

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125509Orig1s000

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 125509

Application Type: New BLA

Name of Drug/Dosage Form: Anthim (obiltoxaximab) Injection, for intravenous use

Applicant: Elusys Therapeutics

Receipt Date: March 20, 2015

Goal Date: March 18, 2016

1. Regulatory History and Applicant's Main Proposals

Elusys Therapeutics, Inc. submitted a new Biologics Licensing Application (BLA) under section 351(a) of the Public Health Service Act and 21CFR Part 601, Subpart H (Approval of a Biologic Product When Human Efficacy Studies are not Ethical or Feasible) Anthim (obiltoxaximab) with the following indications: treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

Selected Requirements of Prescribing Information

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

| Section | Required/Optional |
|--|---|
| • Highlights Heading | Required |
| • Highlights Limitation Statement | Required |
| • Product Title | Required |
| • Initial U.S. Approval | Required |
| • Boxed Warning | Required if a BOXED WARNING is in the FPI |
| • Recent Major Changes | Required for only certain changes to PI* |
| • Indications and Usage | Required |
| • Dosage and Administration | Required |
| • Dosage Forms and Strengths | Required |
| • Contraindications | Required (if no contraindications must state “None.”) |
| • Warnings and Precautions | Not required by regulation, but should be present |
| • Adverse Reactions | Required |
| • Drug Interactions | Optional |
| • Use in Specific Populations | Optional |

Selected Requirements of Prescribing Information

| | |
|---|----------|
| • Patient Counseling Information Statement | Required |
| • Revision Date | Required |

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- YES** 14. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

Selected Requirements of Prescribing Information

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

Selected Requirements of Prescribing Information

- See 17 for PATIENT COUNSELING INFORMATION

If a product has (or will have) FDA-approved patient labeling:

- See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling
- See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Comment:

Revision Date in Highlights

- YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

APPEARS THIS WAY ON ORIGINAL

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

| |
|--|
| BOXED WARNING |
| 1 INDICATIONS AND USAGE |
| 2 DOSAGE AND ADMINISTRATION |
| 3 DOSAGE FORMS AND STRENGTHS |
| 4 CONTRAINDICATIONS |
| 5 WARNINGS AND PRECAUTIONS |
| 6 ADVERSE REACTIONS |
| 7 DRUG INTERACTIONS |
| 8 USE IN SPECIFIC POPULATIONS |
| 8.1 Pregnancy |
| 8.2 Labor and Delivery |
| 8.3 Nursing Mothers |
| 8.4 Pediatric Use |
| 8.5 Geriatric Use |
| 9 DRUG ABUSE AND DEPENDENCE |
| 9.1 Controlled Substance |
| 9.2 Abuse |
| 9.3 Dependence |
| 10 OVERDOSAGE |
| 11 DESCRIPTION |
| 12 CLINICAL PHARMACOLOGY |
| 12.1 Mechanism of Action |
| 12.2 Pharmacodynamics |
| 12.3 Pharmacokinetics |
| 12.4 Microbiology (by guidance) |
| 12.5 Pharmacogenomics (by guidance) |
| 13 NONCLINICAL TOXICOLOGY |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 Animal Toxicology and/or Pharmacology |
| 14 CLINICAL STUDIES |
| 15 REFERENCES |
| 16 HOW SUPPLIED/STORAGE AND HANDLING |
| 17 PATIENT COUNSELING INFORMATION |

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

Comment:

N/A

Selected Requirements of Prescribing Information

33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES 35. All text in the BW should be **bolded**.

Comment:

- YES 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- N/A 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES

Selected Requirements of Prescribing Information

40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JANE A DEAN
03/18/2016



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

FINAL LABEL AND LABELING REVIEW

| | |
|-------------------|--|
| Date: | March 3, 2016 |
| Reviewer: | Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products Jibril Abdus-samad -S <small>Digitally signed by Jibril Abdus-samad -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus-samad -S Date: 2016.03.03 10:01:17 -05'00'</small> |
| Through: | Tao Xie, PhD, Quality Reviewer Division of Biotechnology Review and Research II Tao Xie -S <small>Digitally signed by Tao Xie -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tao Xie -S, 0.9.2342.19200300.100.1.1=0011466376 Date: 2016.03.03 10:12:14 -05'00'</small> |
| Application: | BLA 125509/0 |
| Product: | Anthim (obilttoxaximab) |
| Applicant: | Elusys Therapeutics, Inc. |
| Submission Dates: | March 20 2015; February 11; March 2 2016 |

Executive Summary:

The commercial container label and carton labeling for Anthim (obilttoxaximab) were reviewed and found to comply with the following 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 United States Pharmacopeia (USP), [USP 38/NF 33 December 1, 2015 to April 30, 2016]. Labeling deficiencies were identified and resolved. The commercial container label and carton labeling submitted on March 2, 2016 is acceptable.

The Strategic National Stockpile (SNS) container label and carton labeling (b) (4)

Background and Summary Description:

The Applicant submitted BLA 125509 Anthim (obilttoxaximab) on March 20, 2015. Table 1 lists the proposed characteristics of Anthim (obilttoxaximab).

Table 1: Proposed Product Characteristics of March 20, 2015.

| | |
|--|--|
| Proprietary Name: | Anthim |
| Proper Name: | obiltoximab |
| Indication: | <ul style="list-style-type: none"> • treatment of adult and pediatric patients with inhalational anthrax due to <i>Bacillus anthracis</i> in combination with appropriate antibacterial drugs. • prophylaxis of inhalational anthrax due to <i>Bacillus anthracis</i> when alternative therapies are not available or are not appropriate. |
| Dose: | <p><u>Adults:</u> 16 mg/kg intravenously over 1 hour 30 minutes after dilution in 0.9% Sodium Chloride Injection, USP (normal saline) to a final volume of 250 mL</p> <p><u>Pediatrics:</u></p> <ul style="list-style-type: none"> • 16 mg/kg for pts greater than 40 kg; • 24 mg/kg for patients 15 kg to 40 kg; • 32 mg/kg for patients 15 kg or less |
| Route of Administration: | Intravenous Infusion |
| Dosage Form: | Injection |
| Strength and Container-Closure: | 600 mg/6 mL single-dose vial. |
| Storage and Handling: | Store in refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. |

Materials Reviewed:

- Container Label
 - Carton Labeling
 - Secondary Package Labeling
- *trade and National Stockpile versions were submitted.

Start of Sponsor Material

Commercial Container Label (submitted March 20, 2015)

<\\cdsesub1\evsprod\bla125509\0000\m1\us\114-label\1141-draft-label\contain-commercial.pdf>



SNS Container Label (submitted March 20, 2015)

<\\cdsesub1\evsprod\bla125509\0000\m1\us\114-label\1141-draft-label\contain-stockpile.pdf>



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *conforms*.

(2) The name, address, and license number of manufacturer; *does not conform. The Applicant is*  (b) (4)

OBP Request: Revise the manufacturer information to read:

Manufactured by:
Elusys Therapeutics, Inc.
Pine Brook, NJ 07058

U.S. License Number 1907

The name, address, and license number of the licensed manufacturer must appear labeling per 21 CFR 610.60(a)(2) and 21 CFR 610.61(b). (b) (4)

Applicant revised as requested.

(3) The lot number or other lot identification; *conforms.*

(4) The expiration date; *does not conform*

OBP Request: Add the expiration date per 21 CFR 201.17.

Applicant revised the commercial vial as requested.

See "Discussion of the Applicant's Proposals" below for a discussion of the SNS label and labeling.

(5) The recommended individual dose, for multiple dose containers; *not applicable.*

(6) The statement: "Rx only" for prescription biologicals; *conforms.*

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label; *not applicable.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for

multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms*.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable*.

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *does not conform*.

OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

The Applicant's response included a photo of a labeled vial indicating sufficient area for inspections. Acceptable.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms*. *We concur with DMEPA's request to provide a unique NDC number for each packaging configuration.*

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence. *Does not conform*.

OBP Request: Ensure that the established name is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). *Applicant revised as requested.*

F. 21 CFR 201.15 Drugs; prominence of required label statements. *Does not conform.*

OBP Requests:

Delete or decrease the size of the graphic on the PDP, located above the proprietary name "Anthem" to increase the white space on the label to improve readability per 21 CFR 201.15. *Applicant revised as requested.*

Revise the presentation of the names of the container labels and carton labeling similar to the example below in accordance with Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors , April 2013.

Anthem
(obiltoxaximab)
Injection

Applicant revised as requested.

Add the bolded statement "Single-Dose Vial. Discard Unused Portion" to the side panel. *Applicant revised as requested.*

Add the storage and handling information on the side panel to read "Store at 2°C to 8°C (36°F to 46°F). Protect from light. Do not freeze or shake. *Applicant revised as requested.*

G. 21 CFR 201.17 Drugs; location of expiration date; *does not conform.*

OBP Request: Add the expiration date per 21 CFR 201.17. *Applicant revised the commercial vial as requested.*

See "Discussion of the Applicant's Proposals" below for a discussion of the SNS label and labeling.

H. 21 CFR 201.25 Bar code; *does not conform.*

OBP Request: Add the linear barcode per 21 CFR 201.25. *Applicant revised as requested.*

I. 21 CFR 201.50 Statement of identity; *conforms.*

J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms.*

K. 21 CFR 201.55 Statement of dosage; *conforms.*

L. 21 CFR 201.100 Prescription drugs for human use; *conforms.*

Start of Sponsor Material

Commercial Carton Labeling (submitted March 20, 2015)

[\\cdsesub1\evsprod\bla125509\0000\m1\us\114-label\1141-draft-label\carton-commercial.pdf](#)



(b) (4)



End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. *Conforms.*

b) The name, addresses, and license number of manufacturer; *does not conform. The Applicant i* (b) (4)

OBP Request: Revise the manufacturer information to read:

Manufactured by:
Elusys Therapeutics, Inc.
Pine Brook, NJ 07058
U.S. License Number 1907

The name, address, and license number of the licensed manufacturer must appear labeling per 21 610.60(a)(2) and 21 CFR 610.61(b). (b) (4)

Applicant revised as requested.

- c) The lot number or other lot identification; *conforms.*
- d) The expiration date; *conforms.*
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms.*
- f) The number of containers, if more than one; *not applicable.*
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms.*
- h) The recommended storage temperature; *conforms.*
- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *does not conform.*

OBP Request: Add the statement "Do Not Shake" after "Do Not Freeze." *Applicant revised as requested.*

- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable.*

k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*. Note DAIP (b) (4)

l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.

o) The adjuvant, if present; *not applicable*.

p) The source of the product when a factor in safe administration; *not applicable*.

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels; *not applicable*.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Exempt. Anthim (obiltoxaximab) is a monoclonal antibody.*

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D.  (b) (4)
See above comments regarding name of manufacturer.



E. 21 CFR 610.67 Bar code label requirements: *conforms*.

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] *conforms*. *We concur with DMEPA's request to provide a unique NDC number for each packaging configuration.*

A. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

B. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

C. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *does not conform*.

OBP Request: Ensure that the established name is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). *Applicant revised as requested.*

D. 21 CFR 201.15 Drugs; prominence of required label statements; conforms.

OBP Requests:
Remove bolding from the Rx Only statement and consider relocating to the top of the PDP across from the NDC. *Applicant revised as requested.*

Revise the presentation of the names of the container labels and carton labeling similar to the example below in accordance with Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.

Anthim
(obiltoxaximab)
Injection

Applicant revised as requested.

Revise [REDACTED] ^{(b) (4)} to read "Single-Dose Vial". The Agency recommends consistent use of the appropriate package terms and discard statements. *Applicant revised as requested.*

- E. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*
- F. 21 CFR 201.25 Bar code label requirements; *conforms.*
- G. 21 CFR 201.50 Statement of identity; *conforms.*
- H. 21 CFR 201.51 Declaration of net quantity of contents; *conforms.*
- I. 21 CFR 201.55 Statement of dosage; *conforms.*
- J. 21 CFR 201.100 Prescription drugs for human use; *conforms.*

OBP Request: Revise the list of ingredients to comply with United States Pharmacopeia (USP) General Chapters: <1091> Labeling of Inactive Ingredients. For example:

Each mL contains 100 mg obiltoxaximab, L-histidine (6.2 mg), polysorbate 80 (0.1 mg), and sorbitol (36 mg).

Applicant revised as requested.

Discussion of the Applicant's Proposals:

(b) (4)



¹ Borders-Hemphil, V. Review of Revised Labels and Labeling for Anthim (obiltoximab) Injection (BLA 125509). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 FEB 12.

