

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125509Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
BLA #125509	BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Anthim Established/Proper Name: obiltoximab Dosage Form: injection		Applicant: Elusys Therapeutics, Inc. Agent for Applicant (if applicable):
RPM: Jane A. Dean, RN, MSN		Division: Division of Anti-Infective Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is 3/20/16</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input checked="" type="checkbox"/> Received

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Application Characteristics <sup>3</sup>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority          Chemical classification (new NDAs only):  <i>(confirm chemical classification at time of approval)</i></p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  <input type="checkbox"/> Breakthrough Therapy designation         </p> <p><b>(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: <a href="#">CST SharePoint</a>)</b></p> <p>           NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I <input type="checkbox"/> Approval based on animal studies         </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>           BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H <input checked="" type="checkbox"/> Approval based on animal studies         </p> <p>           REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required         </p> <p>Comments:</p>	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information were issued</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?</li> <li>If so, specify the type</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action: Approval Date: 3/18/16
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	Letter: 5/21/15 Review: 5/15/15
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: 6/2/15; 3/18/16 DMEPA: 8/18/15; 3/2/16 DMPP/PLT (DRISK): 12/21/15 OPDP: 11/27/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: 3/3/16 Clinical Pharmacology: 3/2/16

Administrative / Regulatory Documents	
<ul style="list-style-type: none"> <li>❖ RPM Filing Review<sup>4</sup>/Memo of Filing Meeting (<i>indicate date of each review</i>)</li> <li>❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee</li> </ul>	<p>6/2/15</p> <p><input type="checkbox"/> Not a (b)(2)</p>
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<p><input type="checkbox"/> Included</p>
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• This application is on the AIP               <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="text-align: right;"><input type="checkbox"/> Not an AP action</p>
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)               <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: Orphan drug designation</li> </ul> </li> </ul>	<p>N/A</p>
<ul style="list-style-type: none"> <li>❖ Breakthrough Therapy Designation</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p>
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	<p>X</p>
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	<p>X</p>
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p>
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<p>7/30/13</p>
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<p>3/15/13</p>
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<p>9/1/15</p>
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<p>12/11/15</p>
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p>

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	3/18/16
Division Director Summary Review ( <i>indicate date for each review</i> )	3/11/16
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	2/5/16
PMR/PMC Development Templates ( <i>indicate total number</i> )	11
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	12/29/15; 3/18/16
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Clinical Review, page 525, 12/29/15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	Office of Good Clinical Practice, 11/19/15 Division of Pulmonary, Allergy, and Rheumatology Products, 1/7/16 Division of Cardiovascular and Renal Products, 2/12/16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> )	
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	OSE Review, 11/24/15 Clinical Review, page 522, 12/29/15
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	X
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	12/15/15; 12/16/15
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	12/8/15

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	12/7/15; 3/2/16
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	IND 012285 – 2/17/12; 2/21/12; 6/13/12; 6/25/12; 8/22/12 BLA 125509 - 12/16/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	2/12/16
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	12/1/15
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	12/1/15
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	11/30/15 12/1/15 2/10/16 2/23/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	12/1/15
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANE A DEAN  
03/18/2016

**From:** Dean, Jane  
**Sent:** Thursday, February 25, 2016 5:59 PM  
**To:** 'Cindi Dillon'  
**Cc:** Robin Conrad; Ariane Cutolo  
**Subject:** BLA 125509 (Anthem) - response to email question sent on 2/24/16 re carton and container labels and the (b) (4)

Hi, Cindi – I have received the following response from the team who reviews the carton and container labels and also deals with (b) (4)

**Your Question: We are not clear on the next steps associated with the BLA, specifically how the stockpile (b) (4) cartons are approved in the BLA. Can we discuss the next steps with the labeling reviewer?**

- Commercial container label and carton labeling received via email 2/24/2016 are acceptable. Please proceed to officially submit through the gateway.
- The revised SNS immediate container label and (b) (4) carton labeling received via email 2/24/2016 appear acceptable from a labeling standpoint (b) (4)

- We are available to discuss this issue further via tcon if necessary.

I hope this information is helpful. The “we” referred to in the offer for a telecon includes the labeling reviewer from Product Quality and the DMEPA team.

Jane

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANE A DEAN  
02/25/2016

**From:** Dean, Jane  
**Sent:** Tuesday, February 23, 2016 3:42 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - response to Elusys email sent on 2-18-16

Robin, here is the division's response to your email questions from 2/18/16.

1. URTI: TEAEs in the single-dose population (210 Anthem subjects in AH104 + 20 Anthem alone subjects in AH110 + 70 Anthem subjects in the first treatment period (days1 through 13) of AH109. The following are the PTs in the Infections and Infestations SOC:

AEDECOD	USUBJID	TRTA	
		0 mg/kg PLACEBO	16 mg/kg ETI-204
Asymptomatic bacteriuria	AH109-001-118	0	1
Bronchitis	AH104-001-048	0	1
Cystitis	AH110-001-130	0	1
Folliculitis	AH104-004-308	0	1
	AH109-002-214	0	1
Pharyngitis streptococcal	AH104-002-244	0	1
Pneumonia	AH110-001-102	0	1
Upper respiratory tract infection	AH104-003-103	1	0
	AH104-003-110	0	1
	AH104-003-258	0	1
	AH104-004-138	0	1
	AH104-004-153	0	1
	AH104-004-156	0	1
	AH104-004-305	1	0
	AH109-001-101	0	1
	AH110-001-101	0	1
	AH110-001-106	0	1
	AH110-001-111	0	1
AH110-001-117	0	1	
AH110-001-135	0	1	
Urethritis chlamydial	AH109-001-116	0	1
Urinary tract infection	AH104-004-142	1	0
	AH104-004-150	1	0
Vaginitis bacterial	AH110-001-117	0	1
Viral infection	AH104-004-307	0	1
Vulvovaginal mycotic infection	AH104-004-130	0	1

NB: One subject with Influenza-like illness – AH104-002-237 (listed under General disorders and Administration site conditions). Because of lack of information re: symptomatology, this subject was not included in the count of infections of the upper respiratory tract.

**Thus, the total in Anthim arm = URTI (11) + bronchitis (1) + Pharyngitis streptococcal (1) + viral infection (1) = 14/300 = 4.7%**

Additional cases identified by Elusys are in the table: these infections occurred outside the first treatment period so were not included in the single-dose population

Subject ID	Sequence	PT	Study Day
AH 109-002-204	B	URTI	93
AH109-002-205	A	Pharyngitis	27
AH109-002-214	B	URTI	66

2. Diphenhydramine effect: The percentage of subjects with TEAEs without diphenhydramine treatment has been altered to 58% (43/74) (denominator is based on the inclusion by Elusys of subject AH104-001-026 who appeared to have received ETI-204, but subsequently had a missing treatment record, originally left out by FDA)
3. Percentage of individual events correlated with diphenhydramine administration has been updated in the label.

**From:** Robin Conrad [<mailto:rconrad@elusys.com>]

**Sent:** Thursday, February 18, 2016 5:13 PM

**To:** Dean, Jane

**Cc:** Cindi Dillon; Ariane Cutolo

**Subject:** RE: BLA 125509 ANTHIM - follow up from yesterday's call - response to Q2 - Elusys Reply

**Importance:** High

Hi Jane,

Thanks for the clarification from the clinical reviewers – it was very helpful. We’re providing the following response – can you share with the clinical reviewers in advance of Monday’s TC?

- For URIs we have not been able to resolve why we have a different number of events on the ETI-204 arm than FDA (14 vs 17). We’ve included the subjects/terms that we’re including in our 17 cases below in hopes that FDA can spot the difference?
- We have resolved why we have a difference from FDA for the diphenhydramine percentages and the explanation is provided in the table below.

	FDA Values	Elusys Values	Notes
URTI	2 (3%) vs 14 (5%)	2 (3%) vs 17 (6%)	Elusys identified the following subjects using the terms provided by FDA
			AH104-001-048   Bronchitis
			AH104-002-244   Pharyngitis streptococcal
			AH104-003-110   Upper respiratory tract infection
			AH104-003-258   Upper respiratory tract infection
			AH104-004-138   Upper respiratory tract infection

			<table border="1"> <tbody> <tr> <td>AH104-004-153</td> <td>Upper respiratory tract infection</td> </tr> <tr> <td>AH104-004-156</td> <td>Upper respiratory tract infection</td> </tr> <tr> <td>AH104-004-307</td> <td>Viral infection</td> </tr> <tr> <td>AH109-001-101</td> <td>Upper respiratory tract infection</td> </tr> <tr> <td>AH109-002-204</td> <td>Upper respiratory tract infection</td> </tr> <tr> <td>AH109-002-205</td> <td>Pharyngitis</td> </tr> <tr> <td>AH109-002-214</td> <td>Upper respiratory tract infection</td> </tr> <tr> <td>AH110-001-101</td> <td>Upper respiratory tract infection</td> </tr> <tr> <td>AH110-001-106</td> <td>Upper respiratory tract infection</td> </tr> <tr> <td>AH110-001-111</td> <td>Upper respiratory tract infection</td> </tr> <tr> <td>AH110-001-117</td> <td>Upper respiratory tract infection</td> </tr> <tr> <td>AH110-001-135</td> <td>Upper respiratory tract infection</td> </tr> </tbody> </table>	AH104-004-153	Upper respiratory tract infection	AH104-004-156	Upper respiratory tract infection	AH104-004-307	Viral infection	AH109-001-101	Upper respiratory tract infection	AH109-002-204	Upper respiratory tract infection	AH109-002-205	Pharyngitis	AH109-002-214	Upper respiratory tract infection	AH110-001-101	Upper respiratory tract infection	AH110-001-106	Upper respiratory tract infection	AH110-001-111	Upper respiratory tract infection	AH110-001-117	Upper respiratory tract infection	AH110-001-135	Upper respiratory tract infection
AH104-004-153	Upper respiratory tract infection																										
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AH109-001-101	Upper respiratory tract infection																										
AH109-002-204	Upper respiratory tract infection																										
AH109-002-205	Pharyngitis																										
AH109-002-214	Upper respiratory tract infection																										
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AH110-001-106	Upper respiratory tract infection																										
AH110-001-111	Upper respiratory tract infection																										
AH110-001-117	Upper respiratory tract infection																										
AH110-001-135	Upper respiratory tract infection																										
Diphenhydramine effect [with (n=226) vs without (n=74)]	42% vs 59%	95 (42%) vs 43 (58%)	Overall number of subjects without diphenhydramine pretreatment with TEAEs N = 43/74 (58%),																								
Individual Events	FDA rates calculated based on denominator of <u>subjects with TEAEs</u> who received or didn't receive diphenhydramine (95 vs 43)	Elusys rates calculated based on denominator of <u>all subjects</u> with or without diphenhydramine pretreatment (226 vs 74)	<p>Based on the text in the draft PI Elusys assumed the percentages calculated for the individual events were based on the "overall" safety population. Text as written would lead the reader to imply the overall population (rather than subjects with TEAEs) as the denominator.</p> <p><u>Effect of Diphenhydramine on the Incidence of Adverse Reactions Overall in the single-dose population</u>, subjects who received pre-medication with diphenhydramine were less likely to experience adverse reactions with administration of ANTHIM compared to those who did not (42% vs. 59% respectively). Specifically, the incidence of the following adverse reactions was lower <u>in the subjects who received diphenhydramine prior to ANTHIM infusion compared to those who did not</u>: headache (12% vs. 28%), cough (3% vs. 14%), rash (1% vs. 5%), throat irritation (0 vs. 5%), rhinorrhea (0 vs. 5%), and infusion site erythema (1% vs. 7%).</p>																								
Headache	12% vs 28% (30%?)	11 (5%) vs 13 (18%)																									
Cough	3% vs 14%	3 (1%) vs 6 (8%)																									
Rash	1% vs 5%	3 (1%) vs 3 (4%)																									
Throat	0 vs 5%	0 vs 2																									

irritation		(3%)	
Rhinorrhoea	0 vs 5%	0 vs 2 (3%)	
Infusion site erythema	1% vs 7%	1 (0.4%) vs 3 (4%)	

Thanks!  
Robin

Robin L. Conrad  
VP Regulatory Affairs & Clinical Operations  
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Pine Brook, NJ 07058  
[rconrad@elusys.com](mailto:rconrad@elusys.com)  
office: 973-787-8496  
mobile: (b) (6)

**From:** Dean, Jane [<mailto:Jane.Dean@fda.hhs.gov>]  
**Sent:** Wednesday, February 17, 2016 3:06 PM  
**To:** Robin Conrad <[rconrad@elusys.com](mailto:rconrad@elusys.com)>  
**Cc:** Cindi Dillon <[cdillon@elusys.com](mailto:cdillon@elusys.com)>; Ariane Cutolo <[acutolo@elusys.com](mailto:acutolo@elusys.com)>  
**Subject:** RE: BLA 125509 ANTHIM - follow up from yesterday's call - response to Q2

Robin, I hope this helps. It came from the clinical reviewers.

Question from Elusys:

2. In Section 6 of the USPI under the heading "Effect of Diphenhydramine on the Incidence of Adverse Reactions" we are having trouble replicating the percentages for the individual symptoms. We'd like to confirm the criteria used by the Agency in calculating the numbers. The criteria we've applied are as follows:
  - a. Number of subjects is the single dose pool used in Table 3 (300 ANTHIM treated subjects)
  - b. Of the 300 subjects, 227 received diphenhydramine pre-treatment and 73 did not.
  - c. Study AH109 includes only the AEs associated with the first dose of ETI-204 (all AEs <=Period 2 Dose Date). Can you also confirm that this criteria for handling AH109 AEs was applied to the rates reported in Table 3?

Response from FDA:

- a) Agreed.
- b) FDA analysis from ISS ADSL: 226 of 300 received diphenhydramine and 74 did not.

Out of 370 total subjects in the FDA PSP [ETI-204 (210 subjects from AH104, 70 subjects from the first treatment period of AH109, 20 subjects who received ETI-204 alone in AH110) plus 70 placebo in AH104] , 165 subjects or 44.5% experienced 329 TEAE's – 138 of these were in the obiltoximab arm (138/300 or 46%), and 27 were in the placebo arm (27/70 or 38.6%). Of the 138 subjects with TEAE's in the obiltoximab group, 95 subjects received diphenhydramine, and 43 did not. Of the 27 subjects with TEAE's in the placebo arm, 18 subjects received diphenhydramine, and 9 did not.

**Table 8.36 FDA Analysis of Occurrence of TEAE's Correlated with Diphenhydramine Use in the FDA PSP**

Number of subjects in FDA PSP N=370	Obiltoximab, N=300		Placebo, N=70	
	DPH+ (n=226) (75.3%)	DPH- (n=74)	DPH+ (n=48)	DPH- (n=22)
Number of subjects with TEAE's N=165 (44.5%)	Obiltoximab, N=138		Placebo, N=27	
	DPH+ (n=95) (95/226=42%)	DPH- (n=43)	DPH+ (n=18)	

DPH: diphenhydramine

- c) Yes, the same criteria were used (TEAEs on d1-13 in AH109)

NB. Subject 104-001-026 appeared to receive ETI-204 and had an AE but the treatment record was subsequently lost. The subject has been included by the Applicant in their safety datasets; thus, she was included in FDA analysis as well.

From: Robin Conrad [<mailto:rconrad@elusys.com>]  
 Sent: Friday, February 12, 2016 8:17 AM  
 To: Dean, Jane  
 Cc: Cindi Dillon; Ariane Cutolo  
 Subject: BLA 125509 ANTHIM - follow up from yesterday's call  
 Importance: High

Hi Jane,

I wanted to do a quick follow up from yesterday's TC on two items.

1. The discrepancy in the p-value for Study 4 in Table 4 of the PI. Our statistician re-checked the number and we've attached an output that confirms the p-value of 0.0055 for a 1-sided Boschloo test with Berger-Boos modification of gamma = 0.001. The survival rates were 0 (0/17) for placebo and 35% (6/17) for ANTHIM. The program used is Roger Berger's program for exact unconditional tests in 2 by 2 tables, which is found at <http://www4.stat.ncsu.edu/~boos> . The algorithm is also found in R. It is interesting that the program StatXact sometimes yields inconsistent results for this procedure. We therefore did not use StatXact. We're ok with either number we just wanted to account for the difference between ours and the Agency's.

