2018  
<\\cdsesub1\evsprod\bla761090\0037\m1\us\draft-pi-labeling-text.pdf>)
- Instructions for Use (submitted on July 30, 2018  
<\\cdsesub1\evsprod\bla761090\0037\m1\us\draft-ifu-labeling-text.pdf>)
- Patient Information (submitted on July 30, 2018  
<\\cdsesub1\evsprod\bla761090\0037\m1\us\draft-ppi-labeling-text.pdf>)

Container Labels (submitted on June 29, 2018)



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Vicky  
Borders-Hemphill

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Date: 7/31/2018 09:21:33AM  
GUID: 50814c7000007a3d59329f660d8ddf02



Brian  
Roelofs

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

## PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

**Reviewer:** Aimee L. Cunningham, Ph.D., M.P.H.  
**Quality Assessment Lead (Acting):** Maria Jose Lopez-Barragan, Ph.D.  
**Branch Chief:** Patricia Hughes, Ph.D.

BLA: 761090/0  
Applicant: Dyax Corp.  
US License Number: 1789  
Submission Reviewed: Amended BLA  
Product: Takhzyro (lanadelumab; SHP643, DX-2930)  
Indication: routine prophylaxis to prevent angioedema in HAE patients  
Dosage Form: 150 mg/mL solution for injection by s.c. route  
Manufacturing Site: Rentschler Biopharma SE in Laupheim, Germany  
(FEI: 1000291122)  
FDA Receipt Date: Rolling beginning 10/31/2017  
Action Date: 08/26/2018

### Approvability Recommendation

The drug substance portion of the amended BLA was reviewed from a product quality microbiology perspective and is recommended for approval with the following post-marketing commitment to be fulfilled by September 2018:

1. Conduct a low endotoxin recovery study to determine the detectability of endotoxin in lanadelumab (b) (4) using the kinetic turbidimetric LAL method.

### Review Summary

The amendment to the original BLA reviewed herein was submitted via eCTD on 06/15/2018 (sequence 0032). This amendment included a summary report (RL-REPORT-07090) for the additional low endotoxin recovery (LER) study (b) (4) and the final reports for the (b) (4). In responses submitted on 07/11/2018 (eCTD sequence 0036), Dyax committed to fulfill the additional PMC outlined above by September 2018.

## **Module 3.2**

### **R. Regional Information**

(b) (4)

#### **SATISFACTORY**

#### **Low Endotoxin Recovery (LER) Assessment**

The LER study submitted to the original BLA (RL-REPORT-06486) did not support the claimed hold time for (b) (4) of (b) (4) hours; multiple IRs were sent to request that the study be repeated. The summary report for an additional LER study (RL-REPORT-07090) is reviewed herein. (b) (4)

(b) (4)

(b) (4) The compendial kinetic turbidimetric LAL method (USP <85>) was used to test for endotoxin. Recovery was calculated compared to the nominal spike. As shown in the tables below (adapted from report RL-REPORT-07090), endotoxin recovery for both batches was within acceptance criteria ((b) (4) %), showing no LER in the DS/DP.

(b) (4)



(b) (4)

*Reviewer's comment:* These studies were conducted on [redacted] (b) (4)



[redacted] the following post-marketing commitment was set:

1. Conduct a low endotoxin recovery study to determine the detectability of endotoxin in lanadelumab [redacted] (b) (4) using the kinetic turbidimetric LAL method.

## SATISFACTORY

### Conclusions

- I. The amended DS portion of this BLA was reviewed from a microbial control and product quality microbiology perspective and is recommended for approval with the following PMC:
  - i. Conduct a low endotoxin recovery study to determine the detectability of endotoxin in lanadelumab [redacted] (b) (4) using the kinetic turbidimetric LAL method.
- II. No inspection follow-up items were identified.