Conclusions:

The commercial container label and carton labeling for Anthim (obiltoxaximab) were reviewed and found to comply with the following 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 United States Pharmacopeia (USP), [USP 38/NF 33 December 1, 2015 to April 30, 2016]. Labeling deficiencies were identified and resolved. The commercial container label and carton labeling submitted on March 2, 2016 is acceptable (see below).

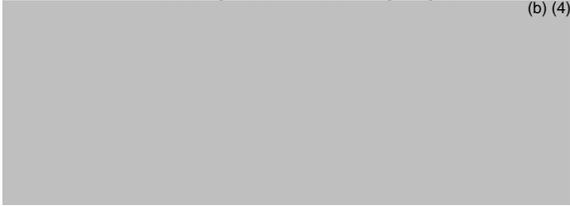
The Strategic National Stockpile (SNS) container label and carton labeling

(b) (4)

Commercial Container Label

[\\cdsesub1\evsprod\bla125509\0050\m1\us\114-label\1142-final-label\rm-3451-rev000-j1684938-mps.pdf](#)

(b) (4)

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Commercial Carton Labeling

[\\cdsesub1\evsprod\bla125509\0050\m1\us\114-label\1142-final-label\rm-3450-rev-000-j1680281-mps.pdf](#)

(b) (4)

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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)

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

Date of This Review: March 2, 2016
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: BLA 125509
Product Name and Strength: Anthim (obiltoxaximab) Injection, 600 mg/6 ml (100 mg/mL)
Product Type: Single-ingredient product
Rx or OTC: Rx
Applicant/Sponsor Name: Elusys Therapeutics
Submission Date: March 2, 2016
OSE RCM #: 2015-874
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Elusys has submitted revised commercial container labels and carton labeling (Appendix A) for Anthim (obiltoximab) injection (BLA 125509). The commercial container label and carton labeling revisions are in response to recommendations that DMEPA^{1,2} and Office of Pharmaceutical Quality/Office of Biotechnology Products (OBP) made during a previous label and labeling review.

We note that Elusys plans to provide revised Strategic National Stockpile (SNS) container labels, commercial (b) (4) carton labeling, and the revised proposed a plan for (b) (4) post approval of this BLA (b) (4).

2 CONCLUSION

The revised commercial container labels and carton labeling are acceptable from a medication error perspective.

¹ Sheppard J. Label and Labeling Review for Anthim (obiltoxaximab) Injection (BLA 125509). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 AUG 17. 13 p. OSE RCM No.: 2015-874.

² Borders-Hemphill V. Label and Labeling Review for Anthim (obiltoxaximab) Injection (BLA 125509). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 FEB 12. 16 p. OSE RCM No.: 2015-874.

APPENDICES:

APPENDIX A. Label and Labeling Images submitted on March 2, 2016

Commercial Container label



Commercial Carton labeling



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/s/

BRENDA V BORDERS-HEMPHILL
03/02/2016

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This field study is the required postmarketing field study under the Animal Rule to verify and describe the drug's clinical benefit and to assess safety when such a study is feasible and ethical.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)
-
- Other
- Other: Applicant agrees to conduct a field study of human subjects with suspected or confirmed inhalational anthrax in the event of unintentional or deliberate release of *B. anthracis* spores.
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs? **Response: Yes**
- Are the objectives clear from the description of the PMR/PMC? **Response: Yes**
- Has the applicant adequately justified the choice of schedule milestone dates? **Response: Yes**
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? **Response: Yes.**
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

JANE A DEAN
02/26/2016

JOSEPH G TOERNER
02/26/2016

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 12, 2015

TO: Sumathi Nambiar, M.D.
Director, Division of Anti-Infective Products (DAIP)
Office of Antimicrobial Products (OAP)
Office of New Drugs

FROM: Mohsen Rajabi, Ph.D.
Senior Staff Fellow
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm. D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of establishment inspection reports (EIRs),
covering BLA 125509 (Obilitoxaximab sponsored by
Elusys Therapeutics, USA).

Inspection Summary:

At the request of the Division of Anti-Infective Products, the Office of Study Integrity and Surveillance (OSIS) arranged clinical inspections for five studies conducted at six clinical sites. Following the inspections, Form 483 was issued to Quintiles Phase One Services, Overland Park, KS related to studies **AH109** and **AH110**. The final classification of the inspection for that site is voluntary action indicated (VAI). Form FDA 483 was not issued to the remaining five clinical sites and the final classification was No Action Indicated (NAI) at those sites. This reviewer recommends that the clinical portion of the audited studies be accepted for further Agency review.

Studies audited during the inspections:

Study Number: AH104

Study Title: "A double-blind, randomized, placebo-controlled study to assess the safety, tolerability, and pharmacokinetics (PK) of a single intravenous (IV) dose of ETI-204 in adult volunteers"

Study Dates: July 9, 2013 - November 29, 2013

Study Number: AH105
Study Title: "A randomized, double-blind, placebo-controlled, sequential group, single dose, dose-escalation study to evaluate the safety and pharmacokinetics of ETI-204 in healthy subjects"
Study Dates: September 14, 2011 - June 29, 2012

Study Number: AH106
Study Title: "A randomized, double-blind, single-ascending-dose study to assess the safety, tolerability, and pharmacokinetics of single intramuscular doses of ETI-204 in adult volunteers"
Study Date: July 26, 2013 - July 3, 2014

Study Number: AH109
Study Title: "A double-blind, randomized, placebo-controlled study to assess the safety, tolerability, and pharmacokinetics of repeat administration of intravenous ETI-204 in adult volunteers"
Study Dates: July 23, 2013 - April 19, 2014

Study #: AH110
Study Title: "An open-label, randomized, parallel group study to assess the safety, tolerability and pharmacokinetics of ETI-204 alone and in the presence of ciprofloxacin in adult volunteers"
Study Dates: October 29, 2013 - April 9, 2014

The following clinical sites were inspected:

1. Covance Clinical Development, Daytona Beach, FL

The inspection at Covance Clinical Development, Daytona Beach, FL was conducted by ORA investigator Brunilda Torres from July 6-9, 2015. [Study AH104]

2. Covance Clinical Research Unit, Inc., Madison, WI

The inspection of Covance Clinical Research Unit, Madison, WI was conducted by ORA investigator Scott Laufenberg from August 4-14, 2015. [Study AH104]

3. Covance Clinical Research Unit, Evansville, IN

The inspection of Covance Clinical Research Unit, Evansville,

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Indiana was conducted by ORA investigator Myra Casey from November 30 to December 4, 2015. [Study AH104]

4. Quintiles Phase One Services, Overland Park, KS

The inspection at Quintiles Phase One Services, Overland Park, KS was conducted by ORA investigator Carmen Fisher and Jonathan Campos from January 6-16, 2016. [Studies AH105, AH109, AH110]

5. Covance Clinical Research Unit, Inc., Dallas, TX

The inspection of Covance Clinical Research Unit, Dallas, TX was conducted by ORA investigator Camille Brown from January 11-19, 2016. [Study AH106]

6. DaVita Clinical Research Unit, Inc., Minneapolis, MN

The inspection at DaVita Clinical Research Unit, Minneapolis, MN was conducted by ORA investigator Sharon Matson from October 26-30, 2015. [Studies AH109, AH110]

Clinical Site #1: Covance Clinical Development
1900 Mason Ave, Suite 140
Daytona Beach, FL

The inspection included a thorough review of the records for study AH104, clinical study protocols, source documents in comparison to CRFs, subject selection criteria, informed consent forms, drug accountability and dispensing records, delegation of authority, adverse events reporting, employee training, and interviews and discussions with the firm's management and staff.

Following the inspection at Covance Clinical Development, Daytona Beach, FL, no significant findings were identified and no Form FDA 483 was issued. However, the following item was discussed with the firm's management.

Discussion Items:

1) As per study protocol Section 3 (study design), the investigator in conjunction with the study Steering Committee was required to conduct a blinded safety review of the available clinical and AE data up to and including Day 2. The protocol states that if the outcome of this review was deemed to be satisfactory, dosing of additional subjects will be permitted to continue. The meeting of the Steering Committee to evaluate the first 12 subjects dosed under Study AH104 study took place eight

days after dosing of all 12 subjects at the Dallas site and one day after dosing at the other remaining sites. The Steering Committee meeting outcome was that no infusion reaction had occurred and that no clinically significant changes in vital signs, ECG parameters, or safety laboratory results for any of the 12 subjects had been reported. The failure for the Steering Committee to hold the safety meeting prior to allowing dosing of additional subjects was documented as a protocol deviation. However, the event was deemed not related to subject safety and was not reported to the IRB.

Firm Response: In their response, the firm provided additional documents showing that the study data was shared with committee members as it was available.

OSIS evaluation: The firm's response is acceptable. Since the safety data was shared with the committee members and no subjects experienced significant AEs, this item is unlikely to impact the study outcome.

Clinical Site #2: Covance Clinical Research Unit, Inc.
3402 Kinsman Blvd.
Madison, WI

The inspection included a thorough review of the records for study **AH104**, clinical study protocols, source documents in comparison to CRFs, subject selection criteria, informed consent forms, drug accountability and dispensing records, delegation of authority, adverse events reporting, employee training, and interviews and discussions with the firm's management and staff.

Following the inspection at Covance Clinical Research Unit, Madison, WI, no significant findings were identified and no Form FDA 483 was issued. However, the following items were discussed with the firm's management.

Discussion Items:

1) The study protocol and related documents lacked sufficient details regarding subject fasting (e.g., the protocol did not state the length of pre-dose fasting). Based on the study records, subjects fasted 10 hours pre-dose and at least 4 hours post-dose, but it could not be determined why subjects had been fasted for the specified durations pre- and post-dose.

Firm Response: The firm agreed with the lack of information in the study protocol describing the fasting conditions and stated

Page 5 - BLA 125509, Anthim™ (Obiltoxaximab; ETI-204), sponsored by Elusys Therapeutics, Inc. USA.

that the fasting duration is the same as that used in other studies.

OSIS evaluation: Other clinical sites involved in the study used similar fasting durations pre- and post-dose. Therefore, it is possible that clinical sites in the study may have fasted subjects for a similar duration. This item is unlikely to impact the study outcome.

2) Improve documentation of attempts to contact study subjects when they fail to report to the site for "out-patient" study visit.

Firm Response: The firm agreed to review their procedures on documenting attempts to contact study subjects who fail to return to the site for study visits.

OSIS evaluation: The firm's corrective action acceptable and should improve their documentation when contacting subjects in the future.

Clinical Site #3: Covance Clinical Research Unit, Inc.
617 Oakley Street
Evansville, IN

The inspection included a thorough review of the records for study **AH104**, clinical study protocols, source documents in comparison to CRFs, subject selection criteria, informed consent forms, drug accountability and dispensing records, delegation of authority, adverse events reporting, employee training, and interviews and discussions with the firm's management and staff.

Following the inspection at Covance Clinical Research Unit, Evansville, IN, no significant findings were identified and no Form FDA 483 was issued.