2. In Section 6 of the USPI under the heading “Effect of Diphenhydramine on the Incidence of Adverse Reactions” we are having trouble replicating the percentages for the individual symptoms. We’d like to confirm the criteria used by the Agency in calculating the numbers. The criteria we’ve applied are as follows:
  - a. Number of subjects is the single dose pool used in Table 3 (300 ANTHIM treated subjects)
  - b. Of the 300 subjects, 227 received diphenhydramine pre-treatment and 73 did not.
  - c. Study AH109 includes only the AEs associated with the first dose of ETI-204 (all AEs <=Period 2 Dose Date). Can you also confirm that this criteria for handling AH109 AEs was applied to the rates reported in Table 3?

Thanks!

Robin

Robin L. Conrad

VP Regulatory Affairs & Clinical Operations

Elusys Therapeutics, Inc.

25 Riverside Drive - Suite 1

Pine Brook, NJ 07058

[rconrad@elusys.com](mailto:rconrad@elusys.com)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JANE A DEAN  
02/23/2016

**From:** Dean, Jane  
**Sent:** Friday, February 19, 2016 4:12 PM  
**To:** 'Robin Conrad'  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** RE: BLA 125509 (Anthem) - next step for you [REDACTED] (b) (4) - Question

Robin, we cannot send you the label today. Hopefully, it will be ready Monday morning and I can send it to you then. I apologize for giving you such short notice.

Referring to the questions you sent 2/17/16, see responses in [blue](#) below.

Jane

---

**From:** Robin Conrad [<mailto:rconrad@elusys.com>]  
**Sent:** Wednesday, February 17, 2016 5:03 PM  
**To:** Dean, Jane  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** RE: BLA 125509 (Anthem) - next step for you [REDACTED] (b) (4) - Question

Hi Jane,

Based on the responses below we have the following question:

1. Do we need a [REDACTED] (b) (4) prior to approval of the BLA if there is no intent to [REDACTED] (b) (4)?

**No, you do not need a [REDACTED] (b) (4) prior to approval of the BLA if you do not intend to [REDACTED] (b) (4) from the individual container label and carton labeling.**

2. Is this something that can be requested [REDACTED] (b) (4)  
[REDACTED] We understand that we cannot [REDACTED] (b) (4).

**Yes, you can request [REDACTED] (b) (4)**  
[REDACTED].

**Additionally if you plan to [REDACTED] (b) (4)**  
[REDACTED] **In this case, only the commercial container label and carton labeling will be considered.**

Thanks,  
Robin

Robin L. Conrad

VP Regulatory Affairs & Clinical Operations  
Elusys Therapeutics, Inc.  
25 Riverside Drive - Suite 1  
Pine Brook, NJ 07058  
[rconrad@elusys.com](mailto:rconrad@elusys.com)  
office: 973-787-8496  
mobile: [REDACTED] (b) (6)

---

**From:** Dean, Jane [<mailto:Jane.Dean@fda.hhs.gov>]  
**Sent:** Wednesday, February 17, 2016 4:12 PM  
**To:** Robin Conrad <[rconrad@elusys.com](mailto:rconrad@elusys.com)>  
**Cc:** Cindi Dillon <[cdillon@elusys.com](mailto:cdillon@elusys.com)>; Ariane Cutolo <[acutolo@elusys.com](mailto:acutolo@elusys.com)>  
**Subject:** RE: BLA 125509 (Anthem) - next step for you [REDACTED] (b) (4) - Question

Robin, here is the response (below in red) from the product quality team.

Jane

---

**From:** Robin Conrad [<mailto:rconrad@elusys.com>]  
**Sent:** Wednesday, February 17, 2016 10:07 AM  
**To:** Dean, Jane  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** RE: BLA 125509 (Anthem) - next step for you [REDACTED] (b) (4) - Question

Hi Jane,

We've been reviewing the regs you cited below and are drafting our request. The regulations require that we [REDACTED] (b) (4); "

Is it acceptable to [REDACTED] (b) (4) [REDACTED] (b) (4)  
[REDACTED] (b) (4) No, it is  
unacceptable to [REDACTED] (b) (4)  
[REDACTED] (b) (4) should be submitted as a  
separate request.

Also as you suggested we'll include the current draft carton/container labels and indicate that they are near final drafts still under discussion with the Division.

Thanks  
Robin

Robin L. Conrad  
VP Regulatory Affairs & Clinical Operations

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[rconrad@elusys.com](mailto:rconrad@elusys.com)  
office: 973-787-8496  
mobile: [REDACTED] (b) (6)

---

**From:** Dean, Jane [<mailto:Jane.Dean@fda.hhs.gov>]  
**Sent:** Friday, February 12, 2016 3:20 PM  
**To:** Robin Conrad <[rconrad@elusys.com](mailto:rconrad@elusys.com)>  
**Cc:** Cindi Dillon <[cdillon@elusys.com](mailto:cdillon@elusys.com)>; Ariane Cutolo <[acutolo@elusys.com](mailto:acutolo@elusys.com)>  
**Subject:** BLA 125509 (Anthem) - next step for you [REDACTED] (b) (4)  
**Importance:** High

Robin, please look at [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]. Please let the division know when you send your request (in that way, I can stay on top of it!) and also, of course, send me a copy as well.

Thanks!

Jane

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/s/  
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JANE A DEAN  
02/19/2016

**From:** Dean, Jane  
**Sent:** Wednesday, February 17, 2016 4:12 PM  
**To:** 'Robin Conrad'  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** RE: BLA 125509 (Anthem) - next step for you [REDACTED] (b) (4) - Question

Robin, here is the response (below in red) from the product quality team.

Jane

**From:** Robin Conrad [<mailto:rconrad@elusys.com>]  
**Sent:** Wednesday, February 17, 2016 10:07 AM  
**To:** Dean, Jane  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** RE: BLA 125509 (Anthem) - next step for you [REDACTED] (b) (4) - Question

Hi Jane,

We've been reviewing the regs you cited below and are drafting our request. The regulations require that we "[REDACTED] (b) (4)

Is it acceptable to [REDACTED] (b) (4) [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] "No, it is unacceptable to write a general provision. [REDACTED] (b) (4)  
[REDACTED] should be submitted as a separate request.

Also as you suggested we'll include the current draft carton/container labels and indicate that they are near final drafts still under discussion with the Division.

Thanks  
Robin

Robin L. Conrad  
VP Regulatory Affairs & Clinical Operations  
Elusys Therapeutics, Inc.  
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Pine Brook, NJ 07058  
[rconrad@elusys.com](mailto:rconrad@elusys.com)  
office: 973-787-8496  
mobile: [REDACTED] (b) (6)

Robin, here is the response (below in red) from the product quality team.

Jane

**From:** Robin Conrad [<mailto:rconrad@elusys.com>]  
**Sent:** Wednesday, February 17, 2016 10:07 AM  
**To:** Dean, Jane  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** RE: BLA 125509 (Anthem) - next step for you [REDACTED] (b) (4) - Question

Hi Jane,

We've been reviewing the regs you cited below and are drafting our request. The regulations require that we "[REDACTED] (b) (4)

Is it acceptable to write [REDACTED] (b) (4)

[REDACTED] ."? No, it is unacceptable to [REDACTED] (b) (4)

[REDACTED] should be submitted as a separate request.

Also as you suggested we'll include the current draft carton/container labels and indicate that they are near final drafts still under discussion with the Division.

Thanks  
Robin

Robin L. Conrad  
VP Regulatory Affairs & Clinical Operations  
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[rconrad@elusys.com](mailto:rconrad@elusys.com)  
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/s/  
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JANE A DEAN  
02/17/2016

**From:** Dean, Jane  
**Sent:** Wednesday, February 17, 2016 3:29 PM  
**To:** 'Robin Conrad'  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** RE: BLA 125509 ANTHIM - follow up from yesterday's call

Hi, Robin, for the record, the stats reviewer has the following response to Q1:

For question 1: Thanks for providing the program for calculating the p-values. The difference is due to different programs used (NCSU versus StatXact). Either p-value (0.0055 or 0.0051) is fine. You can keep the p-values you proposed in Table 4.

Jane

**From:** Robin Conrad [<mailto:rconrad@elusys.com>]  
**Sent:** Friday, February 12, 2016 8:17 AM  
**To:** Dean, Jane  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** BLA 125509 ANTHIM - follow up from yesterday's call  
**Importance:** High

Hi Jane,

I wanted to do a quick follow up from yesterday's TC on two items.

1. The discrepancy in the p-value for Study 4 in Table 4 of the PI. Our statistician re-checked the number and we've attached an output that confirms the p-value of 0.0055 for a 1-sided Boschloo test with Berger-Boos modification of  $\gamma = 0.001$ . The survival rates were 0 (0/17) for placebo and 35% (6/17) for ANTHIM. The program used is Roger Berger's program for exact unconditional tests in 2 by 2 tables, which is found at <http://www4.stat.ncsu.edu/~boos>. The algorithm is also found in R. It is interesting that the program StatXact sometimes yields inconsistent results for this procedure. We therefore did not use StatXact. We're ok with either number we just wanted to account for the difference between ours and the Agency's.
2. In Section 6 of the USPI under the heading "Effect of Diphenhydramine on the Incidence of Adverse Reactions" we are having trouble replicating the percentages for the individual symptoms. We'd like to confirm the criteria used by the Agency in calculating the numbers. The criteria we've applied are as follows:
  - a. Number of subjects is the single dose pool used in Table 3 (300 ANTHIM treated subjects)
  - b. Of the 300 subjects, 227 received diphenhydramine pre-treatment and 73 did not.
  - c. Study AH109 includes only the AEs associated with the first dose of ETI-204 (all AEs  $\leq$  Period 2 Dose Date). Can you also confirm that this criteria for handling AH109 AEs was applied to the rates reported in Table 3?

Thanks!  
Robin  
Robin L. Conrad  
VP Regulatory Affairs & Clinical Operations  
Elusys Therapeutics, Inc.  
25 Riverside Drive - Suite 1

Pine Brook, NJ 07058  
[rconrad@elusys.com](mailto:rconrad@elusys.com)  
office: 973-787-8496  
mobile: (b) (6)

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/s/  
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JANE A DEAN  
02/17/2016

**From:** Dean, Jane  
**Sent:** Wednesday, February 17, 2016 3:06 PM  
**To:** 'Robin Conrad'  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** RE: BLA 125509 ANTHIM - follow up from yesterday's call - response to Q2

Robin, I hope this helps. It came from the clinical reviewers.

Question from Elusys:

2. In Section 6 of the USPI under the heading “Effect of Diphenhydramine on the Incidence of Adverse Reactions” we are having trouble replicating the percentages for the individual symptoms. We’d like to confirm the criteria used by the Agency in calculating the numbers. The criteria we’ve applied are as follows:
  - a. Number of subjects is the single dose pool used in Table 3 (300 ANTHIM treated subjects)
  - b. Of the 300 subjects, 227 received diphenhydramine pre-treatment and 73 did not.
  - c. Study AH109 includes only the AEs associated with the first dose of ETI-204 (all AEs <=Period 2 Dose Date). Can you also confirm that this criteria for handling AH109 AEs was applied to the rates reported in Table 3?

Response from FDA:

- a) Agreed.
- b) FDA analysis from ISS ADSL: 226 of 300 received diphenhydramine and 74 did not.

Out of 370 total subjects in the FDA PSP [ETI-204 (210 subjects from AH104, 70 subjects from the first treatment period of AH109, 20 subjects who received ETI-204 alone in AH110) plus 70 placebo in AH104] , 165 subjects or 44.5% experienced 329 TEAE’s – 138 of these were in the obiltoximab arm (138/300 or 46%), and 27 were in the placebo arm (27/70 or 38.6%). Of the 138 subjects with TEAE’s in the obiltoximab group, 95 subjects received diphenhydramine, and 43 did not. Of the 27 subjects with TEAE’s in the placebo arm, 18 subjects received diphenhydramine, and 9 did not.

**Table 8.36 FDA Analysis of Occurrence of TEAE’s Correlated with Diphenhydramine Use in the FDA PSP**

Number of subjects in FDA PSP N=370	Obiltoximab, N=300		Placebo, N=70	
	DPH+ (n=226) (75.3%)	DPH- (n=74) (24.7%)	DPH+ (n=48) (68.6%)	DPH- (n=22) (31.4%)
Number of subjects with TEAE’s N=165 (44.5%)	Obiltoximab, N=138		Placebo, N=27	
	DPH+ (n=95) (95/226=42%)	DPH- (n=43) (43/74=58.1%)	DPH+ (n=18) (18/48=37.5%)	DPH- (n=9) (9/22=40.9%)

DPH: diphenhydramine

- c) Yes, the same criteria were used (TEAEs on d1-13 in AH109)

NB. Subject 104-001-026 appeared to receive ETI-204 and had an AE but the treatment record was subsequently lost. The subject has been included by the Applicant in their safety datasets; thus, she was included in FDA analysis as well.

**From:** Robin Conrad [<mailto:rconrad@elusys.com>]  
**Sent:** Friday, February 12, 2016 8:17 AM  
**To:** Dean, Jane  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** BLA 125509 ANTHIM - follow up from yesterday's call  
**Importance:** High

Hi Jane,

I wanted to do a quick follow up from yesterday's TC on two items.

1. The discrepancy in the p-value for Study 4 in Table 4 of the PI. Our statistician re-checked the number and we've attached an output that confirms the p-value of 0.0055 for a 1-sided Boschloo test with Berger-Boos modification of  $\gamma = 0.001$ . The survival rates were 0 (0/17) for placebo and 35% (6/17) for ANTHIM. The program used is Roger Berger's program for exact unconditional tests in 2 by 2 tables, which is found at <http://www4.stat.ncsu.edu/~boos>. The algorithm is also found in R. It is interesting that the program StatXact sometimes yields inconsistent results for this procedure. We therefore did not use StatXact. We're ok with either number we just wanted to account for the difference between ours and the Agency's.
2. In Section 6 of the USPI under the heading "Effect of Diphenhydramine on the Incidence of Adverse Reactions" we are having trouble replicating the percentages for the individual symptoms. We'd like to confirm the criteria used by the Agency in calculating the numbers. The criteria we've applied are as follows:
  - a. Number of subjects is the single dose pool used in Table 3 (300 ANTHIM treated subjects)
  - b. Of the 300 subjects, 227 received diphenhydramine pre-treatment and 73 did not.
  - c. Study AH109 includes only the AEs associated with the first dose of ETI-204 (all AEs  $\leq$  Period 2 Dose Date). Can you also confirm that this criteria for handling AH109 AEs was applied to the rates reported in Table 3?

Thanks!

Robin

Robin L. Conrad

VP Regulatory Affairs & Clinical Operations

Elusys Therapeutics, Inc.

25 Riverside Drive - Suite 1

Pine Brook, NJ 07058

[rconrad@elusys.com](mailto:rconrad@elusys.com)

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JANE A DEAN  
02/17/2016

**From:** Dean, Jane  
**Sent:** Friday, February 12, 2016 2:51 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - carton/container comments 2-12-16

Robin, here are the final carton/container comments for you:

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

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

The proposed plan to ensure the (b) (4) is appropriately labeled (b) (4) appears reasonable. However, the proposed plan to ensure that the (b) (4) will be labeled with the appropriate (b) (4) needs improvement and we provide the following recommendations:

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.



**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

[Redacted text block with (b) (4) annotations]

**B.**

[Large redacted text block with (b) (4) annotation]

**C.**

**D. Commercial and SNS Vial Cap**

1. Per OBP, your vial cap

[Redacted text block with (b) (4) annotation]

Jane

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/s/  
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JANE A DEAN  
02/12/2016

**From:** Dean, Jane  
**Sent:** Tuesday, February 09, 2016 11:12 AM  
**To:** 'Cindi Dillon'; Bauerlien, Melinda  
**Cc:** Robin Conrad; Ariane Cutolo  
**Subject:** RE: Request to retract (b) (4)

Hi, Cindi – I have checked with the product quality team and they have the following response to your request:

We agree to the retraction (b) (4)

(b) (4)

This email will become part of your official administrative record.

Jane

---

**From:** Cindi Dillon [<mailto:cdillon@elusys.com>]  
**Sent:** Thursday, February 04, 2016 4:25 PM  
**To:** Dean, Jane; Bauerlien, Melinda  
**Cc:** Robin Conrad; Ariane Cutolo  
**Subject:** Request to retract (b) (4)

Hi Jane,  
Elusys requests retracting (b) (4) for the following reason:

(b) (4)

(b) (4)

Does the FDA agree with Elusys request to retract [REDACTED] (b) (4) ?