Aimee  
Cunningham

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Maria Jose  
Lopez-Barragan

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Center for Drug Evaluation and Research  
Office of Pharmaceutical Quality  
Office of Process and Facilities  
Division of Microbiology Assessment

## **PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION**

**REVIEWER:** Jessica Hankins, Ph.D.  
**ACTING QAL:** Maria Jose Lopez-Barragan, Ph.D.  
**BRANCH CHIEF:** Patricia Hughes, Ph.D.

BLA: 761090  
Applicant: Dyax Corp.  
US License Number: 1789  
Submission Reviewed: Original BLA (Rolling submission)  
Product: Lanadelumab (SHP643)  
Indication: Routine prophylaxis to prevent angioedema attacks in HAE patients  
Dosage Form: Solution for subcutaneous injection (150 mg/mL)  
Manufacturing Sites: Drug Product - Cook Pharmica LLC (FEI: 3005949964)  
FDA Receipt Date: November 17, 2017 (Rolling; Module 3 receipt)  
Action Date: August 26, 2018

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### **Conclusion and Approvability Recommendation**

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

### **Product Quality Microbiology Assessment: Drug Product Summary**

#### **Drug Product Quality Microbiology Information Reviewed**

<b>Sequence number</b>	<b>Date</b>	<b>Description</b>
0029	05/25/18	Response to information request

*Reviewer comment: As noted in the interim review uploaded in Panorama on May 24, 2018, two review issues were pending:*

1. The applicant was requested to remove (b) (4) from the stability program.
2. Additional data from low endotoxin recovery (LER) studies.

In sequence 0029, the applicant updated the BLA (section P.5.1 and P.8.2) to remove (b) (4) from the stability program. Refer to the review memo below.

Results for the LER studies were submitted in sequence 0032 and were reviewed by the drug substance microbiology reviewer (Dr. Aimee Cunningham). The DS microbiology review addendum by Dr. Aimee Cunningham indicated that LER was not observed in the (b) (4) study. (b) (4)

In lieu of the data presented in sequence 0032, the DP may be released using the LAL kinetic turbidimetric assay (previously reviewed in the DP microbiology memo uploaded in Panorama on May 24, 2018).

## **Module 3.2**

### **P.5.1 Specifications**

Reviewer comment: As indicated in the review memo archived in Panorama on May 24, 2018, endotoxin and sterility are tested on release. Additionally, CCIT is performed on stability. (b) (4) was removed from the stability program in sequence 0029.

The review memo archived in Panorama on May 24, 2018 indicated that (b) (4)

Additionally, given the proposed dosing regimen (300 mg every 2 weeks) the risk to patient safety is deemed low.

SATISFACTORY

### **P.5.2 Analytical Procedures**

#### **Endotoxin**

Reviewer comment: The LAL kinetic turbidimetric method is adequate for endotoxin release testing of the DP, as no LER was observed in the (b) (4) study reviewed by the DS microbiology reviewer. Refer to the DS microbiology addendum for additional information.

SATISFACTORY

### **P.5.3 Validation of Analytical Procedures**

### Endotoxin

*Reviewer comment: The method qualification is reviewed in the interim review memo, uploaded and archived in Panorama on May 24, 2018. As noted above, the LAL kinetic turbidimetric method is adequate for endotoxin release testing of the DP, as no LER was observed in the (b) (4) study reviewed by the DS microbiology reviewer. Refer to the DS microbiology addendum for additional information.*

### **P.8.2 Post-approval Stability Protocol and Stability Commitment**

*Reviewer comment: (b) (4) was removed from the stability program. Table 1 of section P.8.2 was updated accordingly.*

### **Conclusion**

- I. The drug product section of this BLA was reviewed from a sterility assurance and product quality perspective and is recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. Inspection follow-up items were not identified.



Jessica  
Hankins

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Maria Jose  
Lopez-Barragan

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**Office of Pharmaceutical Quality Integrated Review**  
**BLA 761090 Takhzyro (lanadelumab)**  
**May 25, 2018 (Priority Review)**

**Recommendation:** This BLA is recommended for approval, pending the sponsor’s response to two outstanding DMA information requests (IR) in their primary review.