Clinical Site #4: Quintiles Phase One Services
6700 West 115th Street
Overland Park, KS

The inspection included a thorough review of the records for studies **AH105**, **AH109**, and **AH110**, clinical study protocols, source documents in comparison to CRFs, subject selection criteria, informed consent forms, drug accountability and dispensing records, delegation of authority, adverse events

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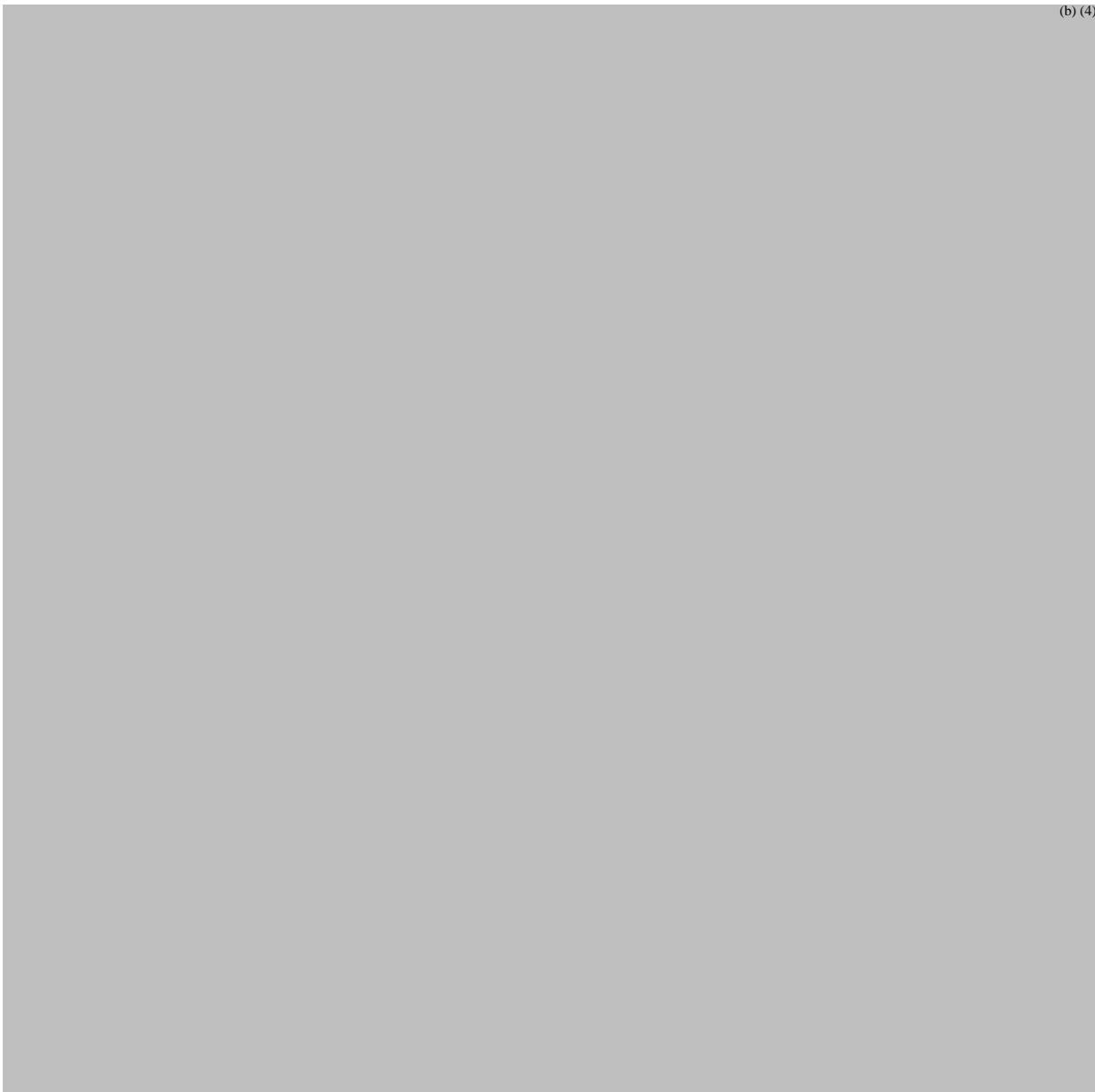
reporting, employee training, and interviews and discussions with the firm's management and staff.

Following the inspection at Quintiles, Overland Park, KS, no significant findings impacting study **AH105** were identified. However, Form FDA 483 was issued regarding studies **AH109** and **AH110**. The Form FDA 483 observation, the firm's response dated January 29, 2016, and our evaluation follow.

OBSERVATION 1

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,



(b) (4)

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Clinical Site #5: Covance Clinical Research Unit, Inc.
1341 W. Mockingbird Lane
Dallas, TX

The inspection included a thorough review of the records for study **AH106**, clinical study protocols, source documents in comparison to CRFs, subject selection criteria, informed consent forms, drug accountability and dispensing records, delegation of authority, adverse events reporting, employee training, and interviews and discussions with the firm's management and staff.

Following the inspection at Covance, Dallas, TX, no significant findings were identified and no Form FDA 483 was issued. However, the following items were discussed with the firm's management and staff.

Discussion Items:

1) Sample Processing and Storage Prior to Shipping:

The -70°C temperature probes in the freezer where the study subject samples were stored was out of range.

Firm Response: The firm acknowledged the issue and stated that the freezer temperature probes were set incorrectly. Based on the new SOP [REDACTED] (b) (4), an alarm temperature of -50°C has been set for the probes. The firm's management stated that faulty probes have since been decommissioned with new freezers purchased prior to the inspection.

OSIS evaluation: The firm's corrective actions are acceptable. Because the freezer temperatures were monitored separately, the item has no impact on the audited studies.

2) Written SOPs and/or work instructions were not followed:

a. A daily check was not completed for the emergency equipment in accordance with SOP [REDACTED] (b) (4). [REDACTED].

b. Not all the dosing source documents were signed or initialed by the investigator in accordance SOP [REDACTED] (b) (4). However, the investigator did not note any issues with dosing.

c. The atomic clock was not used to record the ECG timing on all the subjects in accordance SOP [REDACTED] (b) (4). However,

Page 11 - BLA 125509, Anthim™ (Obiltoxaximab; ETI-204), sponsored by Elusys Therapeutics, Inc. USA.

the discrepancy is minimal for the subject that was checked by the investigator.

Firm's Response: The firm's management stated that daily checks were completed for the days that screenings were conducted.

OSIS evaluation: In the opinion of the OSIS reviewer, these SOP deficiencies are unlikely to impact the study data.

3) Quality control of source documentation - late or missing

Not all the source documents, such as ECGs, were checked in a timely manner.

Firm's Response: The firm's management stated that they will take corrective actions to ensure that the study team is aware of the deficiencies and provide training to prevent recurrence in future studies.

OSIS evaluation: The firm's corrective actions are acceptable. It is unlikely that the item impacted the audited studies.

Clinical Site #6: DaVita Clinical Research Unit, Inc.
825 South 18th Street. Suite 300
Minneapolis, MN

The inspection included a thorough review of records for studies **AH109** and **AH110**, clinical protocols, source documents in comparison to CRFs, subject selection criteria, informed consent forms, drug accountability and dispensing records, delegation of authority, adverse events reporting, employee training, and interviews and discussions with the firm's management and staff.

Following the inspection at DaVita Clinical Research Unit, Minneapolis, MN, no significant findings were identified and no Form FDA 483 was issued. However, the following issues were discussed with the firm's management:

Discussion Items:

1) There were no examples of individual test article dose labeling on the IV bags to document that it contained all elements required by the study protocol, section 7.5: randomization number, study ID, data and time prepared, and total volume, e.g. a retain bag, photocopy, duplicate tear-off label, etc.

Firm Response: The firm stated that the IV bag label had the subject's initials, screen number, and randomization number and that a sample had been sent to the study monitor, (b) (4) for review and approval before use.

OSIS evaluation: Although not all the information specified in the study protocol was included in the IV bag label, the labels contained information to properly dose subjects there was no documentation in dose prep batch records that subjects may have received the wrong dose. Thus, the item is unlikely to impact the study outcome.

2) Although there was documentation to support that a second person checked more than half the dose preparations in the pharmacy, not all the dose preparation records were verified by a second person.

Firm's Response: The firm stated that their practice is to always have a second person check the dose preparations, but acknowledged that it was not always documented at the time. Since the study, the batch records have been revised such that identification of two persons is required.

OSIS evaluation: The firm's corrective action is acceptable and should prevent recurrence of the finding.

3) The written procedures for dose prep should address the areas noted in 1) and 2).

Firm's Response: The firm agreed to further review the issue and make necessary corrections.

OSIS evaluation: The firm's corrective action appears to be acceptable.

Recommendations:

Following the evaluation of the EIR, inspectional findings and the response to Form FDA 483, the clinical portion of the audited studies were found to be reliable. Therefore, this reviewer recommends that the clinical portion of the audited studies be accepted for further Agency review.

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Mohsen Rajabi, Ph.D.
Senior Staff Fellow
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

Final Classification:

NAI: Covance Clinical Development, Daytona Beach, FL
NAI: Covance Clinical Research Unit, Inc., Madison, WI
NAI: Covance Clinical Research Unit, Evansville, IN
VAI: Quintiles Phase One Services, Overland Park, KS
NAI: Covance Clinical Research Unit, Inc., Dallas, TX
NAI: DaVita Clinical Research Unit, Inc., Minneapolis, MN

DARRTS CC:

OTS/OSIS/Kassim/Taylor/Nkah/Fenty-Stewart
OTS/OSIS/DGDBE/Cho/Haidar/Skelly/Choi
OTS/OSI/DNDEB/Bonapace/Dasgupta/Rajabi
CDER/OND/DEAN/Nambiar
Draft: MR 02/08/2016
Edit: JC 2/10/2016, CB 2/10/2016
OSI: BE 6809
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Covance Clinical Development, Daytona Beach, FL, Covance Clinical Research Unit, Dallas, TX, Covance Clinical Research Unit, Evansville, IN, Covance Clinical Research Unit, Madison, WI, DaVita Clinical Research, Minneapolis, MN, Quintiles Global Phase I Services, USA/ BLA 125509- ETI-204

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/s/

MOHSEN RAJABI ABHARI
02/14/2016

CHARLES R BONAPACE
02/14/2016

PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

(b) (4)

FDA Participants: (b) (4)

C.J. George Chang, OSIS-DNDBE Pharmacologist (on Detail)
Zhou Chen, OSIS-DNDBE Pharmacologist
Abhijit Raha, OSIS-DNDBE Pharmacologist

(b) (4) conducted at the request of the Division of Anti-Infective Products (DAIP). (b) (4) no Form FDA 483 was issued, (b) (4) were discussed (b) (4) (b) (4) is No Action Indicated (NAI). Because none of the discussion items impact the quality of the data, the audited studies are acceptable for review by the Agency.

Studies Audited (b) (4)

(b) (4) Study No.: 832-G924202 (Elusys Therapeutics Study AR021)
Study Title: Evaluating the Efficacy of ETI-204 when Administered Therapeutically in the New Zealand White Rabbit Inhalational Anthrax Model
Study Initiation Date: July 29, 2008
Final Report Date: October 8, 2009
Study Director: (b) (4)

(b) (4) Study No.: 1185-100003006 (Elusys Therapeutics Study AR033)
Study Title: Evaluating the Efficacy of ETI-204 when Administered Therapeutically in New Zealand White Rabbits
Study Initiation Date: July 12, 2011
Final Report Date: February 28, 2013
Study Director: (b) (4)

(b) (4) Study No.: 834-G924202 (Elusys Therapeutics Study AP201)
Study Title: Evaluating the Efficacy of ETI-204 when Administered Therapeutically in the Cynomolgus Macaque Inhalational Anthrax Model
Study Initiation Date: June 22, 2009
Final Report Date: August 25, 2011
Study Director: (b) (4)

(b) (4) Study No.: 2826-100020847 (Elusys Therapeutics Study AP202)
Study Title: Three Armed Trigger-to-Treat Efficacy Study of Intravenously Administered ETI-204 in Cynomolgus Monkeys with Inhalational Anthrax
Study Initiation Date: January 6, 2014
Final Report Date: January 23, 2015
Study Director: (b) (4)

(b) (4) Study No.: 1219-100005989 (Elusys Therapeutics Study AP203)
Study Title: Evaluating the Efficacy of Intravenous ETI-204 when Administered

(b) (4)

Therapeutically in the Cynomolgus Macaque Inhalational Anthrax Model

Study Initiation Date: October 17, 2011

Final Report Date: December 20, 2012

Study Director: (b) (4)

(b) (4) Study No.: 1121-G924204 (Elusys Therapeutics Study AP204)

Study Title: Evaluating the Efficacy of ETI-204 when Administered Therapeutically in the Cynomolgus Macaque Inhalational Anthrax Model

Study Initiation Date: August 20, 2010

Final Report Date: December 20, 2012

Study Director: (b) (4)

(b) (4) Study No.: 2720-100014200 (Elusys Therapeutics Study AP301)

Study Title: Study AP301: Study To Evaluate the Pharmacokinetics of ETI-204 Administered via Intramuscular (IM) Route in a Time of Treatment Post-Exposure Prophylaxis Model of Cynomolgus Monkey Anthrax Infection

Study Initiation Date: September 26, 2012

Final Report Date: July 31, 2014

Study Directors: (b) (4)

Information common to all 7 audited studies cited above:

Sponsor: Elusys Therapeutics, Inc. (Pine Wood, NJ)

Relevant Application: BLA-125509

Review Division: Division of Anti-Infective Products (DAIP)

(b) (4)

specializes in research development, testing and evaluation of medical countermeasures used against pathogenic micro-organisms, bio-toxins, and various highly toxic chemical agents. (b) (4)

facilities are to test the efficacy of various medical countermeasures with animals exposed to agents via the inhalation route in aerosol chambers which require aerosolization of the pathogenic micro-organisms, bio-toxins and various highly toxic chemical agents. (b) (4)

(b) (4)

and involve aerosol/inhalation biology, microbiology, virology, immunology, cell biology, analytical chemistry, pharmacology and various branches of toxicology. Research activities involving toxicology include inhalational, biochemical, molecular and skin toxicology. The primary test systems are (b) (4)

(b) (4)

(b) (4)

(b) (4) in response to a surveillance inspection assignment issued by CBER. That inspection was classified as NAI. No Form FDA 483, Inspectional Observations, was issued. However, a discussion was held with (b) (4) for the following items: 1) Source data did not match the data line listing for two animals; 2) There was no documentation demonstrating five bubble meter readings were measured; 3) There was no documentation demonstrating cleaning and maintenance had been performed on the Plethysmograph Boxes used during the aerosol challenges; 4) There was no documentation demonstrating which impingers were used during the aerosol challenges; and 5) Failure to update SOP # (b) (4) as promised from the previous inspection of (b) (4) in a timely fashion. During the inspection, the firm updated SOP # (b) (4) and promised voluntary corrections to the other discussion items.