**PMC**

[REDACTED] (b) (4)

Thanks,  
Cindi

Cindi Dillon  
Sr. Director, Regulatory Affairs  
Elusys Therapeutics, Inc.  
25 Riverside Drive - Suite 1  
Pine Brook, NJ 07058  
[cdillon@elusys.com](mailto:cdillon@elusys.com)  
office: 973-787-8463

This email message, and any attachments, are intended only for the use of the addressee named above and may contain information that is privileged and confidential. If you received this email in error, please return it to [info@elusys.com](mailto:info@elusys.com) immediately. Please be aware that if you are not the intended recipient, you are hereby notified that any use, disclosure, copying or distribution of this message, or any of the information included in it, is unauthorized and strictly prohibited. Thank you.

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/s/  
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JANE A DEAN  
02/09/2016



BLA 125509

INFORMATION REQUEST

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by February 10, 2016 in order to continue our evaluation of your application.

1. Based on the endotoxin spiking and hold study data, the current LAL endotoxin release tests for DS and DP are acceptable. The rabbit pyrogen test used to release DP may be removed from the BLA.
2. Please provide the study report for the following PMC in a PMC submission instead of an annual report by November 2016.
  - Conduct a study to qualify the bioburden test for the primary recovery samples using the increased sample volume (10 mL).

If you have questions, call me at (301) 796-0906.

Sincerely,

Melinda J.  
Bauerlien -A

Melinda Bauerlien, M.S.

Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Digitally signed by Melinda J. Bauerlien -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300178565,  
cn=Melinda J. Bauerlien -A  
Date: 2016.02.09 06:50:40 -05'00'

**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] Labeling

### 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 [REDACTED] 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. Elusys proposes [REDACTED]*

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

- 1- Can we meet [REDACTED] requirements and [REDACTED] ?

### Agency Response

#### a. Commercial Vial Container Label

No. [REDACTED]

See the Agency's thinking in [Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf). Draft Guidance, April 2013.  
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

#### b. SNS Vial Container Label

Your proposal [REDACTED]

Please submit a detailed plan [REDACTED] (b) (4)

- 2- For the stockpile cartons only, [REDACTED] (b) (4)  
[REDACTED] ?

### 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:

I wanted to inform you and the team that we are planning to [REDACTED] (b) (4)

Also, we request not having [REDACTED] (b) (4)

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 [REDACTED] (b) (4)
- b. Your proposal to omit [REDACTED] (b) (4) is acceptable.

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881

Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
01/15/2016

**From:** Dean, Jane  
**Sent:** Friday, January 15, 2016 2:02 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - additional product quality information request about PMCs

Hi, Robin – we have an additional product quality information request about PMCs:

Provide Elusys' agreement on the following product quality post-marketing commitment (PMC) and provide the reporting category as per CFR 601.12 for the following PMCs. Include a timeline (month and year) by which the final reports for this PMCs will be submitted to the obiltoximab BLA.

To conduct drug substance specific leachable and extractable studies on the [REDACTED] (b) (4) [REDACTED]. The drug substance manufacturing processes will be optimized, as needed, based on the results.

Thanks.

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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JANE A DEAN  
01/15/2016

**From:** Dean, Jane  
**Sent:** Friday, January 15, 2016 1:26 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - product quality information request about PMCs

Hi, Robin – the product quality review team has the following information request:

The commitment for the PMCs does not provide actual completion date for PMC #1 and #6 because the drug product manufacture is dependent upon [REDACTED] (b) (4)  
[REDACTED] Revise the evaluation date in these PMCs to state that “when data from 20 lots of DP becomes available or 5 years after the BLA being approved, whichever comes first.”

Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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JANE A DEAN  
01/15/2016

**From:** Dean, Jane  
**Sent:** Friday, January 15, 2016 11:43 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - product quality information request - response needed NLT 1/28/16

Hi, Robin – the product quality team has the following information request. They are asking that a response be provided by 1/28/16.

We note that no product specific extractable and leachable studies were performed on the [REDACTED] (b) (4)  
[REDACTED]  
Therefore provide commitment to implement a [REDACTED] (b) (4)  
[REDACTED] until the product specific extractable and leachable studies are submitted to the FDA.

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
01/15/2016



BLA 125509

INFORMATION REQUEST

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obilttoximaxib), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by November 30, 2015 in order to continue our evaluation of your application.

1. Reference is made to module 3.2.P.3.3.2 which summarizes the drug product manufacturing process. We note that the formulated BDS [REDACTED] (b) (4).  
[REDACTED] Provide the following or a reference to its location in the application:
  - A certificate of analysis for the [REDACTED] (b) (4).
  - A description of how [REDACTED] (b) (4).
  - Validation data for [REDACTED] (b) (4).
2. Reference is made to table 4 of module 3.2.P.3.4 which identifies the [REDACTED] (b) (4) controls for manufacture of the drug product. We note that the volume of the [REDACTED] (b) (4) bioburden sample is not provided.
  - Amend table 4 of module 3.2.P.3.4 with the [REDACTED] (b) (4) bioburden sample volume. If the volume is less than 100 mL, provide a rationale for the size of the sample.
3. Reference is made to table 4 of module 3.2.P.3.4 which identifies the [REDACTED] (b) (4) controls for manufacture of the drug product. We note that the [REDACTED] (b) (4) [REDACTED] (b) (4) is not identified.

- Amend table 4 of module 3.2.P.3.4 with the [REDACTED] (b) (4).

If you have questions, call me at (301) 796-0906.

Sincerely,

Melinda J.  
Bauerlien -S

Digitally signed by Melinda J.  
Bauerlien -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=13001785  
65, cn=Melinda J. Bauerlien -S  
Date: 2015.11.23 11:21:06 -05'00'

Melinda Bauerlien, M.S.  
Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



BLA 125509

**INFORMATION REQUEST**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoxaximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by November 17, 2015 in order to continue our evaluation of your application.

**Product Quality**

1. We do not agree with the proposed shelf life of (b)(4) months for obiltoxaximab DP. The stability data provided to support the (b)(4) months expiry is not sufficient. Specifically:
  - The DP stability data indicate that, although the PV and engineering DP lots are free of visible particulates at release, visible particulate are forming over time under long term and accelerated storage conditions.
  - The characterization of the visible particulates shows that some of the particles contain (b)(4). This may indicate issues with the drug product formulation.

Therefore, at this time, the Agency (b)(4) agree to a shelf life of 18 months based on the real time data from the process validation (PV) lots. (b)(4)

2. From the information provided in the BLA it appears that the visible particulate test for the DP release and stability testing is performed at (b)(4) respectively. Provide information to support that the procedures and the acceptance criteria are the same at the different sites.

3. Update section P.5.2 to provide information on the visible particle test used at (b) (4) including a description of the analytical procedure and its acceptance criteria.
4. Update BLA section P.5.1, table 1, to include visible particulate testing under (b) (4) method (USPO-6731) for 'appearance'.
5. We note that in Table 1 in DS (S.4.1) and DP (P.5.1) the second column of the table is referred to as 'Specification.' This should be labeled as acceptance criteria. As per 21CFR600.3 (kk) 'specification,' means tests, analytical procedures and acceptance criteria. Revise Table 1 in section S.4.1 and P.5.1 to replace heading 'specification' with the 'acceptance criteria.'
6. We do not agree with the proposed combined acceptance criterion of (b) (4) for aggregates plus fragments by SEC-HPLC in DS and DP release and stability specifications. Revise the DS and DP specifications to include individual acceptance criteria for the aggregates and fragments by SEC-HPLC. Submit the updated acceptance criteria to the BLA.

### Quality Microbiology

1. Please conduct the endotoxin spiking and hold study using CSE/RSE and provide the results as soon as possible within the BLA review cycle. The reliability of the endotoxin release tests for DS and DP need to be evaluated and a path forward established prior to the action date of the BLA as required by 21 CFR 211.167(a).
2. With regard to the acceptance criteria provided in Table 1 in protocol PV-5069-X-01, for
  - (b) (4) chromatography resins
    - Please tighten the endotoxin acceptance criterion of (b) (4) to (b) (4) EU/mL as agreed in your response in amendment dated 10/27/15.
    - Establish bioburden and endotoxin acceptance criteria for (b) (4).
    - Establish endotoxin acceptance criterion for (b) (4).
  - (b) (4) and (b) (4) chromatography resins
    - Establish bioburden and endotoxin acceptance criteria for (b) (4).
    - Establish endotoxin acceptance criterion for (b) (4).
    - Replace the bioburden and endotoxin acceptance criteria for the (b) (4) as agreed in your response in amendment dated 11/9/15.
  - Post (b) (4)
    - Tighten the endotoxin acceptance criterion for (b) (4). The  $\leq$  (b) (4) EU/mL endotoxin acceptance criterion could potentially contribute high endotoxin (b) (4).
    - Include (b) (4) bioburden and endotoxin acceptance criteria for the (b) (4) in the study.

If you have questions, call me at (301) 796-0906.

Sincerely,  
Melinda J.  
Bauerlien -S

Digitally signed by Melinda J. Bauerlien -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, o.9.2342.19200300.100.1.1=1300178565,  
cn=Melinda J. Bauerlien -S  
Date: 2015.11.13 10:55:02 -05'00'

Melinda Bauerlien, M.S.  
Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



BLA 125509

**INFORMATION REQUEST**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by November 17, 2015 in order to continue our evaluation of your application.

**Product Quality**

1. Please conduct the endotoxin spiking and hold study using CSE/RSE and provide the results as soon as possible within the BLA review cycle. The reliability of the endotoxin release tests for DS and DP need to be evaluated and a path forward established prior to the action date of the BLA as required by 21 CFR 211.167(a).
2. With regard to the acceptance criteria provided in Table 1 in protocol PV-5069-X-01, for
  - (b) (4) chromatography resins
    - Please tighten the endotoxin acceptance criterion of (b) (4) to (b) (4) EU/mL as agreed in your response in amendment dated 10/27/15.
    - Establish bioburden and endotoxin acceptance criteria (b) (4)
    - Establish endotoxin acceptance criterion for (b) (4)
  - (b) (4) and (b) (4) chromatography resins
    - Establish bioburden and endotoxin acceptance criteria for (b) (4)
    - Establish endotoxin acceptance criterion for (b) (4)
    - Replace the bioburden and endotoxin acceptance criteria for the (b) (4) as agreed in your response in amendment dated 11/9/15.
  - Post (b) (4)

- Tighten the endotoxin acceptance criterion for (b) (4). The  $\leq$  (b) (4) EU/mL endotoxin acceptance criterion could potentially contribute high endotoxin (b) (4).
- Include (b) (4) bioburden and endotoxin acceptance criteria for the (b) (4) in the study.

**Quality Microbiology**

3. Please conduct the endotoxin spiking and hold study using CSE/RSE and provide the results as soon as possible within the BLA review cycle. The reliability of the endotoxin release tests for DS and DP need to be evaluated and a path forward established prior to the action date of the BLA as required by 21 CFR 211.167(a).
4. With regard to the acceptance criteria provided in Table 1 in protocol PV-5069-X-01, for
  - (b) (4) chromatography resins
    - Please tighten the endotoxin acceptance criterion of (b) (4) to (b) (4) EU/mL as agreed in your response in amendment dated 10/27/15.
    - Establish bioburden and endotoxin acceptance criteria for (b) (4).
    - Establish endotoxin acceptance criterion for (b) (4).
  - (b) (4) and (b) (4) chromatography resins
    - Establish bioburden and endotoxin acceptance criteria for (b) (4).
    - Establish endotoxin acceptance criterion for (b) (4).
    - Replace the bioburden and endotoxin acceptance criteria for the (b) (4) as agreed in your response in amendment dated 11/9/15.
  - Post (b) (4)
    - Tighten the endotoxin acceptance criterion for (b) (4). The  $\leq$  (b) (4) EU/mL endotoxin acceptance criterion could potentially contribute high endotoxin (b) (4).
    - Include (b) (4) bioburden and endotoxin acceptance criteria for the (b) (4) in the study.

If you have questions, call me at (301) 796-0906.

Sincerely,

Melinda J.  
Bauerlien -S

Melinda Bauerlien, M.S.

Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Digitally signed by Melinda J. Bauerlien -S  
DN: c=US, o=U.S. Government, ou=FDA,  
ou=People, ou=242, cn=Melinda J. Bauerlien -S  
Date: 2015.11.13 10:18:40 -0500

## MEMORANDUM OF CORRESPONDENCE

DATE: 10/19/15

APPLICATION NUMBER: BLA 125509

DRUG PRODUCT: Anthim (obilttoximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion

BETWEEN:

Name: Elusys Therapeutics, Inc.

Greg Birrer, PhD, Senior Director, Quality Assurance

Colin Campbell, PhD, Director, Process Development

Doreen Ciolek, MS, Senior CMC Analytical Analyst

Robin Conrad, MS, Vice President, Regulatory Affairs

Cynthia Dillon, Senior Director, Regulatory Affairs

Henry Founds, PhD, Senior Manager, Manufacturing

Jim Porter, MS, Vice President Development and Manufacturing

Cristen Taft-Bourgo, Manufacturing Specialists

Pamela Wright, PhD, Senior Director, Manufacturing

Karen Blodgett, MS, Director Program Management/Contracts

(b) (4) MS, Manufacturing Advisor Contractor

(b) (4), MS, Manufacturing Quality and Operations Advisor Contractor

Chia-Wei Tsai, PhD, Project Officer, Division of CBRN Countermeasures

(b) (4), MS, RAC, Regulatory Advisor Contractor

AND

Name: Food and Drug Administration

Rashmi Rawat, Ph.D., Team Lead, OBP, DBRR II

Rashmi Rawat - S Copyright Lexipol, Inc. 2015. All rights reserved. Published with permission by the FDA. For more information, please contact Lexipol at 800.541.9111 or www.lexipol.com.

Tao Xie, Ph.D., Quality Reviewer, OBP, DBRR II

Juhong Liu, Ph.D., Lead Biologist, OBP, DBRR II

Melinda Bauerlien, M.S., Senior Regulatory Business Process Manager, OPRO

The Agency requested the teleconference to discuss the pending BLA and an information request sent on October 15, 2015.

1. Response to Q2 indicate that you will include the cell banks' stability testing frequency, tests and acceptance criteria in the BLA instead of submitting the protocol under PAS. However the last sentence of the response state that the PAS will be submitted by 2016. Please clarify which PAS submission you are referring to.

### Meeting Discussion

Elusys clarified that the original plan was to submit the cell bank stability protocol as a PAS. The working cell bank (WCB) viability is continually assessed during the

production campaign. For the working cell bank if there is no production annually, they will assess its stability at Day 0 under the Lonza protocol. The current cell bank protocol only looks at Day 0 viability but they could discuss monitoring cells for additional passages.

The Agency responded that to monitor master and working cell banks stability, in addition to monitor cell viability at 'day 0' Elusys should also monitor cells' performance in subsequent 4 to 5 passages against pre-specified acceptance criteria for cell viability and viable cell density.

Elusys stated that they could use the standard acceptance criteria for these parameters that are already in place at Lonza. For the testing of the master cell bank Elusys expressed that they cannot perform more frequent stability testing on the master cell bank because it would (b) (4). Elusys proposed the test parameters for MCB stability testing (b) (4). The MCB stability will be assessed on a (b) (4).

The Agency agreed to Elusys' proposal for MCB testing. Elusys stated that the information on the stability protocols for the MCB and WCB will be provided by the end of the week.

2. In your response to Q5 you indicate that the next reference standard manufacture is planned for 1<sup>st</sup> Q of 2016 and the requalification protocol of the new reference standard will be submitted for review in Nov 2015 as opposed to the PAS submission after BLA approval. Please note that in addition to the requalification protocol, you also need the qualification protocol for the introduction of the new reference standard. Based on our internal review time line under PDUFA V we will not be able to review the proposed amendment for the qualification and requalification of the reference standard. We strongly recommend that you submit these protocols as a PAS post BLA approval.

#### Meeting Discussion

The Agency reiterated that the sponsor must provide the qualification protocol for the new reference standard as the PAS. The sponsor agreed to submit the qualification of the new reference standard as the PAS. The agency asked if the new reference standard will be qualified as the primary or secondary reference standard.