The OBP and DIA primary reviews recommend approval of this BLA and are signed in Panorama. DMA has recommended tentative approval. The two outstanding DMA IR items include:

- 1) Removing the [REDACTED] (b) (4) for the drug product stability program.
- 2) Updating the Endotoxin recovery studies requested in an Information Request. The Applicant has stated that study results will be provided mid-June and addenda to both the Micro DS and DP reviews will be added at that time.

The evaluation of the two DMA IR items will be covered in a future amendment to the primary DMA reviews. This ATL memo will only be amended if there are deficiencies with the IR items.

Drug Name/Dosage Form	Takhzyro (lanadelumab) / liquid in a single-dose vial
Strength/Potency	[REDACTED] (b) (4) 300 mg/2 mL solution in a single dose vial
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Routine prophylaxis to prevent attacks [REDACTED] (b) (4) of hereditary angioedema (HAE) in patients 12 years and older
Applicant/Sponsor	Dyax Corp.
US agent, if applicable	n/a

**Product Overview**

Takhzyro (lanadelumab) is a fully human IgG1/κ-light chain antibody that specifically binds and inhibits active plasma kallikrein proteolytic activity without binding prekallikrein, the inactive precursor found in the circulation. Lanadelumab is produced in a recombinant Chinese Hamster Ovary (CHO) cell line and has an approximate molecular mass of 146 kilodaltons. Takhzyro is a sterile, preservative-free, colorless to slightly yellow solution. Takhzyro is supplied in [REDACTED] (b) (4) 300 mg/2 mL in a single-dose vial. Each mL of ready-to-use Takhzyro solution contains lanadelumab (150 mg), citric acid monohydrate (4.1 mg), L-histidine (7.8 mg), polysorbate 80 (0.1 mg), sodium chloride (5.3 mg), sodium phosphate dibasic dihydrate (5.3 mg), and Water for Injection, USP. The solution has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.

<b>Discipline</b>	<b>Reviewer</b>	<b>Branch/Division</b>
Drug Substance	Timothy Wadkins	OBP/DBRRII
Drug Product	Brian Roelofs	OBP/DBRRII
Immunogenicity Assay and DS/DP Assay Validation	Zhaohua Zhou (Primary); Howard Anderson (team lead)	OBP/DBRRII
Labeling	Vicky Hemphill-Borders	OBP
Facility	Steven Fong	OPF/DIA
Microbiology – DS	Aimee Cunningham	OPF/DMA
Microbiology – DP	Jessica Hankins	OPF/DMA
QAL Microbiology	Maria Lopez-Barragan	OPF/DMA
Application Team Lead	Xianghong Jing	OBP/DBRRII

Multidisciplinary Review Team:

<b>Discipline</b>	<b>Reviewer</b>	<b>Office/Division</b>
RPM	Colette Jackson	ODEII/DPARP
Cross-disciplinary Team Lead	Sally Seymour	ODEII/DPARP
Medical Officer	Stacy Chin	ODEII/DPARP
Pharm/Tox	Matthew Whittaker	ODEII/DPARP
Clinical Pharmacology	Jianmeng Chen	OCP/DCPII
Statistics	Susan Duke & Yongman Kim	OB/DBII

1. Names:

- a. Proprietary Name: Takhzyro
- b. Trade Name: Takhzyro
- c. Non-Proprietary/USAN: lanadelumab
- d. CAS name: 1426055-14-2
- e. Common name: SHP643; DX-2930
- f. INN Name: Lanadelumab
- g. Compendial Name: None
- i. OBP systematic name: MAB HUMAN (IGG1) ANTI P03952 (KLKB1\_HUMAN) [SHP643]
- h. Other Names: None

2. Pharmacologic category: Therapeutic recombinant human monoclonal antibody

Submissions Reviewed:

<b>Submission(s) Reviewed</b>	<b>Document Date</b>
Module 3 Quality #0002	11/17/2017
Information Request Response #0007	01/19/2018 (OPF)
Information Request Response #0008	01/25/2018 (OBP)
Information Request response #0011	02/15/2018 (OBP)

Information Request Response #0013	03/05/2018 (OBP)
Information Request response #0014	03/15/2018 (OBP)
Information Request response #0015	03/16/2018 (OBP)
Information Request response #0018	03/27/2018 (OBP)
Information Request response #0020	03/29/2018 (OPF)
Information Request response #0021	04/04/2018 (OPF)
Information Request response #0026	05/07/2018 (OBP, OPF)
Information Request response #0027	05/18/2018 (OPF)

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

A. DMFs:

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Codes (Comments)
(b) (4) (Type V)	(b) (4)	(b) (4)	Yes	2
(b) (4) (Type III)		(b) (4)	Yes	3
(b) (4) (Type V)		(b) (4)	Yes	3
(b) (4) (Type V)		(b) (4)	Yes	3
(b) (4) (Type V)		(b) (4)	Yes	3
(b) (4) (Type III)		(b) (4)	Yes	3
(b) (4) (Type II)		(b) (4)	Yes	3

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

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

B. Other documents: IND 116647

## Executive Summary

### I. Recommendations:

#### A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Biotechnology Products, OPQ, CDER, recommends approval of STN 761090 for Takhzyro manufactured by Dyax Corp/Shire, pending review of two outstanding DMA microbial information requests. The data submitted in this application are adequate to support the conclusion that the manufacture of Takhzyro is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

#### B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance: Rentschler Biopharma SE,  
Erwin-Rentschler-Str. 21, 88471  
Laupheim, Germany  
FEI: 1000291122
  - Drug Product: Cook Pharmica LLC,  
1300 South Patterson Drive  
Bloomington, IN 47403, US  
FEI: 3005949964
- Fill size and dosage form: (b) (4) 300 mg/2 mL  
dosage in a 5 mL single-dose vial
- Dating period:
  - Drug Substance: (b) (4) months: (b) (4)
  - Drug Product: 24 months: 5°C ± 3°C
- Exempt from lot release:
  - Takhzyro is exempted from lot release because it is a specified product per 601.2(a)

#### Benefit/Risk Considerations:

Lanadelumab is an inhibitor of plasma kallikrein indicated for the treatment of hereditary angioedema. The data submitted in this application support the conclusion that the manufacture of lanadelumab is well controlled and yields a consistently high quality product. The conditions used in manufacturing have been sufficiently validated, and a consistent product is prepared from the multiple production runs presented. From a product quality perspective, this product is approvable for human use.

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

There is one PMC from the CMC review team:

[Redacted content] (b) (4)

**II. Summary of Quality Assessments:**

Table 1 below is a summary of critical quality attributes and the associated control strategies for attributes that are relevant to both Drug Substance and Drug Product. For additional information, see the technical document on primary reviews of the Drug Substance Quality and Drug Product Quality by OBP/DBRR-II and the Drug Substance Microbiology and the Drug Product Microbiology by OPF/DMA.

**A. CQA Identification, Risk and Lifecycle Knowledge Management**

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

CQA (type)	Risk	Origin	Control Strategy	Other
Biological Potency: Kallikrein Activity Inhibition Assay	Efficacy	Intrinsic to the molecule, impacted by oxidation, glycation, deamidation, aggregation, and fragmentation	(b) (4)	N/A
Protein Concentration	Efficacy and Safety	Manufacturing Process		N/A
Identity	Safety and Efficacy	Intrinsic to molecule		N/A
High Molecular Weight (HMW) species/Aggregates	Efficacy, Pharmacokinetics, and Safety/Immunogenicity	Manufacturing process and exposure to heat, light, and low and high pH stress		N/A
Fragmentation (%IgG monomer)	Efficacy, Pharmacokinetics, and Immunogenicity	Affected by manufacturing and storage conditions. Can form due to agitation, temperature, or light.		N/A
Fragmentation (%light chain and %heavy chain)	Efficacy, Pharmacokinetics, and Immunogenicity	Affected by manufacturing and storage conditions. Can form due to agitation, temperature, or light.		N/A
Charge Variant Profile (deamidation, C-terminal and N-terminal variants, and oxidation)	Efficacy, Pharmacokinetics, and Immunogenicity	Bioreactor conditions and degradation during manufacture and storage		N/A