(b) (4) to assess the GLP compliance with regard to facility operations and conduct of seven Animal Efficacy Rule studies audited at the request of DAIP. (b) (4) by ORA Investigators (b) (4) and CDER-OSIS pharmacologists Dr. Zhou Chen, Dr. Ching-Jey George Chang, and Dr. Abhijit Raha.

(b) (4) reviewed (b) (4) Master Schedule, Standard Operating Procedures (SOPs), equipment maintenance and calibration records, Organization and Personnel (e.g., performance of the Quality Assurance Unit [QAU] and study directors), test and control article handling (e.g., receipt, preparation, distribution, disposition and storage) and (b) (4) study records of seven Animal Efficacy Rule studies. This inspection also verified that (b) (4) corrective actions for the deficiencies discovered during the previous inspection.

For Elusys Therapeutics Studies AR021, AR033, AR201, AR202, AR203, AR204, and AR301 all study protocols, records and raw data in the study files were reviewed. The study protocols had all 12 required elements in 21 CFR 58.120 and all final reports contained the 14 required elements in 21 CFR 58.185. Information found in the protocols, raw data, specimens and records were compared to that reported in the final study reports. All samples of raw data audited (b) (4) confirmed that the findings documented (b) (4) were complete and accurate. (b) (4) the audited studies were conducted in adherence with their respective protocols/amendments and SOP requirements. There were no significant deficiencies observed (b) (4). (b) (4) these deficiencies were not found in any study audited (b) (4). Although Form FDA 483 was not issued (b) (4) (b) (4) were discussed (b) (4) follow.

DISCUSSION (b) (4)

(b) (4) studies 1210-100005989 and 834-G924202, minor documentation errors were noted.

(b) (4)

(b) (4) study 1210-100005989, the 2012 water analysis reports provided by a third party contractor had holes punched through some of the results, obscuring the data.

(b) (4) study (b) (4), the mediastinal lymph node on an original tissue section (together with a piece of liver and spleen) from Animal C39076 (Pathology Number 0907370) did not have sufficient tissue for histopathology examination. That lymph node was re-embedded and sectioned. The re-embedded paraffin block of that lymph node and the penciled code on the new lymph node section were correctly labeled for the pathology number (0907370), but the final paper label on the new slide of lymph node tissue had an incorrect histopathology processing code (0907371) with an incorrect animal number (CM 207M). Animal C39076 was not selected into the final study groups, while Animal CM 207M was in Group 2.

(b) (4) **Response:** (b) (4) acknowledged the discussion item. As a corrective measure, the documentation errors noted in the study records were corrected.

OSIS Evaluation: (b) (4) response to this item of discussion is adequate. This discussion item does not impact the quality and integrity of data for (b) (4) study 834-G924202, as Animal C39076 was not selected into the final study groups.

(b) (4) **Multiple protocol and SOP deviations were documented 3.5 to 20.5 months after their occurrence during the conduct of** (b) (4) study 834-G924202, (b) (4)

(b) (4) **Response:** (b) (4) acknowledged the discussion item and stated that the deviation documentation process would be reviewed by management. No specific corrective actions were proposed in the response letter.

OSIS Evaluation: Timely and prospective documentation of deviations in ongoing studies help to ensure the integrity of the data and reconstruction of the study. (b) (4) is encouraged to document deviations in a timely fashion in future studies.

(b) (4) **Investigation reports generated by the study director were reviewed and approved by the study director for** (b) (4) study 834-G924202.

(b) (4) **Response:** (b) (4) acknowledged the discussion item. In order to correct this deficiency, the applicable SOP, SOP (b) (4) will be revised to include a second level approver other than the study director by December 31, 2015.

OSIS Evaluation: (b) (4) response to this discussion item is adequate. This discussion item does not appreciably impact the quality and integrity of data generated for the audited studies where the study director approved his own Investigation reports, as the study director serves as the single point of control for the study.

(b) (4)

(b) (4) For (b) (4) study 832-G924202, the sponsor did not provide the expiration date of the lot number of anthrax protective antigen (PA) that they used for conducting their immunoassay for determination of ETI-204 in rabbit serum samples.

(b) (4) Response: (b) (4) acknowledged the discussion and stated that (b) (4) will provide this information after the inspection. The specific lot of anthrax protective antigen (PA) used by the sponsor to conduct the immunoassay for determination of ETI-204 in rabbit serum samples collected in (b) (4) study 832-G924202 had not expired.

OSIS Evaluation: In their response, (b) (4) provided documentation to support that the specific lot of anthrax protective antigen (PA) had not expired. Thus, this discussion item does not impact the quality and integrity of data for (b) (4) study 832-G924202.

(b) (4) the data from the audited studies were found to be reliable. These reviewers recommend that the data from Elusys studies AR021, AR033, AR201, AR202, AR203, AR204 and AR301 be accepted for Agency review.

- (b) (4) routine surveillance in another two years.
- (b) (4) verify the corrective actions mentioned (b) (4) of discussion.
- (b) (4) No Action Indicated (NAI).

Abhijit Raha, Ph.D.
Pharmacologist

C.J. George Chang, DVM, Ph.D.
Pharmacologist

Zhou Chen, MD, Ph.D.
Pharmacologist

Date Assigned:
EI Dates:
District Office:
FDA Investigators:

(b) (4)

Dr. Zhou Chen, OSIS Pharmacologist
Dr. C.J. George Chang, OSIS Pharmacologist (on detail from OND)
Dr. Abhijit Raha, OSIS Pharmacologist

Inspection Type: Routine Surveillance Directed
FDA-483 Issued: No Yes
Letter Issued: None Untitled Letter

Date EIR Received by OSIS: 02/08/2016 (found as file in OSAR database)
Date EIR Received by Reviewer: 02/08/2016
1st Draft Review Completed: 02/09/2016

(b) (4)

Inspection Conclusion: NAI
District Decision: NAI
Final HQ Classification: NAI

cc: via DARRTS

OSIS/Kassim/Taylor/Nkah/Fenty-Stewart/Miller/Johnson
OSIS/DNDBE/Bonapace/ChenZ/Raha
DAIP/Amy C. Nostrandt/Pharmacologist (BLA 125509)
DAIP/Jane A. Dean/Regulatory Project Manager (BLA 125509)
HFR-CE450/Cassandra L. Winters (BIMO)
HFR-CE502/Heather A. McCauley (DIB)

(b) (4)

Draft: AR 02/09/2016, 02/12/2016; ZC 02/09/2016, 02/10/2016; CGC 02/10/2016, 02/11/2016

Edits: CB 02/12/2016

OSIS File: GLP0912

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/GLP Program

(b) (4)

ATTACHMENT:

1. (b) (4) Response Letter, (b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ABHIJIT RAHA
02/12/2016

ZHOU CHEN
02/12/2016

CHING-JEY G CHANG
02/12/2016

CHARLES R BONAPACE
02/12/2016

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)

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

Date of This Review: February 12, 2016
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: BLA 125509
Product Name and Strength: Anthim (obiltoxaximab) Injection, 600 mg/6 ml (100 mg/mL)
Product Type: Single-ingredient product
Rx or OTC: Rx
Applicant/Sponsor Name: Elusys Therapeutics
Submission Date: February 11, 2016
OSE RCM #: 2015-874
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Elusys proposes the introduction of a new biologic agent to the market for the prophylaxis and treatment of inhalational anthrax due to *Bacillus anthracis*. This review evaluates the revised container labels and (b) (4) carton labeling (Appendix A) for Anthim (obiltoximab) injection (BLA 125509). Since our previous review, the Applicant has proposed a plan for (b) (4) (b) (4) the Strategic National Stockpile (Appendix B). The label and labeling revisions and proposed plan are in response to recommendations that DMEPA¹ and Office of Pharmaceutical Quality/Office of Biotechnology Products (OBP) (Appendix C) made during a previous label and labeling review and emailed labeling negotiations.

2 DISCUSSION

Labels and Labeling

(b) (4)

We reviewed the revised container labels and (b) (4) carton labeling to determine if recommendations from the previous DMEPA review were implemented and we note the following:

- (b) (4)
- After further consideration and discussion with OBP, we determined that the revised container labels for both the commercial and Strategic National Stockpile (SNS) should have a linear barcode per 21 CFR 201.25 on the side panel in a vertical position where the barcode can be scanned by hospitals (b) (4) (b) (4). We provide recommendations in Section 3.

Proposed Plan (b) (4) for Strategic National Stockpile (SNS) Label and Labeling

(b) (4)

¹ Sheppard J. Label and Labeling Review for Anthim (obiltoximab) Injection (BLA 125509). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 AUG 17. 13 p. OSE RCM No.: 2015-874.

3 CONCLUSION & RECOMMENDATIONS

In collaboration with OBP, we determined that the commercial and Strategic National Stockpile (SNS) container label, SNS (b) (4) carton labeling, (b) (4) can be improved for clarity and revised to promote safe use of this product.

Proposed Plan (b) (4) for Strategic National Stockpile Label and Labeling

Labels and Labeling

The proposed labels and labeling for Anthim may be improved to provide important use information and to improve readability of important product information. We recommend the revisions be implemented prior to the approval of the BLA.

A. Commercial and National Strategic Stockpile (SNS) Container Label

1. After further consideration and discussion with OBP, we determined that the commercial and SNS container label should have a linear barcode. Add a linear barcode per 21 CFR 201.25 on the side panel in a vertical position where the barcode can be scanned to allow hospitals (b) (4) to scan the product. (b) (4)

(b) (4)

D. Commercial and SNS Vial Cap

1. Per OBP, your vial cap (b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix C. Communications with Applicant

Elusys responses to the Anthim® (obiltoxaximab) Injection container and carton labeling comments received from Agency via email on December 16, 2015 and January 15, 2016 are provided below. The revised container and carton labels for commercial and Strategic National Stockpile (SNS) are provided.

Responses from FDA email comments on 12/16/2015

A. All Container Labels and Carton Labeling

- 1. Revise the appearance and presentation of the proprietary and proper name to improve readability. Ensure the proper name is at least half the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).**

Response:

The size of obiltoxaximab has been increased to be ½ the size of Anthim on all container and carton labeling. The font and font sizes are detailed below.

Container Labels (commercial and stockpile)

(b) (4)

Carton Labels (commercial and stockpile)

(b) (4)

- 2. Revise the presentation of the names and dosage form on the container labels and carton labeling similar to the example below in accordance with the presentation for biological products in the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.**

**Anthim
(obiltoxaximab)
Injection**

Response:

The presentation of the proprietary and proper names on all container and carton labeling have been revised accordingly.

- 3. Add a unique NDC number for each packaging configuration. The NDC code is an important check used by pharmacists to assist in drug selection and dispensing.**

Response:

The unique NDC numbers have been added to all container and carton labeling.

B. Container Label (Commercial and National Strategic Stockpile)

1. Delete or decrease the size of the graphic on the PDP, located above the proprietary name "Anthem" to increase the white space on the label to improve readability per 21 CFR 201.15. Consider removing the (b) (4)
(b) (4)

Response:

To increase the size of the white space above the Anthem, (b) (4)
(b) (4) has been removed from the bottom of the panel and the graphic was slightly decreased on the commercial and SNS container label.

2. Revise the statement (b) (4)
(b) (4) to read "Usual Dosage: see insert." This recommendation aims to create space on the label for the recommendations below.

Response:

The statement (b) (4)
has been revised to read "Usual Dosage: see insert" on the commercial and SNS container label.

3. Add the bolded statement "Single-Dose Vial. Discard Unused Portion" to the side panel.

Response:

The bolded statement "Single-Dose Vial. Discard Unused Portion" has been added to the commercial and SNS container label.

4. Add the storage and handling information on the side panel to read "Store at 2°C to 8°C (36°F to 46°F). Protect from light. Do not freeze or shake.

Response:

The storage and handling information indicated has been added to the commercial and SNS container label.

5. Revise the manufacturer information to read:

Mfd by: Elusvs Therapeutics, Inc.
(b) (4)

U.S. Lic. No. 1907

The name, address, and license number of the licensed manufacturer must appear in labeling per 21 610.60(a)(2).

Response:

The manufacturer information has been revised as requested on the commercial and SNS container label.