Elusys stated that (b) (4) is the current reference standard and is used for release and stability testing. (b) (4)

The Agency recommended that (b) (4)

(b) (4). The Agency's current thinking is to have a two-tiered reference standard system. The primary reference standard (b) (4)

The sponsor agreed to establish a (b) (4) system for obiltoximab.

3. Please clarify on if the (b) (4)

The proposed potency testing acceptance criteria of +/- (b) (4)% for the requalification of (b) (4) reference standard may not be acceptable.

**Meeting Discussion**

The sponsor stated that  $\pm$  (b) (4)% range is (b) (4)% tightening of the potency acceptance criterion and it reflects the assay variability. The drift in potency is covered by the acceptance criteria (b) (4)

The Agency responded that it is not clear how the sponsor is determining potency for the reference standard. The Agency recommends an approach in which the assignment of the 100% potency can be made by the use of predetermined confidence interval of the mean relative potency. To account for the assay variability multiple replicates should be run in the assay.

The sponsor stated they run the test for determining RS potency using (b) (4)

4. We note that the relative potency (RP) of the (b) (4) is listed as (b) (4)% in Table 1 in section 3.2.S.5 (Reference standard (b) (4)). Clarify how these RP values were assigned and what was the assigned potency for (b) (4) reference standard used for the release and stability testing of the Lonza DS (b) (4)? Generally the primary reference standard should be assigned a 100% using the approach and criteria that should minimize the drift in the potency. For example an acceptable approach to assign 100% potency is the use of predetermined confidence interval of the mean. Using this approach the 100% potency assignment requires the mean relative potency and the 95% confidence interval (CI) are included within a sufficiently narrow range, e.g.95-105% potency.

**Meeting Discussion:** The sponsor stated that the relative potency values for (b) (4) as (b) (4)% in Table 1 were calculated using (b) (4) as the reference standard. The reported potency values for (b) (4) represent the intra-assay variability for the (b) (4) assay. The Agency stressed that since the potency value is expressed as % of reference standard, a drift of the reference standard value will impact the potency results of future commercial lots. For establishing true potency value of the reference material, sufficient number of assays should be performed to minimize the impact of assay variation on the final assigned potency value.

Elusys stated that the qualification results will be submitted as a part of the RS qualification protocol PAS.

**From:** Dean, Jane  
**Sent:** Thursday, November 05, 2015 6:40 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - statistics information request

Hi, Robin – the statistics reviewer has the following information request:

Study AR007 had a low survival rate in animals treated with antibiotics monotherapy (33%, 4/12) despite animal receiving a human equivalent dose prior to developing symptoms. Do you have an explanation as to why the survival rate was so low in this trial?

Could you please let me know your turn around time? Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
11/05/2015



BLA 125509

INFORMATION REQUEST

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by November 9, 2015 in order to continue our evaluation of your application.

Reference is made to your response to microbiology information request submitted on 27 October 2015. We note your commitment to using a (b) (4) of the drug product. Reference is also made to table 54 of module 3.2.P.3.5.9.2.2.5 which provides three different (b) (4) for the process validation lots (b) (4).

- These three process validation lots were manufactured using a (b) (4). Have you performed an investigation related to these manufacturing excursions? What is your plan regarding disposition of these lots? Provide a rationale for the disposition of these and any other lots of drug product that were manufactured using (b) (4) that were validated.

If you have questions, call me at (301) 796-0906.

Sincerely,  
Melinda J.

Bauerlien -S  
Melinda Bauerlien, M.S.

Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Digitally signed by Melinda J. Bauerlien -S  
DN: cn=US, ou=U.S. Government, ou=HHS, ou=FDA,  
ou=People,  
o=9 2342: 19200300:100:1-130017865,  
c=Melinda J. Bauerlien -S  
Date: 2015.11.05 10:20:39 -05'00'



BLA 125509

INFORMATION REQUEST

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obilttoximaxib), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by November 9, 2015 in order to continue our evaluation of your application.

1. With regard to your response to question 4 provided in amendment dated 10/27/2015 (Sequence 29), please monitor the bioburden and endotoxin levels of the (b) (4)

The bioburden and endotoxin results of the (b) (4). Update Table 7 accordingly.

2. Please provide protocol (PV-5069-X-01) for obilttoximaxib (b) (4).

If you have questions, call me at (301) 796-0906.

Sincerely,

Melinda J.  
Bauerlien -S

Digitally signed by Melinda J. Bauerlien -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300178565,  
cn=Melinda J. Bauerlien -S  
Date: 2015.11.04 07:09:33 -05'00'

Melinda Bauerlien, M.S.  
Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

**From:** Dean, Jane  
**Sent:** Tuesday, November 03, 2015 2:50 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthim) - clin micro information request

Robin, the clinical microbiology has the following information request:

It will aid in our review if the following table is provided.

Table : Summary of anti-PA IgG ELISA								
Study no.	Site	Analysis report no.	Assay method ID	Validation report no.	LLOD	LLOQ	ULOQ	Detects ETI-204
<b>NZW rabbits</b>								
AR028	(b) (4)	(b) (4) 12-059	(b) (4) -0204	(b) (4) 11-010				Yes
AR034								Yes
AR035								
AR037								
AR0315					1 µg/mL			No
<b>Cynomolgus monkeys</b>								
AP202								
2469					1 µg/mL			No
Surviving animals from Studies AP201, AP203, AP204								

Note: Please list all the rabbit and monkey studies where anti-PA IgG antibody testing was performed.

Please let me know your TAT – thanks!

Jane

Jane A. Dean, RN, MSN  
 Project Manager  
 DAIP/OAP/OND  
 Building 22, Room 6397  
 Office: 301-796-1202  
 Fax: 301-796-9881  
 Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
11/03/2015

**From:** Dean, Jane  
**Sent:** Tuesday, November 03, 2015 5:07 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - statistics information request

Hi, Robin – our stats reviewer has the following IR:

Regarding Study AR037, in the study report Table 4 (page 39) all mean challenge doses by group were <170 LD50s, but in the ADSL data set, all means were greater than 222 LD50s and the overall mean was 255 LD50s. Please clarify if the challenge dose in the ADSL data set is correct.

Please let me know your TAT – thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
11/03/2015



BLA 125509

**INFORMATION REQUEST**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoxaximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by November 9, 2015 in order to continue our evaluation of your application.

**Quality CMC microbiology information request:**

The use of (b) (4) is currently not considered acceptable for LER studies because (b) (4) is not a standard. Endotoxins from different Gram negative bacterial species have different potencies. There is no agreement on the type and preparation methods of (b) (4) that should be used. It is not clear that the use of (b) (4) in your LER study is representative of endotoxin contamination (b) (4).

21 CFR 211.167(a) states that “for each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements.” To meet regulatory requirements for release testing, please conduct LER study using CSE/RSE to demonstrate that the endotoxin release testing for obiltoxaximab drug substance and drug product are able to recover bacterial endotoxin present in the product.

**Quality CMC information request:**

1. The following information requests are for updates to the BLA as agreed upon by the Elusys.
  - a. In your response to the questions 12 and 13 in FDA information request (IR)-2, dated May 28, 2015, you proposed to remove (b) (4) as an alternate testing facility for a number of analytical methods used for the DP and the DS release and stability testing and to update BLA by the end of August 2015 to reflect these changes. However, we notice that the documents of (b) (4) test methods and their validation reports have not yet been removed from the BLA. Please remove these files from the BLA and update sections 3.2.S.4.2 and 3.2.S.4.4 to reflect these changes.

- b. In response to FDA's information request-3 (dated August 20, 2015), question 12, Elusys proposed the acceptance criteria (AC) for the following DP process parameters. FDA agrees with the proposed AC, please update section 3.2.P.3.4, Table 4 "(b) (4)"

" with the following proposed acceptance criteria:

- (b) (4)
- 
- 
- 
- 

2. Provide available data to support the proposed overfill volume of (b) (4) mL for obiltoximab DP. Specifically, provide summary data from the studies conducted demonstrating that a minimum (b) (4) mL overfill is required in order to withdraw the correct dose.
3. Regarding DS and DP lot release and stability specifications we have following comments:
  - a. We do not agree with the proposed acceptance criterion of (b) (4) mg/mL for the protein concentration in the DP lot release and stability testing. The proposed acceptance criterion is too wide and does not provide sufficient control over the DP strength. Revise the acceptance criteria for the DP protein concentration to (b) (4) mg/mL.
  - b. We do not agree with the proposed acceptance criterion of "pI of main peak (b) (4)," for the DS and DP identity and purity testing by icIEF. The proposed acceptance criterion is too wide to provide adequate control of the DS and DP identity and purity. Revise the acceptance criteria for the DS and DP identity and purity testing by icIEF to "pI of main peak (b) (4)," for the DS and DP identity and purity testing by icIEF.
  - c. Acceptance criterion for (b) (4) assay in DS release specification is too wide. Tighten the HCP assay acceptance criterion in DS release specifications.

Revise DS and DP release and stability specifications and update section 3.2.S.4.1 and 3.2.P.5.1 respectively.

4. We note that the stability protocols for the engineering, validation and post approval DS and DP lots do not include the acceptance criteria for the stability tests. Revise the stability protocols to include specifications (test and the acceptance criteria) that will be used to monitor stability of the engineering, process validation and post-approval DS and DP lots. Revise BLA section 3.2.S.7.1, 3.2.S.7.2, 3.2. P.8.1 and 3.2.P.8.2 to include updated stability protocols.
5. We note that the stability sample stored at T=18 months 2-8°C (upright) for DP lot 3-FIN-1703 contained unidentified organic, inorganic material and protein particulates when tested for visible particulates. With the exception of protein particles we do not expect any organic or inorganic particles to form in the DP vials. Provide information on

the investigation performed to identify the origin of organic and inorganic material in this vial.

6. Please address the following regarding the requalification protocol for the Reference Standard (b) (4):
  - a. In the requalification/stability protocol for reference standard (b) (4) submitted in response to question 5 IR-4 (dated Sept 24, 2015), the acceptance criteria for the potency assays and protein content are too wide to provide sufficient control to prevent drift in the potency of the reference standard and subsequently drug product over time. Revise the acceptance criteria for the potency assays for (b) (4) requalification to include a requirement that the results be sufficiently similar to the potency values obtained at the time of the initial qualification of the RS. The current potency of the RS should be significantly tighter than proposed acceptance criteria of (b) (4) ng/mL for LNA (EC50) and (b) (4) units/mL PAA3 potency assays. Additionally, tighten the acceptance criterion for protein concentration by UV/vis assay; identity and purity testing by icIEF for "pI of main peak;" and include test for appearance (color, clarity and visible particulates). Submit revised requalification/stability protocol for the reference standard (b) (4) to the BLA. The stability protocol should include stability test, acceptance criteria, storage conditions and test intervals.
  - b. The stability data provided to support the stability of the (b) (4) indicates a significant variability in the potency assay results both for LNA and PAA3 assays for (b) (4). Provide additional EC50 tracking and trending data for the LNA and PAA3 potency assays obtained for (b) (4) during its use in routine release and stability testing of obiltoximab DS and DP lots to support the stability of the (b) (4).
7. The Post-approval Stability Protocol and Stability Commitments sections (3.2.S.7.2 and 3.2.P.8.2) do not include information regarding the intention to submit data from the stability studies. Update section 3.2.S.7.2 and 3.2.P.8.2 with the commitments to submit the data from all ongoing stability studies, including the leachable study, and the data from annual stability lots in the BLA annual reports.
8. The following information request is for the immunogenicity assays:
  - a. Provide information on what statistical method was used to calculate positive cut point of (b) (4)% inhibition for the anti-drug antibodies (ADA) confirmatory assay.
  - b. Provide information on the false positive rate of the screening and confirmatory ADA assays.

If you have questions, call me at (301) 796-0906.

Sincerely,

**Melinda J.  
Bauerlien -S**

Digitally signed by Melinda J. Bauerlien -  
S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300178565  
, cn=Melinda J. Bauerlien -S  
Date: 2015.11.02 12:12:18 -05'00'

**Melinda Bauerlien, M.S.  
Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research**

**From:** Dean, Jane  
**Sent:** Monday, October 26, 2015 10:07 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - clinical microbiology information request

Hi, Robin – we have the following information request from clinical microbiology:

1. Please clarify if a rat toxin neutralization stud was performed. If yes, please provide the study report for our review.
2. Please clarify if the Baxter product of ETI-204 was used for study 2469.

Please let me know your turn around time. Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
10/26/2015

**From:** Dean, Jane  
**Sent:** Thursday, October 22, 2015 1:34 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthem) - nonclinical information request  
**Importance:** High

Hi, Robin – we have the following nonclinical information request:

The monkey efficacy studies AP-203 and AP-204 indicate that brain and spinal cord tissue was sent away for specialty neuropathology evaluation. Where can we find the appended reports for those two studies in the study reports? (In AP-201, the neuropathology report was appended to the pathology report that was appended to the study report).

Please let us know when you can provide a response. Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
10/22/2015

**From:** Dean, Jane  
**Sent:** Wednesday, October 21, 2015 9:57 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - clinical microbiology request  
**Importance:** High

Hi, Robin – the reviewers express their thanks for you all providing your responses so quickly to their information requests. They have another one, as follows:

For the ECL assays, we had reviewed the information in the ELR001 (section 3.4.2.1) as well as report VP2008-199. However, the report does not include any LOD information. It will aid in our review if you could please provide a copy of the report that supports LOD of 1 ng/mL in rabbits or 2 ng/mL in monkeys by the ECL assay.

As usual, if you can give me an idea of your turn around time, that would be greatly appreciated!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
10/21/2015



BLA 125509

**INFORMATION REQUEST**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoxaximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by October 26, 2015 in order to continue our evaluation of your application.

1. In response to question 12 in FDA information request dated September 24, 2015, Elusys proposed (b) (4)

[REDACTED]

Alternatively, Elusys could keep the option for syringe administration for the pediatric doses, provided Elusys commits to conduct a post-approval compatibility / in-use stability of drug product with syringe components. The compatibility study will include monitoring samples for protein concentration, purity by SEC-HPLC, icIEF, sub-visible particulates, and potency. The data from this study should be submitted as a prior approval supplement.

If you have questions, call me at (301) 796-0906.

Sincerely,

**Melinda J.  
Bauerlien -S**

Digitally signed by Melinda J. Bauerlien  
-S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=130017856  
5, cn=Melinda J. Bauerlien -S  
Date: 2015.10.21 11:25:23 -04'00'

**Melinda Bauerlien, M.S.  
Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research**

**From:** Dean, Jane  
**Sent:** Friday, October 16, 2015 10:18 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthem) - clinical microbiology information request

Hi, Robin – the clinical microbiology reviewer has the following information request:

1. Please clarify if the ETI-204 product used in Studies 1030, 1045, and 1056 is the Baxter product.
2. In different animal efficacy studies, the lower limit of detection (LOD) for the ECL assays were stated to be 1 or 2 ng/mL for the rabbit and monkey studies, respectively. The LODs for the anti-PA IgG concentrations in different rabbit and monkey studies were different e.g., 50 ng/mL and 100 ng/mL. Please clarify if the testing of the animal sera from efficacy studies were based on the validation reports stated in the clinical microbiology comment communicated on 10/13/2015 regarding lower limit of detections for the PA ECL and anti-PA IgG ELISA assays OR different assays were used.

Please let me know what your turn around time will be. Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
10/16/2015



BLA 125509

**INFORMATION REQUEST**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your application.

1. Response to Q2 indicate that you will include the cell banks' stability testing frequency, tests and acceptance criteria in the BLA instead of submitting the protocol under PAS. However the last sentence of the response state that the PAS will be submitted by 2016. Please clarify which PAS submission you are referring to.
2. In your response to Q5 you indicate that the next reference standard manufacture is planned for 1<sup>st</sup> Q of 2016 and the requalification protocol of the new reference standard will be submitted for review in Nov 2015 as opposed to the PAS submission after BLA approval. Please note that in addition to the requalification protocol, you also need the qualification protocol for the introduction of the new reference standard. Based on our internal review time line under PDUFA V we will not be able to review the proposed amendment for the qualification and requalification of the reference standard. We strongly recommend that you submit these protocols as a PAS post BLA approval.
3. Please clarify on if the new reference standard would be qualified as a primary or a secondary reference standard. We strongly recommend that the new reference should be established based on the two tier approach as noted in FDA comment 6 in IR-3 dated Aug 21, 2015. The proposed potency testing acceptance criteria of (b) (4)% for the requalification of (b) (4) reference standard may not be acceptable.
4. We note that the relative potency (RP) of the (b) (4) is listed as (b) (4)% in Table 1 in section 3.2.S.5 (Reference standard- (b) (4)). Clarify how these RP values were assigned and what was the assigned potency for (b) (4) reference standard used for the release and stability testing of the Lonza DS (b) (4)? Generally the primary

reference standard should be assigned a 100% using the approach and criteria that should minimize the drift in the potency. For example an acceptable approach to assign 100% potency is the use of predetermined confidence interval of the mean. Using this approach the 100% potency assignment requires the mean relative potency and the 95% confidence interval (CI) are included within a sufficiently narrow range e.g.95-105%.potency.