**B. Takhzyro Drug Substance Quality Summary**

**CQA Identification, Risk, and Lifecycle Knowledge Management**

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

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance	Safety	Controlled by the manufacturing process	(b) (4)	N/A
Kallikrein Activity Inhibition (Potency)	Efficacy	Changes to protein composition during manufacture or storage		N/A
High-molecular weight (HMW) species	Efficacy, pharmacokinetics and immunogenicity	Affected by manufacturing and storage conditions. Can form due to agitation, temperature, or light exposure.		N/A
Low-molecular weight (LMW) species	Efficacy, pharmacokinetics and immunogenicity	Affected by manufacturing and storage conditions. Can form due to agitation, temperature, or light exposure.		N/A
Charge Variant Profile (deamidation, C-terminal variants and oxidation)	Efficacy, pharmacokinetics and immunogenicity	Bioreactor conditions and degradation during manufacture and storage		N/A
Host Cell Proteins (process-related impurity)	Safety and Immunogenicity	Production cell line		Process Validation studies show minimal host cell protein level observed (b) (4). A DS release specification at (b) (4).
Host Cell DNA (process-related impurity)	Safety	Production cell line		In process clearance studies showed robust clearance. Specification is not required for lot release.
Residual (b) (4)	Safety and Immunogenicity	Process-related (b) (4)		N/A
Residual (b) (4)	Safety	Production bioreactor		N/A

Viruses (contaminant)	Safety	Contamination during manufacture, mostly likely during cell culture operations	(b) (4)	N/A
Mycoplasma (contaminant)	Safety	Mycoplasma would most likely be introduced during cell culture operations	(b) (4)	N/A
Leachables (Process-related impurity)	Safety	Process-related impurities potentially from manufacture and the DS container closure system (CCS)	(b) (4)	N/A
Endotoxin	Safety and Purity	Raw materials or contamination during manufacturing	(b) (4)	N/A
Bioburden	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing	(b) (4)	N/A

- **Description:**

Takhzyro (lanadelumab) is a non-plasma derived, recombinant, fully human, monoclonal antibody (IgG1/κ-light chain) produced in Chinese Hamster Ovary (CHO) cells. Takhzyro is composed of two light (213 residues) and two heavy (451 residues) chains with a single N-glycosylation site within the constant domain of the heavy chain (CH2) at Asn302. Based on the amino acid sequence, the molecular weight of the non-glycosylated lanadelumab is 146 kDa. The calculated molecular mass of the fully reduced light chain is 23 kDa. The calculated molecular mass of the fully reduced and non-glycosylated heavy chain is 49 kDa. Amino acid sequencing and tryptic peptide mapping with mass spectrometry analysis confirms the correct amino acid sequence. (b) (4)

- **Mechanism of Action (MoA):**

Takhzyro (lanadelumab) inhibits active plasma kallikrein proteolytic activity without binding prekallikrein, the inactive precursor found in the circulation. Increased plasma kallikrein activity leads to angioedema attacks in patients with HAE through the proteolysis of high molecular weight kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin,

a potent vasodilator that increases vascular permeability resulting in swelling and pain associated with HAE. It has been demonstrated that patients with HAE due to C1-inhibitor (C1-INH) deficiency or dysfunction have increased plasma kallikrein activity, as indirectly measured by amount of cHMWK, both during and between HAE attacks. Lanadelumab provides sustained control of plasma kallikrein activity and thereby limits bradykinin generation in patients with HAE.