6. Add the expiration date per 21 CFR 201.17 and a linear barcode per 21 CFR 201.25 on the side panel in a vertical position where the barcode can be scanned. This may be done by removing the unbolding and relocating the "Rx only" statement to the top right corner of the PDP and reducing the size of the manufacturer information as mentioned above.

Response:



C. Carton Labeling (Commercial and National Strategic Stockpile)

1. Remove bolding from the Rx Only statement and consider relocating to the top of the PDP across from the NDC.

Response:

The statement "Rx Only" was relocated to the top of the PDP across from the NDC and the bolding has been removed on the commercial and SNS carton label.

2. Bold the route of administration statement "For Intravenous Infusion"

Response:

"For Intravenous Infusion" has been bolded on the commercial and SNS carton label.

3. Revise (b) (4) to read "Single-Dose Vial". The Agency recommends consistent use of the appropriate package terms and discard statements. See the Agency's current thinking on this issue (FDA Draft Guidance: 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).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

Response:

The statement (b) (4) has been revised to read "Single-Dose Vial" on the commercial and SNS carton label.

4. Add the statement "Do Not Shake" after "Do Not Freeze" on the side panel per 21 CFR 610.61(i).

Response:

The statement "Do Not Shake" has been added to the side panel after "Do Not Freeze" on the commercial and SNS carton label.

5. Revise the list of ingredients to comply with United States Pharmacopeia (USP) General Chapters: <1091> Labeling of Inactive Ingredients. For example:

Each mL contains 100 mg obiltoximab, L-histidine (6.2 mg), polysorbate 80 (0.1 mg), and sorbitol (36 mg).

Response:

The list of ingredients has been revised as requested on the commercial and SNS carton label.

6. Revise the manufacturer information to read:

Manufactured by:
Elusys Therapeutics, Inc.
Pine Brook, NJ 07058
U.S. License Number 1907

The name, address, and license number of the licensed manufacturer must appear labeling per 21 610.60(a)(2) and 21 CFR 610.61(b). The name and address of a distributor may appear if the licensed manufacturer name, address, and license number appear per 21 CFR 610.64.

Response:

The manufacturer information has been revised as requested on the commercial and SNS carton label.

D. General Comment

1. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

Response:

The label is affixed to the approximate center of the vial. There is an area at the bottom and top of the vial where product can be seen through the glass. The label does not wrap all the way around the vial, so there is a gap of a few millimeters allowing the product to be seen vertically from the bottom to the top of the vial. See Labeling Feasibility Picture using a test label that is the same dimensions as the Anthim drug product vial label.

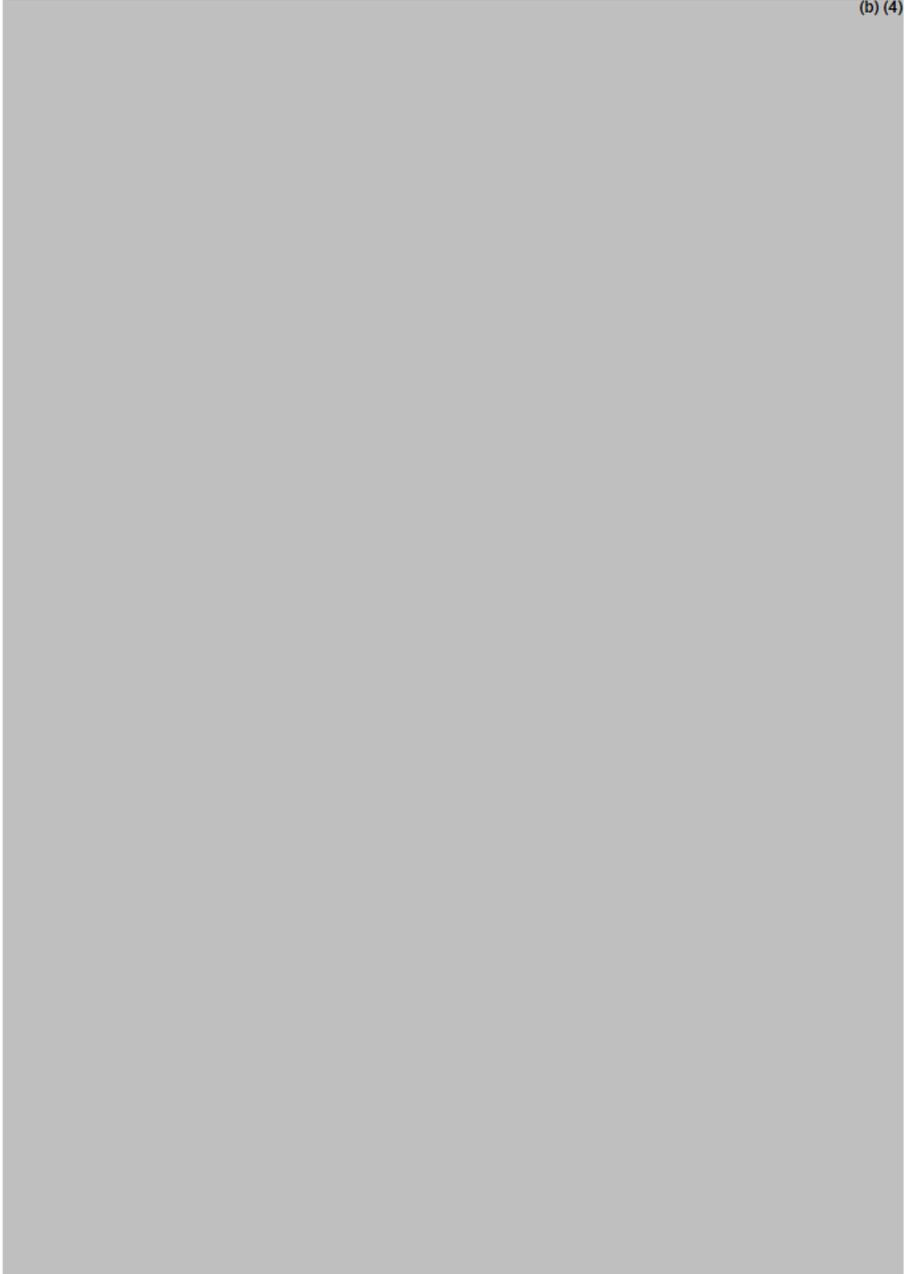
2. Confirm there is no text on top of the ferrule and cap overseal of the vials to comply with USP General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals.

Response:

(b) (4)

Responses from FDA email comments on 1/15/2016

(b) (4)



From: Dean, Jane
Sent: Friday, January 15, 2016 5:39 PM
To: Robin Conrad (rconrad@elusys.com)
Cc: Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)
Subject: BLA 125509 (Anthem) - responses to your questions in the 12/21/15 and 1/15/16 emails

BLA 125509 Anthem (oblitoxaximab)
Agency Response to Applicant's Request for [REDACTED] (b) (4)

Applicant's December 21, 2015 email Request

In the reviewer's guide provided in Module 1 of the BLA, we stated the following in italics:

The information contained on the vial labels is in agreement with the minimal requirements for a [REDACTED] (b) (4) label as per 21 CFR 610 (Subpart G) and 21 CFR 201.

The information contained on the individual carton label is in agreement with the requirements as per 21 CFR 610 (Subpart G) and 21 CFR 201. The draft carton labels include the expiration as per the CFR requirements. [REDACTED] (b) (4)

As a result of the recent FDA feedback on the container (vial) and carton labels we have the following questions: [REDACTED] (b) (4)

(b) (4)

Agency Response

See 1.b. above

Applicant's January 15, 2016 email Request

In the reviewer's guide provided in Module 1 of the BLA, we stated the following in italics:

(b) (4)

(b) (4) since we will be adding the following statements as recommended by

FDA:

1. Add the bolded statement "Single-Dose Vial. Discard Unused Portion" to the side panel.
2. Add the storage and handling information on the side panel to read "Store at 2°C to 8°C (36°F to 46°F). Protect from light. Do not freeze or shake."

Agency Response

- a. Include your plan for the tamper seal within your detailed plan for labeling the (b) (4) requested above.
- b. Your proposal to (b) (4) on the vial container label is acceptable.

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/s/

BRENDA V BORDERS-HEMPHILL
02/12/2016

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

| | |
|--------------------------|--|
| NDA/BLA # | 125509 |
| Product Name: | Anthim (obiltoxaximab) |
| PMC #1 Description: | Develop reduced and non-reduced SDS-based assays capable of providing quantitative data for the evaluation of size related product impurities and implement these assays in the release and stability program for obiltoxaximab drug substance and drug product after sufficient data have been acquired to set appropriate acceptance criteria. Provide the analytical procedure, validation report, proposed acceptance criteria, and data used to set the proposed acceptance criteria. |
| PMC Schedule Milestones: | Final Protocol Submission: _____ Study/Trial Completion: _____ Final Report Submission for DS: <u>March 2019</u> Final Report Submission for DP: To be determined based on when data from 20 lots of DP becomes available or 5 years after the BLA being approved, whichever comes first |
| | Other: _____ |

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis

Other

The Drug substance and Drug Product release specifications approved under the BLA are sufficient to ensure adequate quality and safety of Anthim (obiltoxaximab) for the initial marketed product. The addition of quantitative SDS-based methods for assessing size-related impurities will provide better control of these impurities in DS and DP throughout the product lifecycle. Establishment of an improved SDS based assay requires the acquisition of release data from more product lots and is not feasible prior to approval.

2. Describe the particular review issue and the goal of the study.

The current Anthim/obiltoxaximab Drug Substance and Drug Product release specifications include a qualitative non-reduced SDS-PAGE assay that does not provide control over the amounts of size-related impurities. The addition of quantitative SDS-based methods will provide consistent monitoring of the levels of low molecular weight size-related impurities in DS and DP throughout product lifecycle.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Collecting data of (b) (4) assays for establishing quantitative acceptance criteria for the assays which will eventually replace the current SDS-PAGE test methods.

Evaluation the data of total of 20 lots of Obiltoxaximab drug substance. The data is expected to be available by end of 2018.

Evaluation the data of Anthim drug product, when data from 20 lots of the drug product becomes available or five years post approval, whichever comes first.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

TAO XIE
02/08/2016

RASHMI RAWAT
02/09/2016

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

| | |
|--------------------------|--|
| NDA/BLA # | 125509 |
| Product Name: | Anthim (obilttoxaximab) |
| PMC #2 Description: | Conduct validation studies to confirm the shipper is suitable for maintaining critical quality attributes during shipping of obilttoxaximab drug product. This should include consideration for worst case shipping routes. The study will include monitoring of temperature during the shipment, as well as testing of pre- and post- shipping samples of obilttoxaximab drug product quality (e.g., appearance, protein concentration, purity by SEC-HPLC, reduced and non-reduced SDS-PAGE, icIEF, visible and sub-visible particulates and potency). |
| PMC Schedule Milestones: | Final Protocol Submission: _____ Study/Trial Completion: <u>April 2016</u> Final Report Submission: <u>May 2016</u> Other: _____ |

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAIA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The shipping qualifications studies provided in the BLA did not include product quality data. Additional shipping validation studies are needed to include assessments of product quality in pre- and post-shipment samples of Anthim drug product.

2. Describe the particular review issue and the goal of the study.

Data is needed to support the performance of the commercial shipping configurations and to confirm that there is no adverse impact of shipping on product quality. The shipping validation studies should be performed under representative conditions for commercial shipping of Anthim. All relevant product quality attributes that may be potentially impacted during shipping should be evaluated.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Shipping validation studies using commercial shipping conditions will be performed to evaluate the performance of the commercial shippers and to assess the impact of shipping on product quality.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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TAO XIE
02/08/2016

RASHMI RAWAT
02/09/2016

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

| | |
|--------------------------|---|
| NDA/BLA # | 125509 |
| Product Name: | Anthim (obiltoximab) |
| PMC #3 Description: | Conduct a study to confirm compatibility of the drug product with syringe infusion components used for administration. These studies will include monitoring samples for protein concentration, purity by SEC-HPLC, icIEF, visible and sub-visible particulates; and potency. |
| PMC Schedule Milestones: | Final Protocol Submission: _____ Study/Trial Completion: <u>May 2016</u> Final Report Submission: <u>June 2016</u> Other: _____ |

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Data provided in the BLA support the compatibility of Anthim drug product with intravenous bags and infusion sets. However, there was no information provided on the compatibility of Anthim with syringes that may need to be used for (b) (4) dose administration. Drug product compatibility studies should be performed with the syringes to ensure product quality attributes are not impacted by using the syringe during the IV infusion.