If you have questions, call me at (301) 796-0906.

Sincerely,

**Melinda J.  
Bauerlien -S**

Digitally signed by Melinda J.  
Bauerlien -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=13001785  
65, cn=Melinda J. Bauerlien -S  
Date: 2015.10.15 13:32:45 -04'00'

Melinda Bauerlien, M.S.  
Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

**From:** Dean, Jane  
**Sent:** Wednesday, October 14, 2015 10:03 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthim) - clinical microbiology information request

Hi, Robin! We have another information request – it's fairly straightforward and, hopefully, easy to respond to.

Based on our review of the performance characteristics of the anti-PA IgG and ECL assays the limit of detection (LOD) shown in Table below were found to be appropriate. Please confirm if this is correct.

Tests	Limits of Detection
Anti-PA IgG (VP2008-221)	
Monkey	1.6 µg/mL
Rabbits	1.0 µg/mL
ECL Screening Assay(VP2013-266)	
Monkeys	4 ng/mL
Rabbits	4 ng/mL

Thanks!!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
10/14/2015



BLA 125509

**INFORMATION REQUEST**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a written response by October 22, 2015 in order to continue our evaluation of your application.

**Drug Product Microbiology**

Reference is made to page 18 of 23 of the [REDACTED] (b) (4)

Reference is also made to table 4 of module 3.2.P.3 which provides the [REDACTED] (b) (4)

[REDACTED] Finally, reference is also made to table 54 of module 3.2.P.3.5.9.2.2.5 which provides [REDACTED] (b) (4)

[REDACTED] for the process validation lots using a [REDACTED] (b) (4)

- The [REDACTED] (b) (4) for the process validation lots are outside of the process parameters that were validated by [REDACTED] (b) (4)
- Amend the application with a [REDACTED] (b) (4)
- If the [REDACTED] (b) (4)

[REDACTED] Alternatively, provide a rationale as to how the [REDACTED] (b) (4) is supportive of your drug product manufacturing process.

**Drug Substance Microbiology**

1. During the pre-license inspection, it was verified that bioburden samples are taken from the [REDACTED] (b) (4) at the time of transfer. Please update Table 1 in Section 3.2.S.2.4 with the acceptance criteria of these samples.
2. The low endotoxin recovery (LER) study (Report USPO-14617) was conducted using [REDACTED] (b) (4) is not a currently recognized standard for

endotoxin qualification studies. Please provide data of a LER study performed with CSE/RSE.

3. Please clarify the hold time for [REDACTED] (b) (4) step provided in Table 2 of Section 3.2.S.2.2. Is the product held prior to the [REDACTED] (b) (4)? Please update Table 2 for the correct information.
4. Please implement the following [REDACTED] (b) (4) bioburden and endotoxin sampling points and provide interim acceptance criteria for these samples. Update Table 7 in Section 3.2.S.2.4 accordingly.
  - [REDACTED] (b) (4)
  - [REDACTED] (b) (4)
5. You tightened a few [REDACTED] (b) (4) bioburden and endotoxin acceptance criteria in your response in amendment dated 8/28/15 (Sequence18). Please update Table 3 and Table 7 in Section 3.2.S.2.4 accordingly.
6. The hold time [REDACTED] (b) (4) Please validate the maximum [REDACTED] (b) (4) hold time of this step [REDACTED] (b) (4) from microbiology perspective with three runs.
7. The [REDACTED] (b) (4) bioburden sample for the [REDACTED] (b) (4) listed in Table 8 in Section 3.2.S.2.4 is equivalent to the bioburden release test sample. However, the [REDACTED] (b) (4) [REDACTED] (b) (4) bioburden acceptance criterion ( $< [REDACTED] (b) (4)$  CFU/10 mL) for the [REDACTED] (b) (4) sample is inconsistent with the DS release bioburden specification ( $[REDACTED] (b) (4)$  CFU/10 mL). Please justify the purpose of the [REDACTED] (b) (4) bioburden sample for the [REDACTED] (b) (4) and clarify the discrepancy between the bioburden acceptance criterion and specification at this step.
8. Provide the bioburden and endotoxin limits for the [REDACTED] (b) (4) Documents USPO-9922 and USPO-9923 provided in your response to question 17 in amendment dated 8/28/15 do not appear to contain bioburden and endotoxin limits.
9. The proposed bioburden ( $< [REDACTED] (b) (4)$  CFU/mL) and endotoxin ( $\leq [REDACTED] (b) (4)$  EU/mL) acceptance criteria for the chromatography resins in the lifetime study at commercial scale are high

and could potentially contribute high bioburden and endotoxin (b) (4). Please tighten the bioburden and endotoxin acceptance criteria. Please provide endotoxin acceptance criteria of the (b) (4) for the lifetime study. Include testing volume in the bioburden acceptance criteria. In addition, provide the bioburden and endotoxin limits for the (b) (4).

**Facilities**

Facilities and equipment-BDS Facility in Section 3.2.A.1, indicates that (b) (4)

maybe used for ETI-204 manufacturing. It was verified during the pre-license inspection at Lonza that these areas are not used for ETI-204 manufacturing. Please update the BLA for the correct information.

If you have questions, call me at (301) 796-0906.

Sincerely,

Melinda J.  
Bauerlien -S

Digitally signed by Melinda J.  
Bauerlien -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=13001  
78565, cn=Melinda J. Bauerlien -S  
Date: 2015.10.06 14:03:33 -0400'

Melinda Bauerlien, M.S.  
Senior Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



BLA 125509

**MID-CYCLE COMMUNICATION**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoximab), 600 mg/6 mL single use vial, IV infusion.

We also refer to the teleconference between representatives of your firm and the FDA on September 1, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

John Alexander, MD, MPH  
Cross Discipline Team Leader  
Division of Anti-Infective Products  
Office Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** September 1, 2015, 10:00am – 11:00am

**Application Number:** BLA 125509

**Product Name:** Anthim (obiltoxaximab), 600 mg/6 mL single use vial, IV Infusion.

**Proposed Indication:** Treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate drugs and for prophylaxis of inhalational anthrax

**Applicant Name:** Elusys Therapeutics, Inc.

**Meeting Chair:** John Alexander, MD, MPH

**Meeting Recorder:** Jane A. Dean, RN, MSN

**FDA ATTENDEES**

**Division of Anti-Infective Products:**

Deepak Aggarwal, MS, MPH	Regulatory Health Project Manager
John Alexander, MD, MPH	Cross Discipline Team Leader
Shukal Bala, PhD	Clinical Microbiology Reviewer
Kimberly Bergman, PharmD	Clinical Pharmacology Team Leader
Lynette Berkeley, PhD, MT, (ASCP)	Clinical Microbiology Reviewer
Jane A. Dean, RN, MSN	Regulatory Health Project Manager
John Farley, MD, MPH	Office of Antimicrobial Products, Deputy Director
Jeffrey Florian, PhD	Pharmacometrics Reviewer
Ramya Gopinath, MD	Clinical Reviewer
Karen Higgins, ScD	Statistical Team Leader
Ling Lan, PhD	Statistical Reviewer
Xianbin Li, PhD	Statistical Reviewer
Sumathi Nambiar, MD, MPH	Director *
Amy Nostrandt, DVM, PhD	Pharmacology/Toxicology Reviewer
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Zhixia (Grace) Yan, PhD	Clinical Pharmacology Reviewer
Eva Zuffova, PhD, MS	Regulatory Health Project Manager

**Office of Biotechnology Products:**

David Frucht, MD	Product Quality Team Leader
Rashmi Rawat, PhD	Product Quality Team Leader

**Office of Product Quality:**

Patricia Hughes, PhD	Product Quality Microbiology Branch Chief (Acting)
John Metcalfe, PhD	Product Quality Microbiology Reviewer

**Office of Surveillance and Epidemiology:**

Shawna Hutchins, MPH, BSN, RN	Senior Patient Labeling Reviewer *
Jacqueline Sheppard, PharmD	Safety Evaluator
Joyce Weaver, PharmD	Senior Drug Risk Management Analyst

**Office of Prescription Drug Promotion:**

Adam George, PharmD	Regulatory Review Officer *
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**Counter-Terrorism and Emergency Coordination Staff:**

Andrea Gormley, PharmD, JD	Regulatory Health Project Manager *
Gerald Poley, MD	Medical Officer

**Eastern Research Group:**

Marc Goldstein	Independent Assessor *
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\* via teleconference

**APPLICANT ATTENDEES**

**Elusys:**

Karen Blodgett, MS	Director Program Management
Greg Birrer, PhD	Sr. Director Quality Affairs
Sarah Carpenter, PhD	Director Bioanalytical Development
Robin Conrad, MS	VP Regulatory Affairs
Ariane Cutolo	Sr. Manager Regulatory Affairs
Cynthia Dillon	Sr. Director Regulatory Affairs
Christa Nagy, PhD	Director Clinical Operations
James Porter, MS	VP Manufacturing and Development
Natalya Serbina, PhD	Senior Scientist, Nonclinical Development
Pamela Wright, PhD	Sr. Director, Manufacturing

**Elusys Consultants:**

(b) (4)



Research Consultant
Statistical Consultant
Sr. Consultant DMPK
Clinical Consultant
Sr. Research Scientist

(b) (4)

**Biomedical Advanced Research and Development Authority:**

David Boucher

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

Project Officer  
Contractor  
Subject Matter Expert  
Contractor

**1.0 INTRODUCTION**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle. Discussion taking place during the telecon is captured under Discussion in the minutes.

**2.0 SIGNIFICANT ISSUES**

**Clinical**

1. Hypersensitivity reactions: In the healthy volunteer safety studies, infusion of ETI-204 was discontinued prematurely in several patients due to signs or symptoms suggesting hypersensitivity. In an Information Request dated June 22<sup>nd</sup> 2015, clarification of your categorization of the 6 such subjects in AH104 was requested. The clinical reviewers feel that the entire complex of symptoms and signs necessitating discontinuation of the infusion, taken together, is more clinically relevant than the severity of each individual symptom or sign. The reviewers do not consider this an approvability issue for the treatment indication, though it could be an issue for prophylaxis, product labeling, and the IM use of ETI-204.

2. (b) (4)

**Discussion:**

- It is unknown if the frequency of hypersensitivity reactions may differ by the route of administration, that is, intravenous or intramuscular. An adequate safety database is needed to ascertain if hypersensitivity reactions may be more frequent with IM administration.

-  (b) (4)

**Quality Microbiology**

The endotoxin spiking and recovery study data for drug substance and drug product samples are pending. If obiltoximab drug substance and drug product samples are confirmed to have low endotoxin recovery, a path forward for releasing drug substance and drug product must be determined prior to approval.

There are no significant issues from other review disciplines at this time.

**Discussion:**

Elusys noted there was no discussion of the rationale supporting the proposed human dose of obiltoximab, specifically the comparison of human and animal exposures. Elusys asked if that meant that the dose justification was considered acceptable. The Division responded that the issues identified were preliminary issues raised by the review team, and reviews were ongoing. All that could be said is that the review team did not raise the human dose as a significant issue at this time.

**3.0 INFORMATION REQUESTS**

There are two outstanding information requests from Product Quality dated August 10, 2015 and August 21, 2015.

**Discussion:**

- The Agency acknowledged receipt of the Elusys August 28, 2015, submission in response to the information request sent on August 10, 2015. The response is currently being reviewed. If, after reviewing it, more information is needed, another information request will be sent.
- Elusys will be providing their response to the August 21, 2015, information request by September, 4, 2015.

The Division also sent an information request from Clinical Microbiology on August 26, 2015 and from Product Quality Microbiology on August 27, 2015.

**Discussion:**

- The Agency acknowledged receipt of the Elusys August 31, 2015, email in response to the information request sent on August 26, 2015.
- Elusys will be providing the response to the August 27, 2015, information request by September 11, 2015.

**4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have not conclusively determined whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. A final determination on the need for a REMS will be made during the review of your application.

**5.0 ADVISORY COMMITTEE MEETING**

There are no plans at this time for an Advisory Committee meeting.

**6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

1. Draft labeling will be sent to Elusys by November 23, 2015.
2. The Late Cycle meeting package will be sent to Elusys by December 1, 2015.
3. The Late Cycle meeting with Elusys is scheduled for December 11, 2015.
4. Final labeling and any possible PMR/PMC discussion with Elusys will be scheduled for December 15, 2015.

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/s/  
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JANE A DEAN  
09/28/2015

JOHN J ALEXANDER  
09/29/2015

**From:** Dean, Jane  
**Sent:** Thursday, September 24, 2015 4:12 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthim) - information request (stats)

Hi, Robin – we have an additional information request (stats) for you:

We need the followings information regarding Study AR028:

1. Include the following information in the ADSL dataset and submit the updated data for review purpose.
  - a. Age for treated animals in Phase II
  - b. Pre-challenge quantitative bacteremia and PA-ELISA levels and corresponding sample time

Verify the challenge date and time (INOCSTDT and INOCSTTM) in the ADSL dataset. There were several challenge dates and times from LB.xpt data (LBRFTDTC) that were different from the challenge dates and times from adsl.xpt submitted

Please let me know what your turnaround time will be. Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
09/24/2015



BLA 125509

**INFORMATION REQUEST**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoxaximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a written response by October 8, 2015 in order to continue our evaluation of your application.

1. In response to FDA question 2 in information request (IR)-1 (dated May 28, 2015), regarding the (b) (4)  

2. We have following comment with regard to your response to FDA question 9 (ii-b) in IR-3 (dated August 21, 2015) that should be addressed:  
You do not need to submit a separate protocol to the BLA for stability testing of the master and working cell banks. This information can be included in section 3.2.S.3.3.2 of the BLA. The information should include the frequency of cell bank stability testing, the testing that will be performed, and the acceptance criteria that will be used.
3. If available, provide phenotypic characterization data on the end of production cell lines.
4. In your response to question 8 in IR-3(dated August 21, 2015), the data provided to support the cumulative hold times are not adequate to support the worst case cumulative hold times proposed in the BLA. The worst case in-process cumulative hold time proposed in the BLA are (b) (4)  


- (b) (4). Therefore provide commitment to conduct, post-approval, a reduced scale study to support the worst case cumulative hold times study to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of obiltoxaximab DS.
5. In response to question 6 in IR-3 (dated August 21, 2015), you have indicated that the stability (re-qualification) of the (b) (4) reference standard, that is (b) (4), will be performed per the DS stability protocol at (b) (4). Please note that the acceptance criteria used in the stability testing are wider than the current expectations for re-qualification of primary or working RS. The acceptance criteria for reference standard requalification and qualification should be sufficiently narrow to prevent product drift and ensure that the reference standard remains reflective of material used in the clinical studies and animal efficacy studies. For requalification, the acceptance criterion for potency should include comparison to the (b) (4) reference and the initial qualification, as well as an evaluation of trending of results obtained in routine release and stability tests. The acceptance criterion should be set so that the result is sufficiently similar to the potency value at the time of initial qualification. Provide the requalification/stability protocol for the (b) (4) reference standard (b) (4). This stability protocol should include tests and acceptance criteria; and testing intervals. If agreed upon the finalized protocol should be submitted to the BLA.
  6. Provide available data to support the stability of the (b) (4). This can include tracking and trending of routine release and stability test data.
  7. The non-reduced SDS-PAGE assay mainly detects the % intact protein. The levels of % intact protein detected by nr SDS-PAGE are > (b) (4)%. However data provided in the BLA from the nr-CE-SDS assay indicate that the samples contain fragments and aggregates. This suggests that the current SDS-PAGE assay does not adequately detect size-variants in obiltoxaximab DS and DP samples. Therefore, provide a commitment to update, post-approval, DS and DP release and stability specifications with acceptance criteria for the CE-SDS assays.
  8. Because the charge isoforms of the ETI-204 have not been characterized with respect to their activity, the control strategy for charge isoforms needs to be updated. We recommend that DS and DP release and stability specifications for the iCIEF method be updated to include ‘compare to reference’ in addition to the quantitative limits of the charge isoforms.
  9. Provide data to support that identity tests used for EIT-204 would be able to sensitively discriminate it from other products manufactured in the same facility. If necessary, propose revised acceptance criterion for the identity tests and provide justification for the revised criteria. If agreed upon, the BLA should be updated with the revised specification.
  10. We note that the acceptance criteria for the biological activity assays, antigen binding ELISA and Lethal Neutralization (LNA) assays are expressed as units/mg and EC<sub>50</sub>