The potential for lanadelumab to induce antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) was assessed *in vitro* using cultured human umbilical vein endothelial cells (HUVECs). No HUVEC cell lysis was observed in the assays, indicating a lack of lanadelumab-mediated ADCC and CDC activity.

- Potency Assay:

The biological activity (potency) of lanadelumab DS is determined by measuring the equilibrium inhibition constant ( $K_i$ ) for its ability to inhibit human plasma kallikrein (pKal) activity, which is directly related to the mechanism of action of the DS. The assay uses a recombinant pKal catalytic domain as the enzyme and a synthetic peptide (Pro-Phe-Arg-7-amido-4-methylcoumarin) as a substrate in a 96-well plate format. The substrate undergoes an increase in fluorescence when proteolytically cleaved by the enzyme. The lanadelumab reference standard is tested in parallel on each plate along with the DS sample and dilution buffer (blank). The  $K_i$  of the reference standard is divided by the  $K_i$  of the lanadelumab DS sample, and the result is reported in percent potency relative to the reference standard.

- Reference Materials:

(b) (4)

- Critical starting materials or intermediates:

(b) (4)

- Manufacturing process summary:

(b) (4)



- Container closure:



- Dating period and storage conditions:



**C. Takhzyro Drug Product Quality Summary:**

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

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

CQA (type)	Risk	Origin	Control Strategy
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contaminants may be introduced during the manufacturing process	(b) (4)
Endotoxin (contaminant)	Safety, Purity, Immunogenicity	Raw materials may be introduced throughout the DP manufacturing process	
Container Closure Integrity (maintenance of sterility during shelf life)	Safety	Container closure breaches during storage	
Appearance	Safety and Efficacy	Formulation, Contamination, or Degradation	
Polysorbate 80 Concentration	Safety	Manufacturing process	
Protein content	Efficacy and pharmacokinetics	Manufacturing process	
pH	Safety and Efficacy	Formulation	
Particulate Matter	Safety / Immunogenicity	Manufacturing process and container closure system	
Extractable Volume	Efficacy / Dosing	Manufacturing process	
Leachables (process-related impurities)	Safety	Manufacturing equipment and CCS	

- Potency and Strength:**  
Takhzyro at a concentration of 150 mg/mL is provided in [REDACTED] (b) (4) a 300 mg dosage in a 5 mL vial. Potency of lanadelumab is determined as a percent of inhibition human plasma kallikrein (pKal) activity to the reference standard. The potency assay is the same as described in the drug substance section of this review.
- Summary of Product Design:**

Takhzyro is supplied as a sterile, single-dose, preservative-free solution for subcutaneous injection in a single dose vial that is assembled with a safety device. Each mL of ready to use Takhzyro solution contains lanadelumab (150 mg), citric acid monohydrate (4.1 mg), L-histidine (7.8 mg), polysorbate 80 (0.1 mg), sodium chloride (5.3 mg), sodium phosphate dibasic dihydrate (5.3 mg), and Water for Injection, USP. The solution has a pH of approximately 6.0 and an osmolality of approximately 300 mOsm/kg.

- List of Excipients:

Excipients include sodium phosphate dibasic dihydrate (5.3 mg), citric acid monohydrate (4.1 mg), L-histidine (7.8 mg), sodium chloride (5.3 mg), and polysorbate 80 (0.1 mg).

- Reference Materials:

The same reference material is used for drug substance and drug product.

- Manufacturing process summary:



- Container closure:

The primary container closure system for lanadelumab drug product consists of a (b) (4) glass vial, a rubber stopper, and a crimp seal with cap. Appropriate compatibility studies were performed for the container closure system.

- Dating period and storage conditions:

The dating period for lanadelumab drug product is 24 months at  $5 \pm 3^{\circ}\text{C}$ , protected from light.