2. Describe the particular review issue and the goal of the study.

The compatibility studies reported in the BLA did not document the compatibility of Anthim drug product with syringes to be used in administration of (b) (4) doses. Additional drug product compatibility studies will need to be performed.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will perform studies that confirm the compatibility of the Anthim drug product with syringes to be used in administration of (b) (4) doses.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

| | |
|--------------------------|--|
| NDA/BLA # | 125509 |
| Product Name: | Anthim (obilttoximab) |
| PMC #4 Description: | Conduct a study to support the worst case cumulative hold times in obilttoximab drug substance manufacturing process to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of obilttoximab drug substance. These data are expected to demonstrate that there is no adverse impact to product quality when the manufacturing of a drug substance batch involves (b) (4) |
| PMC Schedule Milestones: | Final Protocol Submission: _____ Study/Trial Completion: <u>January 2018</u> Final Report Submission: <u>March 2018</u> Other: _____ |

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.
 - Need for drug (unmet need/life-threatening condition)
 - Long-term data needed (e.g., stability data)
 - Only feasible to conduct post-approval
 - Improvements to methods
 - Theoretical concern
 - Manufacturing process analysis
 - Other

BLA provided data that qualified the maximum allowable hold time (b) (4) in the DS manufacturing process. Conduct study to quality cumulative hold times under worst case scenario would provide higher assurance of the consistent qualification of the DS over product lifecycle.

2. Describe the particular review issue and the goal of the study.

No study information provided to support the worst case cumulative hold times. Conduct a study to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of obiltoximab drug substance.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Conduct a study to support the worst case cumulative hold times in obiltoximab drug substance manufacturing process.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

| | |
|--------------------------|---|
| NDA/BLA # | 125509 |
| Product Name: | Anthim (obilttoxaximab) |
| PMC #5 Description: | Re-evaluate obilttoxaximab drug substance lot release and stability specifications after 20 lots have been manufactured using the commercial manufacturing process. Provide the final report, the corresponding data, the analysis, and the statistical plan used to evaluate the specifications. |
| PMC Schedule Milestones: | Final Protocol Submission: _____ Study/Trial Completion: <u>January 2019</u> Final Report Submission: <u>March 2019</u> Other: _____ |

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Anthim (obilttoxaximab) Drug Substance release and stability specifications approved under BLA are sufficient to ensure adequate quality and safety of Anthem (obilttoxaximab) for the initial marketed product. Additional manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

Anthem (obiltoxaximab) drug substance release and stability specifications are based on clinical and manufacturing experience provided in the BLA and assessed during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Re-evaluate obiltoxaximab drug substance lot release and stability specifications after 20 lots have been manufactured using the commercial manufacturing process.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

| | |
|--------------------------|--|
| NDA/BLA # | 125509 |
| Product Name: | Anthim (obiltoximab) |
| PMC #6 Description: | Re-evaluate obiltoximab drug product lot release and stability specifications after 20 lots have been manufactured using the commercial manufacturing process. Provide the final report, the corresponding data, the analysis, and the statistical plan used to evaluate the specifications. |
| PMC Schedule Milestones: | Final Protocol Submission: _____ Study/Trial Completion: _____ Final Report Submission: _____ To be determined based on when data from 20 lots of DP becomes available or 5 years after the BLA being approved, whichever comes first |
| | Other: _____ |

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The Drug Product release and stability specifications approved under BLA are sufficient to ensure adequate quality and safety of Anthim for the initial marketed product. Additional manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

Anthim drug product release and stability specifications are based on clinical and manufacturing experience provided in the BLA and assessed during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be re-assessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Re-evaluate obiltoximab drug product lot release and stability specifications when data from 20 lots of DP becomes available or five years post approval, whichever comes first.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

| | |
|--------------------------|--|
| NDA/BLA # | 125509 |
| Product Name: | Anthim (obilttoximab) |
| PMC #7 Description: | Establish a permanent control limit for (b) (4) of production (b) (4) and (b) (4) of (b) (4) unit operations after (b) (4) control points have been analyzed. The (b) (4) limits and supportive data should be submitted to the BLA. |
| PMC Schedule Milestones: | Final Protocol Submission: _____ Study/Trial Completion: <u>January 2019</u> Final Report Submission: <u>March 2019</u> Other: _____ |

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

While the (b) (4) of production (b) (4) and (b) (4) for the (b) (4) process were recorded in the batch records, no control limits had been established. Data from seven lots are currently available. It is only feasible to do this as a post-approval commitment

2. Describe the particular review issue and the goal of the study.

21 CFR 211.105 requires yield to be determined at the conclusion of each appropriate phase of manufacturing.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Establishment of (b) (4) and (b) (4) for the manufacturing process after a minimum of (b) (4) control points had been analyzed.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 125509
Product Name: Anthim (obilttoximab)

PMC #8 Description: To conduct drug substance specific leachable and extractable studies (b) (4)
The drug substance manufacturing processes will be optimized, as needed, based on the results.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: April, 2016
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAIA OR WILL BE PUBLICLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The risk assessment of the impact of extractable and Leachables (E&L) should be performed for critical process contact materials. An extractable study from the (b) (4) was used for the risk assessment of E&L from (b) (4). Process optimization based on product specific E&L study and risk assessment would provide higher assurance of the consistent qualification of the DS over product lifecycle.

2. Describe the particular review issue and the goal of the study.

Risk assessment for potential leachable of the

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Elusys reported that an extractable study that was recently completed

(b) (4)

a final report for risk assessment to evaluate the extractable compounds found in the study, and path forward as a PMC with a completion date by April 2016.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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02/09/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # STN125509
Product Name: Obiltoximab

PMR/PMC Description: Conduct a study to qualify the bioburden test for the primary recovery samples using the increased sample volume (10 mL).

| | | |
|------------------------------|----------------------------|-------------------|
| PMR/PMC Schedule Milestones: | Final Protocol Submission: | <u>MM/DD/YYYY</u> |
| | Study/Trial Completion: | <u>08/31/2016</u> |
| | Final Report Submission: | <u>11/30/2016</u> |
| | Other: | <u>MM/DD/YYYY</u> |

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The qualification of the bioburden samples with increased test volumes requires the use of product samples generated at the next product campaign. This is appropriate for a PMC because this does not affect the safety of the product. The risk of microbial contamination is mitigated by other microbial controls in place during manufacturing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The current test volumes for the primary recovery bioburden samples only uses 1 mL. The test volumes need to be increased to 10 mL to improve the sensitivity of the bioburden tests.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

| |
|---|
| Conduct a study to qualify the bioburden test for the primary recovery samples using the increased sample volume (10 mL). |
|---|

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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BO CHI
02/08/2016

The (b) (4) bioburden and endotoxin limits in the BLA are interim limits and need to be replaced with permanent action limits. The sponsor will evaluate data from 10 batches and establish permanent action limits based on manufacturing capability.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Re-evaluate and establish final (b) (4) bioburden and endotoxin limits for all the sampling points.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

BO CHI
02/08/2016

**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**

PATIENT LABELING REVIEW

Date: December 02, 2015

To: Sumathi Nambiar, MD
Director
Division of Anti-Infective Products (DAIP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Marcia Williams, PhD
Team Leader, 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: Focused Review of Patient Labeling: Patient Package Insert
(PPI)

Drug Name (established name): ANTHIM (obiltoximab)

Dosage Form and Route: Injection, for intravenous use

Application Type/Number: BLA 125509

Applicant: Elusys Therapeutics, Inc.

1 INTRODUCTION

On March 20, 2015, Elusys Therapeutics Inc., submitted for the Agency's review a Biologics Licensing Application for ANTHIM (obiltoxaximab) Injection, for intravenous use, indicated for the treatment of adult and pediatric patients with inhalational anthrax due to *bacillus anthracis* in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Anti-Infective Products (DAIP) on May 27, 2015 for DMPP to provide a focused review of the Applicant's proposed Patient Package Insert (PPI) for ANTHIM (obiltoxaximab) Injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft ANTHIM (obiltoxaximab) PPI received on March 20, 2015, and received by DMPP on November 25, 2015.
- Draft ANTHIM (obiltoxaximab) Prescribing Information (PI) received on March 20, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on November 25, 2015.
- RAXIBACUMAB comparator PPI approved December 14, 2012.

3 REVIEW METHODS

In our focused review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
12/02/2015

MARCIA B WILLIAMS
12/02/2015

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

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

Memorandum

Date: November 27, 2015

To: Jane Dean
Regulatory Project Manager
Division of Anti-Infective Products (DAIP)

From: Adam George, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Amy Toscano, Pharm.D, RAC, CPA
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: **BLA 125509 Anthim (obiltoximab) injection, for intravenous use**

This consult review is in response to DAIP's May 27, 2015 request for OPDP's review of the draft package insert (PI) and carton/container labeling for BLA 125509 Anthim (obiltoximab) injection, for intravenous use (Anthim). OPDP's comments on the PI are based on the substantially complete version titled "11-24-15 SCPI Label.docx" accessed via SharePoint on November 27, 2015. We had comments for sections 5.1, 6.1, 12.4 and 17. Our comments are included directly on the attached copy of the labeling, and were uploaded to the DAIP SharePoint site on November 27, 2015. OPDP's review of the carton/container labeling is based on the versions accessed via SharePoint on November 27, 2015. OPDP does not have any comments on the carton/container labeling at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or adam.george@fda.hhs.gov.

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/s/

ADAM N GEORGE
11/27/2015

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

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

Memorandum

Date: November 27, 2015

To: Jane Dean
Regulatory Project Manager
Division of Anti-Infective Products (DAIP)

From: Adam George, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Amy Toscano, Pharm.D, RAC, CPA
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: **BLA 125509 Anthim (obiltoximab) injection, for intravenous use, patient prescribing information (PPI)**

This consult review is in response to DAIP's November 24, 2015 email request for OPDP's review of the draft PPI for BLA 125509 Anthim (obiltoximab) injection, for intravenous use (Anthim). OPDP's comments on the PPI are based on the substantially complete version titled "11-24-15 SCPI Label.docx" accessed via SharePoint on November 27, 2015. OPDP does not have any comments on the proposed PPI at this time.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or adam.george@fda.hhs.gov.

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/s/

ADAM N GEORGE
11/27/2015



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: September 2, 2015

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Jane Dean, RPM
DAIP

Subject: QT-IRT Consult to BLA 125509

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 6/3/2015 regarding the QT assessment in the BLA submission. The QT-IRT received and reviewed the following materials:

- Your consult
- Integrated summary of safety
- Highlights of clinical pharmacology and cardiac safety

QT-IRT Comments for DAIP

ETI-204 as a large targeted protein has a low likelihood of direct ion channel interactions. There is no evidence from nonclinical or clinical data to suggest that ETI-204 has the potential to delay ventricular repolarization. A thorough QT study is not needed.

BACKGROUND

ETI-204 (obiltoximab, Anthim[®]) is an affinity-enhanced, deimmunized IgG1 monoclonal antibody (~148 kDa) produced via cultures of (b) (4) non-secreting GS-NS0 myeloma cells that targets B. anthracis protective antigen (PA). The proposed indication for ETI-204 is for the treatment of adult and pediatric patients with inhalational anthrax due to B. anthracis in combination with antibacterial drugs and for prophylaxis of inhalational anthrax when alternative

therapies are not available or are not appropriate. ETI-204 is to be administered as a single intravenous (IV) 16 mg/kg infusion over 90 minutes.

Preclinical cardiac safety: The CV safety of ETI-204 was evaluated in two monkey studies, one after a single dose up to 5 mg/kg IV bolus or 10 mg/kg IM in anesthetized animals (Study No. AP106), and one after repeated IV infusions of up to 30 mg/kg/dose with 8 days between doses (n=2 doses) in conscious, telemetered animals (Study No. AP115). In the first study, there were no biologically significant ETI-204 effects on CV parameters including electrocardiogram (ECG) waveforms and intervals and peripheral blood pressure (Study No. AP106). Transient, non-biologically significant increases in the instantaneous heart rate (RR) and QT (but not QTc) and systolic and diastolic blood pressure were observed approximately 2 to 4 hours postdose that all resolved by 24 hours postdose. In the second CV safety study, which utilized conscious telemetered animals, there were no ETI-204-related effects on heart rate, QTc (Frederica's heart rate correction), body temperature, blood pressure, mean arterial pressure (MAP), ECG waveform, or activity after 2 IV infusions of up to 30 mg/kg/dose given 8 days apart (Study No. AP115). According to the sponsor, the non-biologically significant changes seen in the first study were likely due to study procedures and not attributable to ETI-204 because there were no correlative changes in the second study where a 6-fold higher IV dose was administered.