- respectively. As per ICH Q6 the results of biological assays should be expressed in units of activity calibrated against reference standard. Therefore propose the revised acceptance criteria for the antigen binding ELISA and Lethal Neutralization assays that are expressed as “percent reference standard,” in obiltoxaximab DS and DP release and stability specifications. The proposed revised criteria should be appropriately justified. If agreed upon, the BLA should be updated with the revised specifications for the antigen binding ELISA and LNA assay.
11. We note that the Elusys commits to continue stability testing for only two drug substance (DS) batches (b) (4). Please note that to (b) (4), stability data from only two DS batches may not be sufficient to adequately assess DS stability. We strongly recommend that at least 3 DS batches be included in stability testing that is intended to provide stability data to (b) (4).
  12. We note that the administration of the ETI-204 is performed using a syringe for pediatric population. However, compatibility studies to support the administration by syringe were not provided in the BLA. Provide in-use compatibility/ stability study data to the BLA to support the administration of ETI-204 using syringe.
  13. Update DP section 3.2.P.3.3 with DP shipping information( e.g., information on DP storage prior to shipping and shipping conditions under which it is transported from manufacturing facility to the packaging, repackaging and storage sites).
  14. The drug product shipping validation protocols, provided in response to the IR-3, question 13 (dated August 21, 2015), did not include assessments of product quality (e.g., opalescence, protein concentration, purity by SE-HPLC, reduced and non-reduced SDS-PAGE, icIEF, sub-visible particulates) in pre- and post-shipping samples of obiltoxaximab DP. Submit the DP quality data from the shipping validation. If the DP product quality data from the shipping validation studies are not available during the review cycle provide commitment to submit this data to the BLA post-approval.
  15. 21 CFR 610.14 states that an identity test must be performed on products after all labeling operations have been completed. Provide information to confirm that identity testing of obiltoxaximab meets this CFR requirement.
  16. We note that for DS batch 103B20-X109-TR06 produced at Baxter was released for DP manufacturing despite an OOS results for the potency assay, LNA EC<sub>50</sub>. Provide summary information on the investigation of this OOS result and the rationale for why this batch was released. Provide clarification on whether this batch was released without being re-tested. Please refer to FDA’s guidance for industry on “Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production.” (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070287.pdf>). We also note that this batch was designated as a non-GMP batch. Provide an explanation on what non-GMP condition(s) existed for this batch.

If you have questions, call Melinda Bauerlien, Senior Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

Rashmi Rawat, Ph.D.  
Team Lead  
Division of Biotechnology Research and Review II  
Office of Biotechnology Products  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

**From:** Dean, Jane  
**Sent:** Thursday, September 03, 2015 2:25 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - clinical microbiology request

Hi, Robin, we have an additional IR for you:

Please submit the Mean ECL values of the Positive Controls used in all tests ( e.g. false positives, false negatives, limit of detection, real world sample detection) by species when applicable, that were performed in the ECL validation report- VP2013-266.

Thanks!!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
09/03/2015

**From:** Dean, Jane  
**Sent:** Tuesday, September 01, 2015 2:20 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - clinical microbiology request

Hi, Robin – our clinical microbiologist has the following information request:

Please provide the following Tables for the rabbit and macaque studies:

Table : Study AP203- Number of animals histologically and culture positive for <i>B. anthracis</i> in tissues						
Tissue	Placebo		ETI-204 8 mg/kg		ETI-204 16 mg/kg	
	Survivors	Non survivors	Survivors	Non survivors	Survivors	Non survivors
<b>Presence of bacteria by microscopy</b>						
Brain	0/2	5/5	0/1	5/5	0/6	5/5
Bronchial lymph node						
Kidney	ND					
Liver						
Lung						
Spleen						
<b>Presence of bacteria by culture</b>						
Brain	1/2	13/14	0/1	15/15	1/6	10/10
Bronchial lymph node	0/2	13/14	0/1	12/15	1/6	7/10
Kidney	0/2	13/14	0/1	9/15	0/6	6/10
Liver	0/2	13/14	0/1	9/15	0/6	7/10
Lung	0/2	13/14	0/1	15/15	5/6	10/10
Spleen	0/2	13/14	0/1	13/15	0/6	8/10

Please let me know your turn around time on this - thanks!

Jane

Jane A. Dean, RN, MSN  
 Project Manager  
 DAIP/OAP/OND  
 Building 22, Room 6397  
 Office: 301-796-1202  
 Fax: 301-796-9881  
 Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
09/01/2015

**From:** Dean, Jane  
**Sent:** Thursday, August 27, 2015 2:43 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthem) - product quality microbiology information request

Hi, Robin, the product quality microbiology reviewer has the following information request:

1. We acknowledge the [REDACTED] (b) (4). However, other drug product manufacturing process time limitations are not provided in the application. Provide the [REDACTED] (b) (4).  
[REDACTED] Include supporting validation data of these holding times.
2. We acknowledge the description of the environmental monitoring program provided in section 1.7 of module 3.2.A.1. However, details of the media and associated incubation conditions are not provided in the application. Provide the type(s) of microbiological media and the incubation temperature(s) used in the environmental monitoring program.
3. The environmental monitoring information should be provided in the drug product quality module (3.2.P) of the application. Please update the BLA file by moving the environmental monitoring information to section 3.2.P.3.3 and removing it from the appendix.
4. We acknowledge the [REDACTED] (b) (4) stated in table 4 of module 3.2.P.3. However, it is difficult to assess whether the [REDACTED] (b) (4) parameters used for bacterial retention validation studies are appropriate, based on this production process specification. Provide the [REDACTED] (b) (4) parameters to include [REDACTED] (b) (4) to be used during manufacture of the drug product.
5. We acknowledge the revalidation protocols in section 5.1.1 of module 3.2.P.3 for the equipment [REDACTED] (b) (4). However, minimum data from these revalidations are provided in the application. Provide the following:
  - a. [REDACTED] (b) (4)
  - b. [REDACTED]
  - c. [REDACTED]
  - d. [REDACTED]
6. Reference is made to section 2.3 ([REDACTED] (b) (4)) of the draft label. The instructions for preparation of the final drug product in an infusion bag state "the prepared solution is stable for [REDACTED] (b) (4) hours stored at room temperature [REDACTED] (b) (4)".

(b) (4)”. However, microbiological stability studies for a post dilution storage time of (b) (4) hours at room temperature are not provided in the application.

Provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.

Generally, "no growth" is interpreted as not more than a 0.5 log<sub>10</sub> increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use the label-recommended fluids inoculated with low numbers ( $\leq 100$  CFU/mL) of challenge microbes. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-dilution storage period is not more than 4 hours at room temperature or 18 hours at refrigerated temperature.

Please let me know what your turnaround time can be.

Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
08/27/2015

**From:** Dean, Jane  
**Sent:** Wednesday, August 26, 2015 3:04 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthem) - clinical microbiology information request  
**Importance:** High

Hi, Robin – our clinical microbiology reviewers have the following information request:

- Detection of anti-PA IgG was performed prior to challenge (screening) in some of the nonhuman primate and rabbit studies. However, such information could not be found in the datasets for all the studies. Please clarify if anti-PA IgG results were included in the datasets. If not, please provide datasets for each study showing animal ID, treatment group, findings from the anti-PA IgG test (positive/negative, titer) and whether the animals survived until the end of study or were found dead or moribund.
- Detection of PA by ELISA or ECL and/or bacteremia by enriched or quantitative culture methods were performed prior to challenge (screening) in some of the nonhuman primate and rabbit studies. Please clarify if any animal that tested positive for PA or was bacteremic prior to challenge was included in the study. If yes, please provide datasets for each study showing animal ID, treatment group, findings available from the PA test [by ECL (positive/negative) and ELISA (positive negative, concentration)] and culture (positive/negative, cfu/mL) and whether the animals survived until the end of study or was found dead or moribund.
- It appears that screening bacterial cultures were performed for some of the nonhuman primate studies (e.g., Study AP202) and presence of *Klebsiella* was documented in medical records of individual animals. However, for some of the other studies (e.g., Study AP 201) it is unclear whether screening bacterial cultures were performed and there was no pathogen was identified, or no cultures were performed. Please clarify.

Please let me know your turnaround time for responding.

Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
08/26/2015



BLA 125509

**INFORMATION REQUEST**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obiltoximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We are reviewing your submission and have the following comments and information requests. We request a written response by September 4, 2015 in order to continue our evaluation of your application.

1. We note that the primary stability data to determine the DS shelf life are derived from engineering batches manufactured prior to process validation. It may be acceptable to use these data provided: (a) there are no process changes between the engineering and the validation runs that could potentially affect DS stability and; (b) a commitment is made to place at least three DS validation batches on stability. Provide information on any differences, if present, in the manufacturing process of the engineering and the validation batches. Also provide a commitment to place a minimum of three DS validation batches in the DS stability program.
2. Regarding your proposal to submit the DS and DP primary stability data 2 months prior to the decision date, we would like to inform you that under PDUFA V, data should not be submitted more than 30 days after the submission of the original application unless it is requested by the Agency. A simple stability update may be submitted upon the request of the Agency. The "simple stability update" submitted, up to month 7, for a standard submission may be reviewed and considered in shelf life determinations. In order to support your proposed shelf life for drug product and drug substance, you may wish to provide a "simple stability update" before October, 20, 2015 to be considered in shelf life determinations. A "Simple stability update" is defined as follows: Stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. This update will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if

any) and will not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA.

3. We do not agree with your DS and DP annual stability commitments to place one, out of every 15 DS and DP lots on stability. Revise the DS and DP annual stability commitments to place on stability one lot of DS and DP, from each manufacturing campaign.
4. Provide proposed stability specifications for the control of oblitoxaximab DS and DP. The final agreement upon the stability specifications for the DS and DP can then be submitted to BLA sections 3.2.S.4.1 and 3.2.P.5.1 respectively.
5. The BLA only contained data from the SEC-HPLC method under forced degradation conditions. The impact of forced degradation conditions on critical quality attributes measured by other methods is unclear. Provide available information regarding the impact of forced degradation conditions on oblitoxaximab with regard to appearance, pH, charge isoforms by icIEF, size-variants by reduced and non-reduced SDS-PAGE, potency and visible and subvisible particulates.
6. We note that the oblitoxaximab reference standard program only uses a primary reference standard (PRS). This approach doesn't provide sufficient control over the drift in product quality attributes that can occur over the lifecycle of the product. We strongly recommend that a two-tiered program with primary and secondary reference standards (SRS) be established. The current reference standard (b) (4) can serve as the primary reference standard. A new DS batch should be qualified, against the PRS, to serve as the secondary RS. Protocols covering future reference standards, including future primary and secondary RS, should be submitted to the BLA. The protocols should include information on manufacturing, qualification, and requalification. When a Reference Standard protocol is agreed upon, that protocol should be followed; update the BLA accordingly. If these reference standard protocol(s) cannot be submitted and agreed upon during the current review cycle, the protocol(s) can be submitted to the BLA as a prior approval supplement (PAS); in this case, section 3.2.S.5 should be updated to reflect that no new reference standard will be implemented until its use is approved by FDA.

We note that the oblitoxaximab reference standard program does not include a requalification protocol for the reference standard that is currently being used (e.g. (b) (4)). A requalification protocol should be submitted for review. The final agreed upon protocol can then be submitted to section 3.2.S.5 of the BLA.

7. We note that the qualification protocol for the replacement of the WCB is not provided in the BLA. Please note that the submission of the WCB qualification protocol or qualification data is considered a major amendment to the BLA. If you plan to submit the WCB qualification protocol post-approval it should be submitted as a prior-approval supplement. Alternatively, you can provide the protocol at this time to the original BLA application.

8. Provide any available data/information to support DS cumulative hold times.
9. The following questions are follow-ups of your responses to FDA Information request (IR)-1 (dated on May 28, 2015):

- i. Your response to FDA IR-1, question 2; regarding [REDACTED] (b) (4)

[REDACTED] Provide detailed information on how this analysis was performed and how the results obtained from this analysis are indicative of a monoclonal origin of these cells.

- ii. Regarding your response to IR-1 question 3 we have following question:
      - a. You indicated that a linear regression analysis was performed on the % viability data [REDACTED] (b) (4) and the result was used to support certification [REDACTED] (b) (4). Please provide the data and the trend analysis that were used to assess the WCB stability.
      - b. We do not agree with the stability protocol for the MCB and the WCB as provided in your response to IR1-question 3 because (a) [REDACTED] (b) (4)

[REDACTED] This runs the risk of the MCB not being tested adequately for stability and thus creates a high degree of uncertainty regarding the status of MCB viability.

10. The following questions are follow-ups of your responses to FDA Information request (IR) -2 dated June 15, 2015:

- i. Regarding your in response to question 7, you state that you do not plan on

[REDACTED] (b) (4)

- ii. Your response to question 10 indicate that you plan to submit the requested information on small scale model qualification and other process characterization data to sections 3.2.S.2 and 3.2.S.2.4 of the BLA at the end of August. We recommend that you submit this information to section 3.2.S.6, "Manufacturing Process Development," as this is the section where all manufacturing process development and characterization data should be provided.

11. In section 3.2.P.3.3. Description of Manufacturing Process and Process Controls you indicate that the [REDACTED] (b) (4)

12. We note that in section 3.2.P.3.4, in table 4, for several process parameters, you do not include quantitative limits, but rather “report results” or qualitative criteria are used. Your control strategy should include appropriate limits or acceptance criteria for the following process parameters for the DP manufacturing process.

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]

You should also provide data to support the proposed limits/acceptance criteria for these parameters based on oblitoxaximab DP process development, validation and/or manufacturing experience. Once there is agreement with the Agency over the proposed limits/acceptance criteria for these parameters, the BLA should be updated with the revised limits/acceptance criteria.

13. Submit oblitoxaximab drug product shipping validation studies to the BLA.

14. You have provided data to support stability at pH 5.5 (b) (4). However, the proposed acceptance criterion for release and stability of the oblitoxaximab DS and DP is pH [REDACTED] (b) (4). Provide data to support the stability of the oblitoxaximab at lower limit of the proposed pH acceptance criteria.

15. We note that the protein concentration assay (cSOP-0221) used for drug product testing at [REDACTED] (b) (4) was transferred from [REDACTED] (b) (4). Provide summary information on the transfer of the protein concentration assay to [REDACTED] (b) (4).

16. We note that the quality attribute assessed in the in-use compatibility study include only purity by SE-HPLC and protein concentration. This is not sufficient to provide assurance of the product stability during administration. In addition to protein concentration and purity by SEC-HPLC tests, in-use compatibility testing should include cIEF, sub-visible particulates, and potency. Provide results of the additional testing to support the in-use compatibility of oblitoxaximab.

If you have questions, call Melinda Bauerlien, Senior Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

Rashmi  
Rawat -S

Digitally signed by Rashmi Rawat -S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Rashmi Rawat -S,  
0.9.2342.19200300.100.1.1=00141375  
32  
Date: 2015.08.20 15:01:11 -04'00'

Rashmi Rawat, Ph.D.

Team Lead

Division of Biotechnology Research and Review II

Office of Biotechnology Products

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research

**From:** Dean, Jane  
**Sent:** Friday, August 14, 2015 1:04 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthim) - stats information request

Hi, Robin – our stats reviewer has the following information request regarding Study NIAID 1056:

1. Please clarify the challenge dose (LD<sub>50</sub> equivalent) for animal A07623 in the ETI-204 & Cipro combination group. This LD<sub>50</sub> value was 259 units in ADSL data and 8760000 in EX data; however Table 9 on page 21-22 of the study report listed 142 units instead.
- 2.
3. Provide subject level data of time from challenge to first positive PA-ELISA for animals in the ETI-204 group. The maximum time to first positive PA-ELISA was 44.15 for animal A07043 based on the reviewer's calculation; however, Table 18 of the study report listed the maximum time as 40.80.
- 4.
5. Provide subject level data of time from challenge to positive bacteremia culture for the ETI-204 group. There is a discrepancy between the mean time calculated by the reviewer and that reported in Table 19 of the study report.