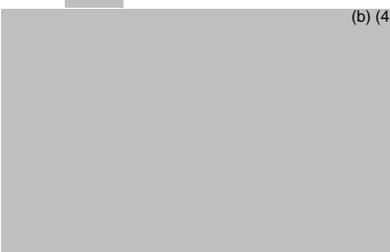
**D. Novel Approaches/Precedents:** None

**E. Any Special Product Quality Labeling Recommendations:**

- Store vials refrigerated at 2°C to 8°C (36°F to 46°F).
- Keep the vial in the original carton in order to protect the vial from light.
- Do not freeze. Do not shake.
- TAKHZYRO should be administered subcutaneously within 2 hours of preparing the dosing syringe at room temperature. After the dosing syringe is prepared, it can be refrigerated at 36°F to 46°F (2°C to 8°C) and must be used within 8 hours.

**F. Establishment Information:**

There are no outstanding inspection or facility issues. The Division of Inspectional Assessment recommends approval of the BLA. The manufacturing and testing facilities, their responsibilities in lanadelumab production, and inspectional outcomes are summarized in the table below.

Overall Recommendation:			
DRUG SUBSTANCE			
Function	Site Information	DUNS/FEI Number	Facility Status
- (b) (4) DS manufacture  (b) (4)	Rentschler Biopharma SE Erwin-Rentschler-Str. 1 88471 Laupheim GERMANY	FEI: 1000291122	PLI 03/05 – 03/08/2018  Acceptable
Batch disposition	Dyax Corp. 300 Shire Way Lexington, MA 02421 U.S.	FEI: 3009340644	Acceptable

(b) (4)

	U.K.		(b) (4)
<b>DRUG PRODUCT</b>			
<b>Function</b>	<b>Site Information</b>	<b>DUNS/FEI Number</b>	<b>Facility Status</b>
- DP manufacture (b) (4)	Cook Pharmica LLC 1300 South Patterson Drive Bloomington, IN 47403	FEI: 3005949964	Acceptable
- (b) (4) DS manufacture (b) (4)	Rentschler Biopharma SE Erwin-Rentschler-Str. 1 88471 Laupheim GERMANY	FEI: 1000291122	PLI 03/05 – 03/08/2018  Acceptable

**G. Facilities:**

Lanadelumab drug substance is manufactured at Rentschler Biopharma, Laupheim, Germany (FEI: 1000291122). A pre-licensing inspection (PLI) of Rentschler was conducted 03/05-08/2018 by DIA and OBP in support of the subject BLA. The inspection focused on upstream and downstream manufacture of Lanadelumab DS as proposed in the submission. General discussions were held regarding enhanced procedures for microbial control in the manufacturing areas and deviation management. No Form FDA 483 was issued. The inspection resulted in an NAI approve conclusion.

Lanadelumab drug product is manufactured at Cook Pharmica, Bloomington, IN (FEI: 3005949964). The most recent inspection of Cook Pharmica consisted of a (b) (4) surveillance inspection (b) (4) that resulted in an NAI approve conclusion. (b) (4)

The second and third most recent DP inspections consisted of a (b) (4) (b) (4) Both resulted in VAI approve conclusions.

Therefore, the PLI inspection on this site is waived.

## H. Lifecycle Knowledge Management:

- **Drug Substance:**

- Protocols approved:
  - Drug substance annual stability protocol
  - Protocol for qualification of future primary and working reference standard
  - Protocol for qualification of future working cell banks
  - concurrent validation protocol for (b) (4)
- Outstanding review issues/residual risk:
  - n/a
- Future inspection points to consider:
  - Evaluate trending of release and in-process tests results
  - Check to ensure that CAPAs 17-0125, 17-0126, and 18-0116 have been closed and adequately implemented. These were in response to Deviation-17-0362 ( (b) (4) ) and were still open as of the time of the PLI. A verbal observation concerning this issue was provided at the close-out meeting for the PLI.

- **Drug Product**

- Protocols approved:
  - Drug product annual stability protocol
- Outstanding review issues/residual risk:
  - See Post-Marketing Commitments in Section IB
- Future inspection points to consider:
  - Evaluate trending of release and in-process tests results

## Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

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



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