Clinical cardiac safety: The clinical development program for intravenous (IV) ETI-204 included 7 clinical trials was conducted in healthy adults of different racial and ethnic backgrounds, including some who had common stable comorbidities, including hypertension, high cholesterol, and obesity without significant organ dysfunction. The primary objectives of the IV development program were to evaluate the safety and tolerability of a single IV dose of ETI-204, both alone and in the presence of ciprofloxacin, and to evaluate the safety and tolerability of repeat administration (i.e., two doses) of IV ETI-204. Secondary objectives were to evaluate the pharmacokinetics (PK) and immunogenicity of ETI-204.

Serial ECG readings were obtained in all subjects participating in all clinical studies, with a concentration of examinations during the 24 hours following the initiation of an ETI-204 or placebo infusion. Accordingly, multiple readings were available before and during the time when drug concentrations were at or near maximal values at the proposed commercial dose of 16 mg/kg delivered intravenously. There were no serious cardiac adverse events reported and specifically there were no cases of torsades de pointes, sudden death, ventricular tachycardia, ventricular fibrillation or flutter, or seizures.

The QTcB and QTcF were not found to be >480 ms in any subject at any post-baseline determination in the clinical program. In the single-dose Primary Safety Population, postbaseline QTcB >450 ms was found for 3 / 70 (4.3%) placebo-treated subjects and 14 / 250 (5.6%) ETI-204-treated subjects. For QTcF, the proportions were 2 / 70 (2.9%) placebo-treated subjects and 9 / 250 (3.6%) ETI-204-treated subjects. The QTcB and QTcF did not increase by >60 ms in any subject at any post-baseline determination in the clinical program. Postbaseline QTcB >30 ms was recorded in 4 / 70 (5.7%) placebo-treated subjects and 13 / 250 (5.2%) ETI-204-treated subjects in the single-dose primary safety population. For QTcF, the proportions were 1 / 70 (1.4%) placebo-treated subjects and 2 / 250 (0.8%) ETI-204-treated subjects.

Thank you for requesting our input into the development of this product under BLA 125509. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

JIANG LIU
09/02/2015

NORMAN L STOCKBRIDGE
09/02/2015

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: August 17, 2015
Requesting Office or Division: Division of Anti-Infective Products (DAIP)
Application Type and Number: BLA 125509
Product Name and Strength: Anthim (obiltoxaximab) Injection, 600 mg/6 ml
Product Type: Single-ingredient product
Rx or OTC: Rx
Applicant/Sponsor Name: Elusys Therapeutics
Submission Date: March 20, 2015
OSE RCM #: 2015-874
DMEPA Primary Reviewer: Jacqueline Sheppard, PharmD
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Elusys proposes the introduction of a new biologic agent to the market for the prophylaxis and treatment of inhalational anthrax due to *Bacillus anthracis*. This review evaluates the proposed container labels, carton labeling, and Prescribing Information (PI) for Anthim (obiltoximab) injection (BLA 125509) for areas of vulnerability that may lead to medication errors in response to a request from the Division of Anti-Infective Products (DAIP).

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.

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B – N/A |
| 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 label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed container label, carton labeling, and PI from a medication error perspective.

We identified areas of the carton labeling and container labels that can be revised to increase clarity, improve readability, add important critical information, or increase prominence of important information (See section 4.2). For all container labels and carton labeling, we recommend revision to the appearance and presentation of the product name in accordance with guidelines for the size of the established name and Biologic Product Labeling, use of unique NDC numbers for each packaging configuration submitted by the Applicant, and revision of the prescribing information statement on the side panel (b) (4)

We recommend that the expiration date and a linear barcode be placed on the side panel of

the vial container label per 21 CFR 201.17 and 21 CFR 201.25, respectively. This may be done by relocating the “Rx only” statement to the top right corner of the PDP and the size reduction of the manufacturer information statement. We recommend that the Applicant ensure that (b) (4) statements are present on the Principal Display Panel (PDP) and maintain the pertinent preparation instruction for the intravenous route.

Additionally, we performed a risk assessment of the proposed PI to identify areas of improvement for clarity. We note (b) (4) in the Dosage and Administration section and recommend (b) (4) removed and replaced with (b) (4). We streamlined and clarified tables describing intravenous dosage and administration for readability. We modified steps for preparation of bags for infusion or syringes for infusion for clarity and usability. These changes are added to DAIP’s working version of PI that is currently undergoing revision (see Appendix G).

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling for Anthim may be improved to communicate important use information and to improve readability of important product information. We recommend the following revisions be implemented prior to the approval of the BLA.

4.1 RECOMMENDATIONS FOR THE DIVISION

We have made revisions to the Full Prescribing Information for review and Consideration by DAIP (Appendix G). These changes are added to DAIP’s working version of PI that is currently undergoing revision.

4.2 RECOMMENDATIONS FOR ELUSYS THERAPEUTICS

We recommend the following be implemented prior to approval of this BLA supplement:

A. All Container Labels and Carton Labeling

1. Revise the appearance and presentation of the proprietary and trade name to improve readability. The established (proper) name should be at least half the size of the proprietary name. Thus, we request you revise the established name to be in accordance with the guidelines for Biologic Product Labeling.
2. Revise the presentation of the names of the container labels and carton labeling similar to the example below in accordance with Draft Guidance: Container and Carton, April 2013.

Anthim
(obilttoxaximab)
Injection

3. Add a unique NDC number for each packaging configuration. The NDC code is an important check used by pharmacists to assist in drug selection and dispensing. Ensure that the numbers assigned to the inner and outer packaging are appropriate to minimize the risk for selecting the wrong package size.
4. To alert providers of the administration (b) (4) (b) (4) revise the prescribing information statement on the side panel from “See prescribing information...” to read as follows:

For Intravenous Infusion: See Prescribing Information for Dilution and Dosage Information

(b) (4)

B. Container Label (Commercial and National Strategic Stockpile)

1. Add the expiration date per 21 CFR 201.17 and a linear barcode per 21 CFR 201.25 on the side panel in a vertical position where the barcode can be scanned. This may be done by unbolding and relocating the “Rx only” statement to the top right corner of the PDP and reducing the size of the manufacturer information.
2. Ensure that (b) (4) present on the principal display panel and that the intravenous statement contains language similar to the “Must Be Diluted Prior to Use” warning statement and can be revised to read as follows, “For Intravenous Infusion after Dilution (b) (4). This may be done by removing the (b) (4) and graphic design that appears above the proprietary name on the Principal Display Panel.

C. Carton Labeling (Commercial and National Strategic Stockpile)

1. Ensure that (b) (4) present on the principal display panel and that the intravenous statement contains language similar to the “Must Be Diluted Prior to Use” warning statement and can be revised to read as follows, “For Intravenous Infusion after Dilution (b) (4). This may be done by relocating the (b) (4) to the upper right hand portion of the Principal Display Panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Anthim that Elusys Pharmaceuticals submitted on March 20, 2015.

| Table 2. Relevant Product Information for Anthim | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredient | Obiltoxaximab |
| Indication | Treatment of adult and pediatric patients with inhalational anthrax due to Bacillus anthracis in combination with appropriate antibacterial drugs and for prophylaxis of inhalational anthrax when alternative therapies are not available or not appropriate |
| Route of Administration | Intravenous (b) (4) |
| Dosage Form | Injection |
| Strength | (b) (4) |
| Dose and Frequency | Adults: 16 mg/kg Pediatric: Greater than (b) (4) kg: 16 mg/kg Greater than 15 kg to (b) (4) kg: 24 mg/kg 15 kg or less: 32 mg/kg |
| How Supplied | Single-use vial |
| Storage | Refrigerated at 2-8 °C |

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,¹ along with postmarket medication error data, we reviewed the following Anthim labels and labeling submitted by Elusys Therapeutics on March 20, 2015.

- Commercial Container label
- Commercial Carton labeling
- National Strategic Stockpile Container label
- National Strategic Stockpile Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

Commercial Container Label



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¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JACQUELINE E SHEPPARD
08/17/2015

BRENDA V BORDERS-HEMPHILL
08/18/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 125509

Application Type: New BLA

Name of Drug/Dosage Form: Anthim (obiltoxaximab) Injection, for intravenous use

Applicant: Elusys Therapeutics

Receipt Date: March 20, 2015

Goal Date: March 18, 2016

1. Regulatory History and Applicant's Main Proposals

Elusys Therapeutics, Inc. submitted a new Biologics Licensing Application (BLA) under section 351(a) of the Public Health Service Act and 21CFR Part 601, Subpart H (Approval of a Biologic Product When Human Efficacy Studies are not Ethical or Feasible) Anthim (obiltoxaximab) with the following indications: treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 23, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
***Comment:** Top margin is less than ½ inch. Increase to ½ inch.*
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
Comment:
- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
***Comment:** Horizontal line separating TOC from the Full Prescribing Information (FPI) is missing. Insert*
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
Comment:
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
Comment:
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
Comment:
- YES** 7. Section headings must be presented in the following order in HL:

| Section | Required/Optional |
|--|---|
| • Highlights Heading | Required |
| • Highlights Limitation Statement | Required |
| • Product Title | Required |
| • Initial U.S. Approval | Required |
| • Boxed Warning | Required if a BOXED WARNING is in the FPI |
| • Recent Major Changes | Required for only certain changes to PI* |
| • Indications and Usage | Required |
| • Dosage and Administration | Required |
| • Dosage Forms and Strengths | Required |
| • Contraindications | Required (if no contraindications must state “None.”) |

Selected Requirements of Prescribing Information

| | |
|---|---|
| • Warnings and Precautions | Not required by regulation, but should be present |
| • Adverse Reactions | Required |
| • Drug Interactions | Optional |
| • Use in Specific Populations | Optional |
| • Patient Counseling Information Statement | Required |
| • Revision Date | Required |

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Comment:

Highlights Limitation Statement

- NO 9. The **bolded** HL Limitation Statement must include the following verbatim statement: **“These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).”** The name of drug product should appear in UPPER CASE letters.

Comment: *The name of the drug product is not in upper case letters. The bolded HL Limitation Statement should read as "These highlights do not include all the information needed to use ANTHIM safely and effectively. See full prescribing information for ANTHIM." instead of "These highlights do not include all the information needed to use Anthim safely and effectively. See full prescribing information for Anthim."*

Product Title in Highlights

- YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement **“Initial U.S. Approval:”** followed by the **4-digit year**.

Comment: *Placeholder included as "Initial U.S. Approval: [year]". Remember to update with 4-digit year on prior to approval.*

Boxed Warning (BW) in Highlights

- N/A 12. All text in the BW must be **bolded**.

Comment:

- N/A 13. The BW must have a heading in UPPER CASE, containing the word **“WARNING”** (even if more than one warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and other words to identify the subject of the warning (e.g., **“WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”**). The BW heading should be centered.

Comment:

Selected Requirements of Prescribing Information

- N/A 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- NO 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *Established Pharmacologic Class (EPC) was not included. If the product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: Anthim is a (name of established pharmacologic class) indicated for (indication)”*

Dosage Forms and Strengths in Highlights

- N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

Selected Requirements of Prescribing Information

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- NO** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”
 - **Comment:** *The Patient Counseling Information statement should read as “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**” instead of “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling.**”*

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- NO** 25. The TOC should be in a two-column format.
***Comment:** The TOC is in a single-column format. Change to a two-column format.*
- YES** 26. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- NO** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
***Comment:** Section headings are not bolded. Bold them*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

| |
|--|
| BOXED WARNING |
| 1 INDICATIONS AND USAGE |
| 2 DOSAGE AND ADMINISTRATION |
| 3 DOSAGE FORMS AND STRENGTHS |
| 4 CONTRAINDICATIONS |
| 5 WARNINGS AND PRECAUTIONS |
| 6 ADVERSE REACTIONS |
| 7 DRUG INTERACTIONS |
| 8 USE IN SPECIFIC POPULATIONS |
| 8.1 Pregnancy |
| 8.2 Labor and Delivery |
| 8.3 Nursing Mothers |
| 8.4 Pediatric Use |
| 8.5 Geriatric Use |
| 9 DRUG ABUSE AND DEPENDENCE |
| 9.1 Controlled Substance |
| 9.2 Abuse |
| 9.3 Dependence |
| 10 OVERDOSAGE |
| 11 DESCRIPTION |
| 12 CLINICAL PHARMACOLOGY |
| 12.1 Mechanism of Action |
| 12.2 Pharmacodynamics |
| 12.3 Pharmacokinetics |
| 12.4 Microbiology (by guidance) |
| 12.5 Pharmacogenomics (by guidance) |
| 13 NONCLINICAL TOXICOLOGY |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 Animal Toxicology and/or Pharmacology |
| 14 CLINICAL STUDIES |
| 15 REFERENCES |
| 16 HOW SUPPLIED/STORAGE AND HANDLING |
| 17 PATIENT COUNSELING INFORMATION |

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment: *In the Full Prescribing Information:*

Selected Requirements of Prescribing Information

Under Indications and Usage subsection 1.2, the cross-reference should include the section heading and not the sub-section heading. It should read as (b) (4)

" instead of (b) (4)
"

Under Dosage and Administration subsection 2.3, the cross-reference should read as " (b) (4)

" instead of (b) (4)
."