Please let me know your TAT – thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
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/s/  
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JANE A DEAN  
08/14/2015

**From:** Dean, Jane  
**Sent:** Monday, August 10, 2015 10:00 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthim) - information request needing a rapid turnaround please - thanks!  
**Importance:** High

Hi, Robin, we have the following information request from the product quality team. They have also asked for a rapid turnaround. Once you read this over, can you give me an idea of when you would be able to provide the information they are requesting? Thanks!!

1. The bioburden sample volumes for the (b) (4)  
[Redacted]  
Please tighten the bioburden acceptance criteria for these samples.
2. The endotoxin acceptance criteria of (b) (4) EU/mL for (b) (4)  
[Redacted]  
Please tighten the endotoxin acceptance criteria for the (b) (4) samples.
3. Please provide a diagram showing all the bioburden and endotoxin sampling points for the commercial Obiltoxaximab recovery and purification process. Indicate on the diagram if the samples are taken before or after (b) (4)  
[Redacted]
4. Please provide the (b) (4)  
[Redacted]
5. Please implement bioburden and endotoxin sampling points (b) (4)  
[Redacted]. Provide the (b) (4) bioburden and endotoxin acceptance criteria and update Table 7 in Section 3.2.S.2.4 accordingly.
6. Please implement a bioburden sampling point (b) (4)  
[Redacted] Provide the bioburden acceptance criterion and update Table 7 in Section 3.2.S.2.4.

7. The endotoxin acceptance criterion [REDACTED] (b) (4)  
[REDACTED] Please tighten the acceptance criterion or justify.
8. Please clarify when and from which [REDACTED] (b) (4)  
bioburden and endotoxin samples are taken.
9. Clarify the sampling location for “[REDACTED] (b) (4) bioburden and  
endotoxin samples indicated in Table 7 in Section 3.2.S.2.4.
10. Clarify if bioburden and endotoxin samples are taken from [REDACTED] (b) (4)  
[REDACTED] and update  
Table 7 in Section 3.2.S.2.4.
11. Please implement bioburden sampling points for the [REDACTED] (b) (4)  
[REDACTED]  
Provide the bioburden acceptance criterion and update Table 7 in Section 3.2.S.2.4.
12. Clarify the sampling location for the [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] Implement the corresponding bioburden and endotoxin sampling points if they  
are not already in place.
13. [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] If not, implement the bioburden and endotoxin sampling points.
14. Clarify the bioburden and endotoxin sampling locations for the [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]? If not, implement the bioburden and endotoxin sampling  
points.
15. Clarify the bioburden and endotoxin sampling points for [REDACTED] (b) (4)  
[REDACTED]
16. Provide the validation study protocol and report for [REDACTED] (b) (4) hold times [REDACTED] (b) (4)  
[REDACTED]

17. Provide the conditions for [REDACTED] (b) (4)  
[REDACTED]  
Specify the bioburden and endotoxin limits.
18. Please clarify the [REDACTED] (b) (4)  
[REDACTED]
19. Please provide a diagram showing all the bioburden and endotoxin sampling points for [REDACTED] (b) (4)  
[REDACTED]
20. Please establish an endotoxin acceptance criterion for the [REDACTED] (b) (4) polysorbate 80 solution.
21. Provide the hold times for the [REDACTED] (b) (4) and the hold time validation data.
22. Please include bioburden and endotoxin monitoring of the [REDACTED] (b) (4)  
[REDACTED] Provide the bioburden and endotoxin limits for the study. In addition, provide the bioburden and endotoxin limits [REDACTED] (b) (4).
23. With regard to BDS shipping validation, clarify the starting point and destination of the PQ runs. Is the shipping route used during shipping validation comparable to that of the BDS commercial shipping in terms of temperature exposure and distance?

Jane

Jane A. Dean, RN, MSN  
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/s/  
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JANE A DEAN  
08/10/2015

**From:** Dean, Jane  
**Sent:** Monday, July 27, 2015 11:48 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - information request (clinical microbiology)

Hi, Robin, we have the following information request from the clinical microbiologist:

Please provide the following Tables<sup>1</sup> for the rabbit and macaque monotherapy and combination treatment studies:

Table 1: Study AR-033 - Agreement among detection methods of bacteremia and serum PA any time prior to treatment of the animals										
Detection Method <sup>†</sup>					Placebo (n=)	Treatment Group				Total (n=)
Qualitative culture (n=)*	Enriched culture (n=) <sup>‡</sup>	Quantitative culture (n=) <sup>‡</sup>	PA Screening ECL (n=)*	PA Quantitative ELISA* (n=) <sup>‡</sup>		ETI-204				
						8 mg/kg (n=14)	4 mg/kg (n=14)	8 mg/kg (n=14)	16 mg/kg (n=14)	
-	-	-	-	-	0	0	0			0
-	-	-	-	+	1	0	1			2
+	-	-	-	-	0	0	1			1
+	+	-	-	-						
+	+	+	-	NV						
‡	‡	‡	‡	‡						
	+	-	+	+						
	-		+	+						
	+		+	-						
	+		+	NV						
	ND		+	NV						
	+	ND	+	+						

Results determined on a per rabbit basis, not for individual tests. Any positive result from any time prior to treatment counted as positive.  
<sup>†</sup> number of positive tests  
 NV = test not valid due to failure in quality control parameters  
 ND = Not Done  
 \*LOD by qualitative culture ...cfu/mL; LOD by enriched culture ...cfu/mL; LOD by PA ECL ...ng/mL  
<sup>‡</sup>LLOQ by quantitative culture 100 cfu/mL; LLOQ by free PA ELISA 9.68 ng/mL

**Comment [CDER user1]:** Add different combinations of +ve and -ve as applicable.  
 The column headings are based on Study AR033. Please change as applicable for other studies

<sup>1</sup> Please note that the numbers in the Tables are mock numbers

Table 2: Study AR033 - Percent rabbits surviving on day 28 pi in different treatment groups based on detection of bacteremia or serum PA						
Treatment Group	Result <sup>1</sup>	Detection Method				
		Qualitative Culture	Enriched culture	Quantitative culture	Screening PA (ECL Assay) <sup>2,3</sup>	Quantitative PA (ELISA Assay) <sup>4</sup>
Placebo n = 14	Total Positive	9/14 (64.3%)	13/14 (92.9%)	.. /14 (%)	.. /14 (%)	.. /14 (%)
	# survived / # positive (% survival)	.. /9 (..%)	.. /13 (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)
<b>ETI-204 Dose</b>						
1 mg/kg n = 14	Total Positive	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)
	# survived / # positive (% survival)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)
4 mg/kg n = 14	Total Positive	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)
	# survived / # positive (% survival)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)
8 mg/kg n = 14	Total Positive	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)
	# survived / # positive (% survival)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)
16 mg/kg n = 14	Total Positive	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)
	# survived / # positive (% survival)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)	.. /.. (..)

<sup>1</sup>Results are for animals that were positive by the indicated assay by the time treatment was initiated. Please specify, if .most of the animals also were positive at the actual time of treatment.

<sup>2</sup>Assays had to pass quality control criteria to be included. If plates failed, then please clarify e.g., several animals in each treatment group had multiple plates that failed quality control criteria.

<sup>3</sup>The serum screening PA/ECL assay was done on site at the (b) (4)

<sup>4</sup>The serum quantitative PA/ELISA assay was done on stored samples at the (b) (4)

\*Add other comments as applicable.....

Table 3: AR033 - Incidence of gross, microscopic, and severity of lesions in rabbits bacteremic at the time of treatment

Organ/Lesion <sup>2</sup>	Placebo n/N (*)	ETI-204			
		1 mg/kg n/N (*)	4 mg/kg n/N (*)	8 mg/kg n/N (*)	16 mg/kg n/N (*)
<b># Necropsied/Total Infected</b>	../14	../14	../14	../14	../14
<b>Brain</b>					
Gross Lesions	1/11	2/6	3/4	3/3	1/2
Bacteria	6/6	5/6	3/4	2/3	2/2
Hemorrhage					
Severity score					
<b>Kidney</b>					
Gross Lesions	0/6	0/6	0/4	0/3	0/2
Bacteria	6/6	5/6	3/4	0/3	2/2
<b>Liver</b>					
Gross Lesions	0/6	0/6	0/4	1/3 <sup>E</sup>	0/2
Bacteria	6/6	5/6	2/4	1/3	1/2
<b>Bronchial Lymph Node</b>					
Gross Lesions	5/5	3/3	2/2	0/1	0/1
Bacteria	3/5	2/3	1/2	0/1	0/1
<b>Mediastinal Lymph Node</b>					
Gross Lesions	6/6	5/5	4/4	1/3	1/2
Bacteria	5/6	2/5	1/4	0/3	1/2
Hemorrhage					
<b>Mesenteric Lymph Node</b>					
Gross Lesions	3/3	NA	NA	NA	1/1
Bacteria	2/3	NA	NA	NA	NA
<b>Lungs</b>					
Gross Lesions	1/3	NA	NA	NA	1/1
Bacteria	1/3	NA	NA	NA	1/1
<b>Spleen</b>					
Gross Lesions	1/6	1/6	0/4	0/3	0/2
Bacteria	2/6	4/6	1/4	1/3	1/2
n/N = number of animals with the indicated lesion/total number of animals necropsied					
*Mean severity of lesion					

Please let me know what your turn around time will be. Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND

<sup>2</sup> List organs and parameters as applicable

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/s/  
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JANE A DEAN  
07/27/2015

**From:** Dean, Jane  
**Sent:** Friday, July 24, 2015 11:29 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - information request (statistics)

Hi, Robin – we have the following information request:

For all rabbit studies using temperature as the treatment trigger, please submit baseline temperature data (except for Study AR021), mean baseline temperature and standard deviation by animal and the time period (AM/PM, hourly, or daily) over which mean and standard deviation were calculated for each animal or if this information is already included in the submitted data sets, please direct us to the right location.

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
07/24/2015

**From:** Dean, Jane  
**Sent:** Wednesday, July 15, 2015 4:13 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthim) - information request

Hi, Robin – the reviewers have the following information request. Please let me know your turn around time – thanks!

1. 25 subjects in AH104 had headache as a TEAE (21 in the ETI-204 arm and 4 in the placebo arm). Of these, 24 were characterized as having a mild headache, while only one (in the ETI-204 group) was characterized as having a moderate one. Further, the headache was thought to be related to the infusion in only 14 of the subjects.
  - a. Could you please clarify what criteria you used to decide relatedness? If it was time of onset, please explain what time criteria after the beginning of the infusion was used to determine this? For example, one subject whose headache was thought to be unrelated, had a time of onset of only 5h and 45 mins after the beginning of the infusion (002-209), whereas another subject whose headache started 14 h later was thought to be related (002-215).
  - b. Since headache was one of the more common TEAE's, what do you think is responsible for this?
2. In AH109, the TEAE's in the Nervous System Disorders SOC consisted primarily of somnolence with many fewer subjects with a headache. In AH104, somnolence did not seem to occur as a TEAE, but many more subjects had a headache. Is somnolence thought to be primarily related to premedication with diphenhydramine? If so, please explain the lack of somnolence as an AE in AH104, and its predominance in AH109? Specifically, was there a difference in how AE's were characterized between the two studies? Also, please explain why there may be many fewer subjects with a headache in AH109.

Jane

PS – just a reminder that I'll be out of the office until next Thursday. If you need any assistance while I'm gone, call 301-796-1400.

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
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/s/  
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JANE A DEAN  
07/15/2015

**From:** Dean, Jane  
**Sent:** Tuesday, July 14, 2015 9:38 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthim) - information request

Hi, Robin – I have the following information request from the clinical microbiology and statistics reviewers. Please let me know what your turn around time can be. Thanks!!

**Bacteremia and Protective Antigen**

We would like some clarification regarding the differences in the lower limit of detection (LOD) for the methods used for reporting blood culture and PA findings. For example, for Studies AP202, AP203, and AP204, the LOD for quantitating bacteremia was 3 cfu/mL whereas for Study AP201, the LOD was 33 cfu/mL. Please complete the following Table to aid in our review or provide the same information in an alternative format.

Study No.	Assay Validation Report No.	Quantitative Bacteremia				PA by ELISA		Comments*
		LOD (cfu/mL)	<LOD as presented in the datasets	LLOQ	<LLOQ as presented in the datasets	LLOQ (ng/mL)	<LLOQ as presented in the datasets	
<b>Cynomolgus macaques</b>								
AP202		3	2	100		5		
AP203		3	2	100		9.68		
AP204		3	2	100		9.68		
AP201		33	17	1000	500			
AP..								
AP..								
<b>New Zealand White Rabbits</b>								
AR021								
AR033								
AR..								
AR..								

\* Comment on the differences in the assays used in the efficacy studies that influenced differences in the LODs especially when the same SOPs were followed and testing was done in the same laboratory.

Jane

Jane A. Dean, RN, MSN  
 Project Manager  
 DAIP/OAP/OND  
 Building 22, Room 6397  
 Office: 301-796-1202  
 Fax: 301-796-9881  
 Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
07/14/2015

**From:** Dean, Jane  
**Sent:** Tuesday, July 07, 2015 5:02 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - information request

Hi, Robin – we have the following information request:

We are unable to locate some information with regard to the ELISA assay for Cynomolgus monkeys-  
Study numbers 2826-100020847 and 1219-100005989

1. Please direct us to the following information for our review, at your earliest opportunity.
  - line data from which linearity testing was validated for reports found in AP202 Appendix K and AP203 Appendix U
  - the stability data for the quality control and standard concentrations of PA for reports found in AP202 Appendix K and AP203 Appendix U
  - the analyte that was used as the negative quality control in the assay for AP203 Appendix U
  - the methodology for determining the absence of cross-reactivity between PA and other molecules within the test sample in protocol report found in AP203 Appendix U
  
2. Please ascertain that line data for all test parameters including linearity and stability are available for all of the other assays used in this BLA. The stability data for PA might be the same for all of the studies performed in this submission. If so, please confirm this information.

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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JANE A DEAN  
07/07/2015

**From:** Dean, Jane  
**Sent:** Monday, June 22, 2015 4:34 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Cindi Dillon (cdillon@elusys.com); Ariane Cutolo (acutolo@elusys.com)  
**Subject:** BLA 125509 (Anthem) - additional information request (clinical)

Hi, Robin – I just received this information request from the clinical reviewer:

In study AH104, you have identified a single subject with a serious adverse event (SAE) – Subject 002-216 – who had a left-sided ovarian cyst for which she required hospitalization. However, the last criterion in your definition of SAE's reads as follows:

- “Jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed above”

Subjects 002-350, 002-053, 002-068, 003-101, 003-107, and 003-258 all had study drug discontinued during the infusion due to an AE, and Subject 003-258 was classified as anaphylaxis. Please explain why these subjects were not classified as having SAE's since they all required medical intervention presumably to prevent a more serious outcome.

Please let me know what your turn around time can be – thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
06/22/2015



BLA 125509

**FILING COMMUNICATION -  
NO FILING REVIEW ISSUES IDENTIFIED**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA) dated March 20, 2015, received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Anthim (obilttoximab), 600 mg/6 mL, single use vial, 100 mg/mL, IV Infusion.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 18, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 23, 2015.

In addition, the planned date for our internal mid-cycle review meeting is August 20, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. In Drug Product (DP) section 3.2.P.3.1, Table 1 no information is provided on manufacturers responsible for the labelling, packaging and re-packaging activities for Anthim. Update DP section 3.2.P.3.1, Table 1 and form 356h in Section 1.1.2 in the BLA to include the name, address and facility establishment Identifier (FEI) of the manufacturers that are responsible for performing the labelling, packaging and re-packaging activities for Anthim.
2. Update form 356h in Section 1.1.2 in the BLA to include name, address and FEI information on the manufacturers responsible for performing adventitious agents testing on oblitoximab master and working cell banks.
3. Case report forms for all patients who withdrew from studies AH101, 102, 104, 105, 106, 109 and 110 for any reason.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments captured in [blue lettering](#):

### **HIGHLIGHTS GENERAL FORMAT**

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. [Top margin is less than ½ inch. Increase to ½ inch.](#)
2. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI. [Insert a horizontal line separating TOC from the Full Prescribing Information \(FPI\)](#)

### **HIGHLIGHTS DETAILS**

### Highlights Limitation Statement

3. 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.