- N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION**". This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A 36. In the BW, all text should be **bolded**.

Comment:

- N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

- YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

- YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

- N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

Selected Requirements of Prescribing Information

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JANE A DEAN
06/02/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

| Application Information | | |
|---|----------------------|--|
| BLA# 125509 | BLA Supplement #: S- | Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric |
| Proprietary Name: Anthim Established/Proper Name: Obiltoxaximab Dosage Form: 600 mg/6 mL single use vial, IV infusion Strengths: 100 mg/mL | | |
| Applicant: Elusys Therapeutics, Inc. Agent for Applicant (if applicable): n/a | | |
| Date of Application: 3/20/15 Date of Receipt: 3/20/15 Date clock started after UN: n/a | | |
| PDUFA/BsUFA Goal Date: 3/18/16 | | Action Goal Date (if different): |
| Filing Date: 5/19/15 | | Date of Filing Meeting: 5/4/15 |
| Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch | | |
| Proposed indication(s)/Proposed change(s): Treatment of adult and pediatric patients with inhalational anthrax due to Bacillus anthracis in combination with appropriate drugs and for prophylaxis of inhalational anthrax | | |
| Type of Original NDA: AND (if applicable) Type of NDA Supplement: | | <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) |
| <i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 | | |

| | | |
|--|---|--|
| Type of BLA | | <input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k) |
| <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i> | | |
| Review Classification: | | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority |
| <p><i>The application will be a priority review if:</i></p> <ul style="list-style-type: none"> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> | | <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher |
| Resubmission after withdrawal? <input type="checkbox"/> | Resubmission after refuse to file? <input type="checkbox"/> | |
| Part 3 Combination Product? <input type="checkbox"/> | <input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product) | |
| <p><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></p> | | |

| | |
|---|---|
| <input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <p><i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i></p> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <ul style="list-style-type: none"> <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) |
|---|---|

Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 012285

| Goal Dates/Product Names/Classification Properties | YES | NO | NA | Comment |
|---|-------------------------------------|--------------------------|----|---------|
| PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |

| | | | | |
|---|--|-------------------------------------|--------------------------|----------------|
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Application Integrity Policy | YES | NO | NA | Comment |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| If yes, explain in comment column. | | | | |
| If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified: | <input type="checkbox"/> | <input type="checkbox"/> | | |
| User Fees | YES | NO | NA | Comment |
| Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i> | Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required | | | |
| <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i> | Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears | | | |
| <u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf | Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No | | | |
| 505(b)(2) (NDAs/NDA Efficacy Supplements only) | YES | NO | NA | Comment |
| Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted questions below: | <input type="checkbox"/> | <input type="checkbox"/> | | |

| <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | | | | | | |
|---|--------------------------|-------------------------------------|-------------------------------------|------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--------------------------|--------------------------|--|--|
| <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | | | | | | |
| <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | | | | | | |
| <ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table> | Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | <input type="checkbox"/> | <input type="checkbox"/> | | |
| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| <p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p> | | | | | | | | | | | | | | | | | | | | |
| Exclusivity | YES | NO | NA | Comment | | | | | | | | | | | | | | | | |
| Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | | | | | | | | | | | | | | | | | |
| If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | | | | | | | | | | | | | | | | |
| <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i> | | | | | | | | | | | | | | | | | | | | |
| NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | | | | | |
| If yes, # years requested: | | | | | | | | | | | | | | | | | | | | |
| <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | | | | | | | | | | | | | | | | | | | | |
| NDA only: Is the proposed product a single enantiomer of a | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | | | | | | | | | | | | | | | | | |

| | | | | |
|---|-------------------------------------|--------------------------|--------------------------|--|
| racemic drug previously approved for a different therapeutic use? | | | | |
| If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |

| Format and Content | | | | |
|--|--|--------------------------|--------------------------|----------------|
| <i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i> | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) | | | |
| | <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) | | | |
| If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format? | | | | |
| Overall Format/Content | YES | NO | NA | Comment |
| If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted). | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Index: Does the submission contain an accurate comprehensive index? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

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|--|-------------------------------------|--------------------------|-------------------------------------|----------------|
| <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) | | | | |
| If no, explain. | | | | |
| BLAs only: Companion application received if a shared or divided manufacturing arrangement? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| If yes, BLA # | | | | |
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| Forms and Certifications | | | | |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> | | | | |
| Application Form | YES | NO | NA | Comment |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Are all establishments and their registration numbers listed on the form/attached to the form? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Patent Information (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Financial Disclosure | YES | NO | NA | Comment |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| Clinical Trials Database | YES | NO | NA | Comment |
| Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |

| Debarment Certification | YES | NO | NA | Comment |
|---|-------------------------------------|-------------------------------------|-------------------------------------|----------------|
| <p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Field Copy Certification (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| <p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Controlled Substance/Product with Abuse Potential | YES | NO | NA | Comment |
| <p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| Pediatrics | YES | NO | NA | Comment |
| <p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and</i></p> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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|--|--|-------------------------------------|-------------------------------------|----------------|
| <i>pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i> | | | | |
| If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| <i>If no, may be an RTF issue - contact DPMH for advice.</i> | | | | |
| If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| <i>If no, may be an RTF issue - contact DPMH for advice.</i> | | | | |
| <u>BPCA:</u> | | | | |
| Is this submission a complete response to a pediatric Written Request? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | | |
| <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i> | | | | |
| Proprietary Name | YES | NO | NA | Comment |
| Is a proposed proprietary name submitted? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i> | | | | |
| REMS | YES | NO | NA | Comment |
| Is a REMS submitted? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i> | | | | |
| Prescription Labeling | <input type="checkbox"/> Not applicable | | | |
| Check all types of labeling submitted. | <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| <i>If no, request applicant to submit SPL before the filing date.</i> | | | | |

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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|--|--|--------------------------|-------------------------------------|----------------|
| Is the PI submitted in PLR format? ⁴ | <input checked="" type="checkbox"/> | <input type="checkbox"/> | | |
| If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| OTC Labeling | <input checked="" type="checkbox"/> Not Applicable | | | |
| Check all types of labeling submitted. | <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | | |
| Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| All labeling/packaging sent to OSE/DMEPA? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| Other Consults | YES | NO | NA | Comment |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

| Meeting Minutes/SPAs | YES | NO | NA | Comment |
|--|-----|----|----|---------|
| End-of Phase 2 meeting(s)? Date(s): 1/7/13 <i>If yes, distribute minutes before filing meeting</i> | ☒ | ☐ | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7/30/13 <i>If yes, distribute minutes before filing meeting</i> | ☒ | ☐ | | |
| Any Special Protocol Assessments (SPAs)? Date(s): 12/23/13 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | ☒ | ☐ | | |

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 11, 2015

BACKGROUND: Elusys Therapeutics, Inc. submitted a new Biologics Licensing Application (BLA) under section 351(a) of the Public Health Service Act and 21CFR Part 601, Subpart H (Approval of a Biologic Product When Human Efficacy Studies are not Ethical or Feasible) for Anthem (obiltoximab) with the following indications: treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs and prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|--|----------------------|--------------------------|-------------------------------------|
| Regulatory Project Management | RPM: | Jane Dean | Y |
| | CPMS/TL: | LeSane | Y |
| Cross-Discipline Team Leader (CDTL) | John Alexander | | Y |
| Division Director/Deputy | Sumathi Nambiar | | Y |
| Office Director/Deputy | Ed Cox/John Farley | | Y/Y |
| Clinical | Reviewer (Efficacy): | Elizabeth O'Shauaghnessy | Y |
| | Reviewer (Safety): | Ramya Gopinath | N |
| | TL: | John Alexander | Y |
| Social Scientist Review (for OTC products) | Reviewer: | N/A | |
| | TL: | | |
| OTC Labeling Review (for OTC products) | Reviewer: | N/A | |
| | TL: | | |
| Clinical Microbiology (for antimicrobial products) | Reviewer: | Shukal Bala | Y |
| | | Lynette Berkeley | N |
| | TL: | Kerry Snow | Y |

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|-----------------------|-----------|--------------------|---|
| Clinical Pharmacology | Reviewer: | Zhixia (Grace) Yan | Y |
| | TL: | Kimberly Bergman | Y |
| Biostatistics | Reviewer: | Xianbin Li | Y |
| | TL: | Karen Higgins | Y |

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|---|-----------|----------------------------|---|
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Amy Nostrandt | Y |
| | TL: | Wendelyn Schmidt | Y |
| Statistics (carcinogenicity) | Reviewer: | N/A | |
| | TL: | | |
| Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i> | Reviewer: | | |
| | TL: | | |
| Product Quality (CMC) | Reviewer: | Jibril Abdus-Samad | Y |
| | TL: | Rashmi Rawat | N |
| Biopharmaceutics | Reviewer: | | |
| | TL: | | |
| Quality Microbiology | Reviewer: | | |
| | TL: | | |
| CMC Labeling Review | Reviewer: | | |
| | TL: | | |
| Facility Review/Inspection | Reviewer: | Bo Chi | Y |
| | TL: | Patricia Hughes | Y |
| OSE/DMEPA (proprietary name, carton/container labels)) | Reviewer: | Sevan Kolejian | N |
| | TL: | Vicky Borders- Hemphill | N |
| OSE/DRISK (REMS) | Reviewer: | Joyce Weaver | Y |
| | TL: | Naomi Redd | Y |
| OC/OSI/DSC/PMSB (REMS) | Reviewer: | | |

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| | TL: | | |
| Bioresearch Monitoring (OSI) | Reviewer: | | |
| | TL: | | |
| Controlled Substance Staff (CSS) | Reviewer: | N/A | |
| | TL: | | |
| Other reviewers/disciplines | Reviewer: | | |
| | TL: | | |
| Other attendees | Karen Townsend (DMEPA) Dionne Price (OB) Patricia Hughes (OBP) Bo Chi (OBP) | | |

FILING MEETING DISCUSSION:

| | |
|--|---|
| <p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> | <p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p> | <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> |
| <ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p> | <p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> No comments</p> |
| <p>CLINICAL</p> | <p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> |

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| <p>Comments:</p> | <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | <input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <ol style="list-style-type: none"> The clinical study design was acceptable The application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease This product is directed at anthrax which was discussed at an Advisory Committee meeting for a similar product |
| <ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL PHARMACOLOGY</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE |

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| Comments: | <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| BIOSTATISTICS | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE |
| Comments: | <input type="checkbox"/> Review issues for 74-day letter |
| NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE |
| Comments: | <input type="checkbox"/> Review issues for 74-day letter |
| IMMUNOGENICITY (protein/peptide products only) | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE |
| Comments: | <input type="checkbox"/> Review issues for 74-day letter |
| PRODUCT QUALITY (CMC) | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE |
| Comments: | <input type="checkbox"/> Review issues for 74-day letter |
| New Molecular Entity (NDAs only) | |
| <ul style="list-style-type: none"> Is the product an NME? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <u>Environmental Assessment</u> | |
| <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| If no , was a complete EA submitted? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| If EA submitted , consulted to EA officer (OPS)? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| Comments: | |
| <u>Quality Microbiology</u> | <input type="checkbox"/> Not Applicable |

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| <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? <p>Comments:</p> | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p><u>CMC Labeling Review</u></p> <p>Comments:</p> | <input type="checkbox"/> Review issues for 74-day letter |
| <p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? | <input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? | |

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| <ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| REGULATORY PROJECT MANAGEMENT | |
| <p>Signatory Authority: Edward Cox, MD, MPH, Director, Office of Antimicrobial Products</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 9/1/15</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p> | |
| REGULATORY CONCLUSIONS/DEFICIENCIES | |
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| <input checked="" type="checkbox"/> | The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review |
| ACTIONS ITEMS | |
| <input type="checkbox"/> | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug). |
| <input type="checkbox"/> | If RTF, notify everyone who already received a consult request, OSE PM, and Product |

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| | Quality PM (to cancel EER/TBP-EER). |
| <input type="checkbox"/> | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | 351(k) BLA/supplement: If filed, send filing notification letter on day 60 |
| <input type="checkbox"/> | If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier) |
| <input checked="" type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input checked="" type="checkbox"/> | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |
| <input checked="" type="checkbox"/> | Update the PDUFA V DARRTS page (for applications in the Program) |
| <input type="checkbox"/> | Other |

Annual review of template by OND ADRA completed: September 2014

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

/s/

JANE A DEAN
06/02/2015