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."

### Indications and Usage in Highlights

4. 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)”. 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)”

### Patient Counseling Information Statement in Highlights

5. 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**”

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

(b) (4)

”

### CONTENTS: TABLE OF CONTENTS (TOC)

6. The TOC should be in a two-column format. The TOC is in a single-column format. Change to a two-column format.
7. In the TOC, all section headings must be **bolded** and should be in UPPER CASE. **Bold Section headings.**

### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

8. 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)*]”.

In the Full 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 “[see *Adverse Reactions (6.1) and Clinical Pharmacology (12.3)*]” instead of [REDACTED] (b) (4)

Under Dosage and Administration subsection 2.3, the cross-reference should read as “[see *Adverse Reactions (6) and Clinical Pharmacology (12.3)*]” instead of “[REDACTED]” (b) (4)

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by June 23, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

Sumathi Nambiar, MD, MPH  
Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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SUMATHI NAMBIAR  
05/22/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

BLA 125509

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Elusys Therapeutics, Inc.  
25 Riverside Drive, Unit 1  
Pine Brook, NJ 07058

ATTENTION: Robin Conrad  
Vice President, Regulatory Affairs

Dear Ms. Conrad:

Please refer to your Biologics License Application (BLA), dated and received March 20, 2015, submitted under section 351(a) of the Public Health Service Act for Obiltoxaximab Injection, 600 mg/6 ml.

We also refer to your correspondence, dated and received April 6, 2015, requesting review of your proposed proprietary name, Anthim.

We have completed our review of the proposed proprietary name, Anthim, and have concluded that this name is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 6, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Jane Dean, Regulatory Project Manager in the Office of New Drugs, at 301-796-1202.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
05/21/2015

**From:** Dean, Jane  
**Sent:** Wednesday, May 20, 2015 1:38 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthem) - information request

Hi, Robin, one of the reviewers has the following information request:

1. Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug substance and drug product samples and then testing for recoverable endotoxin over time. These studies should be conducted in the containers in which the product and samples are held prior to endotoxin testing. Provide the protocol and report for the endotoxin spiking and recovery study results.
2. The labeling in the facility diagrams provided in Section 3.2.A.1, "Facilities and equipment" for the drug substance manufacturing facility is not legible. Provide diagrams of better quality.

Please let me know when you can provide a response. Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
05/20/2015

**From:** Dean, Jane  
**Sent:** Tuesday, May 19, 2015 3:03 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthim) - information request

Hi, Robin, we have another information request:

For study NIAID1045, body weight variable (BWSTRES in define.pdf) cannot be located in the data sets submitted. Please provide the location of this variable or submit data containing the variable body weight.

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
05/19/2015

**From:** Dean, Jane  
**Sent:** Tuesday, May 12, 2015 12:07 PM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthem) - information request

Robin, the clinical reviewer has the following information request:

1. Please provide analyzable electronic ADAE and ADSL datasets and case report forms for studies AH101 and 102.
2. The case report forms for AH104 ( (b) (4) ), AH109 ( (b) (4) ), AH 106 ( (b) (4) ), and AH110 ( (b) (4) ) are each near or over 1000 pages long, and we could not access the actual data (i.e. lab values) through it. Please resubmit these CRF's in a form that allows navigability.

Please let me know what your turn around time will be. Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
05/12/2015

**From:** Dean, Jane  
**Sent:** Tuesday, May 12, 2015 10:01 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthim) - information request

Robin, our clinical microbiology has the following information request:

1. Some of the tests used in the animal efficacy studies such as detection of protective antigen (PA) and anti-PA antibodies are experimental tests. You also refer to (b) (4) IND for (b) (4) for several SOPs. You also included details of the methods and performance characteristics of the assays for quantitation of PA by ELISA. However, performance characteristics of assays used for detecting PA by the ECL assay as well as anti-PA antibodies could not be found. Please clarify if these were included in the BLA submission. If not, electronic copies of the reports should be provided for our review.
2. If any other experimental assays such as PCR or toxin neutralization assays were used in the animal efficacy studies, the details of the method and performance characteristics of the assay in the laboratory where testing was performed should be provided for our review.

Please let me know what your turn around time will be. Thanks!

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
05/12/2015

**From:** Dean, Jane  
**Sent:** Thursday, April 23, 2015 9:59 AM  
**To:** Robin Conrad (rconrad@elusys.com)  
**Cc:** Ariane Cutolo (acutolo@elusys.com); Cindi Dillon (cdillon@elusys.com)  
**Subject:** BLA 125509 (Anthim) - information request

Hi, Robin, the clinical reviewer and statistician have the following request:

We are working with a review tool that is designed to work with multiple data sets in any analysis. In the BLA 125509 submission, after reading into a program, such as SAS, all datasets have the same dataset name, 'PCDATA', for all 26 studies in the non-clinical data. Although the SAS transport file i.e., DM.XPT looks like it is named DM, the actual dataset name is "PCDATA", as are all the datasets. Please modify the datasets names so that they have the same names as the xpt file names.

Thanks, Robin.

Jane

Jane A. Dean, RN, MSN  
Project Manager  
DAIP/OAP/OND  
Building 22, Room 6397  
Office: 301-796-1202  
Fax: 301-796-9881  
Email: [jane.dean@fda.hhs.gov](mailto:jane.dean@fda.hhs.gov)

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/s/  
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JANE A DEAN  
04/23/2015



IND 012285

**MEETING MINUTES**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ETI-204.

We also refer to the meeting between representatives of your firm and the FDA on July 30, 2013. The purpose of the meeting was to discuss your upcoming pre-BLA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

Sumathi Nambiar, MD, MPH  
Acting Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** July 30, 2013, 11:00am – 12:00pm  
**Meeting Location:** Building 22, Conference Room 1421  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

**Application Number:** IND 012285  
**Product Name:** ETI-204  
**Indication:** Evaluation in healthy volunteers for eventual use in the treatment of inhalational anthrax and as a prophylactic agent

**Sponsor/Applicant Name:** Elusys Therapeutics, Inc.

**Meeting Chair:** Sumathi Nambiar, MD, MPH  
**Meeting Recorder:** Jane A. Dean, RN, MSN

### FDA ATTENDEES

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

John Alexander, MD, MPH	Clinical Team Leader
Shukal Bala, PhD	Clinical Microbiology Reviewer
Kimberly Bergman, PharmD	Clinical Pharmacology Team Leader
Edward Cox, MD, MPH	Director, Office of Antimicrobial Products (OAP)
Jane A. Dean, RN, MSN	Regulatory Health Project Manager
John Farley, MD, MPH	Deputy Director, OAP
David Frucht, MD	Product Quality Team Leader
Karen Higgins, ScD	Statistics Team Leader
Seong Jang, PhD	Clinical Pharmacology Reviewer
Katherine Laessig, MD	Deputy Director
Naseya Minor, MPH	Project Manager
Sumathi Nambiar, MD, MPH	Acting Director
Amy Nostrandt, DVM, PhD	Pharmacology/Toxicology Reviewer
Elizabeth O'Shaughnessy, MD	Clinical Reviewer
David Roeder	Associate Director of Regulatory Affairs, OAP
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Kerry Snow, MS	Acting Clinical Microbiology Team Leader
Barbara Styr, MD	Medical Officer (OAP)
Lan Zeng, MS	Statistical Reviewer

**Office of Counterterrorism and Emergency Coordination (OCTEC):**

Jerry Davis, DVM	Veterinary Medical Officer
Gerald Poley, MD	Medical Officer
Rosemary Roberts, MD	Director
Andrea Vincent, PharmD, JD	Pharmacist

**SPONSOR ATTENDEES**

**Elusys Therapeutics, Inc.:**

Leslie Casey, PhD	Vice President, Research
Robin Conrad, MS	Vice President, Regulatory Affairs
Ariane Cutola	Senior Manager, Regulatory Affairs
Cindi Dillon	Director, Regulatory Affairs
Marion McGlynn, MS	Senior Director, Project Management
Natalya Serbina	Senior Scientist, Nonclinical
Annette Shadiack, PhD	Senior Director, Nonclinical
Brent Yamamoto	Senior Scientist

**Biomedical Advanced Research and Development Authority (BARDA):**

Chia-Wei Tsai, PhD	Project Officer
James Wangelin, MS, RAC	Senior Regulatory Advisor

**Consultant:**

(b) (4) MD, FCCP	Consultant
(b) (4), PhD	Statistician

**1.0 BACKGROUND**

On June 13, 2013, Elusys Therapeutics, Inc., hereafter referred to as Elusys, requested a Pre-BLA meeting. The meeting was granted and scheduled for July 30, 2013. Elusys submitted a meeting package on July 1, 2013 which included specific questions. The Division informed Elusys that the focus of the Pre-BLA meeting would be on the need for additional studies rather than the questions in the meeting package. Preliminary responses on the topic were sent to Elusys on July 26, 2013 and included topics that would be discussed at the meeting. Responses to questions in the meeting package will be addressed at a later date.

**2. DISCUSSION**

After introductions, the meeting was turned over to Elusys. The discussion was based on the following comments sent via email on July 26, 2013:

**FDA Preliminary Response sent via email on July 26, 2013:** On July 30<sup>th</sup>, we would like to discuss your July 15, 2013 submission regarding an additional animal efficacy study.

Specifically, we would like to discuss the proposal for an additional study of the efficacy of IV treatment in the cynomolgus monkey model. This should be a “trigger to treat” study of intravenous ETI-204, with the primary objective of demonstrating a statistically significant difference between placebo and ETI-204 (Lonza product). We still recommend the inclusion of a third arm (Baxter product) with equal numbers of animals as the Lonza Product arm. We consider this within-study comparison of the Lonza and Baxter lots to be important, because of the variable mortality outcomes seen across the treatment studies. If for logistical reasons it is not feasible to conduct the three arm study in cynomolgus monkeys, you would still have the option to conduct the three arm study in rabbits, but the additional information you provided (study AR034 in particular) makes another rabbit study less desirable. During the meeting, we’d like to discuss some general aspects of the proposed study and when you think the study could be conducted/completed relative to your clinical program.

We strongly encourage you to submit the protocol for the animal efficacy study for a special protocol assessment.

We recommend that you complete all the animal studies before you submit a rolling BLA. Therefore the questions you submitted on 7/1/2013 will be addressed at a future pre-BLA meeting; however, we have the following general comments which may help you in preparing study reports and datasets for clinical studies and animal efficacy studies.

### **Clinical Studies**

1. Clinical datasets should be submitted as SAS transport files per CDISC standards.
2. We recommend that you also provide case report forms for human subjects who died, experienced a serious adverse event or discontinued due to an adverse event. Please also include case report forms for subjects who experienced allergic/hypersensitivity reactions. Provide narratives for subjects who died, experienced an SAE, withdrew from the human clinical studies, or experienced allergic/hypersensitivity reactions.
3. Financial disclosure certification information should be submitted for all of the clinical studies.

### **Animal Studies**

4. We would like to request analysis data sets and summary tables for evaluation of clinical and microbiological response at different time points for each animal efficacy study. We encourage you to provide templates for summary tables and datasets for our review. The following are some suggestions for measurements to be included in analysis datasets and summary tables for evaluation of clinical and microbiological response by animal at different time points in an efficacy study:

- Body weight.
- Inoculum size (CFU and LD<sub>50</sub>) delivered via aerosol.

- Clinical observations - signs and or symptoms of illness: Provide tabulation of animal activity over the study period, documenting behavior, and appetite, and response to stimuli at each time point when observations were collected from baseline to euthanasia or death.
  - Information on the time to the trigger-to-treat in relation to time of aerosol inhalation and start of treatment.
  - Blood cultures: *B. anthracis* CFU/mL for each animal at baseline, during treatment and follow-up including date and time when the samples were collected.
  - PA findings: PA results for each animal at baseline, during treatment and follow-up including date and time when the samples were collected.
  - Anti-PA antibodies: Anti-PA antibodies for each animal at baseline, during treatment and follow-up including date and time when the samples were collected.
  - Outcome (death/survival).
  - Gross Pathology: Include culture results for specific organs.
5. We recommend that temperature/heart rate/respiratory rate /blood pressure measurements should be presented as averages (SD and range) for each hour for each animal within a study. We request that you provide a summary of vital sign results in the final study report for each study.
  6. In your final study report, please include histopathology data for individual animals and a summary table describing the specific findings (e.g., severity, extent and nature of histologic changes, utilizing a standard scale) in each organ examined.
  7. In your final study report, please include complete medical record/surveillance record that was used to collect data for each animal used in the study during the screening/quarantine period; the complete medical record should provide the information on everything that occurred to the animal prior to entry into the study (e.g., prior infections, vaccinations, screening for pathogens including culture for *B. anthracis*, presence of PA and anti-PA antibodies, when anesthetized, any medications administered, etc.). Also, indicate whether the animals that were used are “experimentally naïve” or if the animals were previously used in any other experimental study(ies).
  8. SOPs and performance characteristics of the assays used for blood culture, detection and quantitation of PA, toxin neutralization assays, anti-ETI-204 antibody titers, etc. should be included.
  9. The source of the *B. anthracis* strain used for efficacy studies in rabbit and nonhuman primates should be specified and details of the methods used for preparation of inoculum for challenge and aerosolization should be included.
  10. Information on natural history studies conducted in New Zealand White rabbits and cynomolgus monkeys should be included in your BLA submission.

### Meeting Discussion:

Elusys stated that they understood the need for a nonhuman primate study as outlined by the Division. They asked for clarification regarding the Division's preference for a three-arm study in nonhuman primates. The Division said that there appeared to be less need for another study in rabbits because Study AR034 evaluated the survival outcome of the Lonza product IV (ETI-204 16mg/kg) in rabbits. The Division's major concern was the variability in survival outcomes, at comparable time points, for the Baxter and Lonza products across the nonhuman primate studies, AP201 (Baxter), AP204 (Baxter), and AP203 (Lonza). Elusys indicated their preference would be to conduct a three-arm study in rabbits and a two-arm study in nonhuman primates. The Division clarified that they would expect the study to be powered to show superiority of Lonza product over placebo. While the Division recommends a comparably sized arm given the Baxter product, the Division would not expect the study to be powered as a non-inferiority study comparing the Lonza product and Baxter product. The Division would be concerned if there was a large difference between the Lonza and Baxter arms in terms of the point estimates. Elusys stated concerns regarding the ambiguity of the assessment of the Lonza product versus the Baxter product.

The Division stated that one trigger-to-treat study of intravenous ETI-204 in the nonhuman primate could capture data addressing all of the concerns related to the variability in survival rates in the completed nonhuman primate treatment studies. An evaluation of the two products within one study would facilitate the detection of a difference in the survival rates of the Lonza versus the Baxter product. Given the current study results, it is not clear if there is a real difference in the cure rates of the Lonza versus the Baxter products. To help address this, Baxter and Lonza products should be compared in one trial. Elusys raised concern about the difficulty of powering a study in nonhuman primates that compared the Lonza versus the Baxter product. The Division suggested another option for Elusys to consider would be to conduct a three-arm study in rabbits and a two-arm study in nonhuman primates. Elusys raised concerns regarding designing a study for which one or two survivors in the placebo arm may impact statistical significance. Elusys calculated that 30 nonhuman primates per arm would be adequate. The Division commented that 30 nonhuman primates per arm was large compared to other efficacy studies conducted under the animal rule and suggested 12 to 18 monkeys per arm.

The Division agreed that it is challenging to balance the concerns of reducing the number of nonhuman primates and having adequate power to provide interpretable results. Elusys questioned if there was an adaptive design that could be used. The Division mentioned that it might be possible to assess the study for futility after the first blocks of animals have completed the study.

Elusys was asked if all the nonhuman primates were naïve prior to enrollment in Studies AP201, AP204, and AP203. Elusys stated that all the animals were naïve and all animals were negative for PA antibodies using a PA test developed by Elusys and cultures for *B. anthracis* were negative during the screening process.

The Division recommended that Elusys submit a Special Protocol Assessment so that feedback could be provided.

Elusys stated that they anticipate the nonhuman primate study could start in early 2014 and that they were still interested in submitting a rolling BLA starting with the product quality section. Elusys would still like to obtain the Division's responses to their questions in the meeting package that addressed the format of the BLA submission and other technical questions not related to specific protocols. The Division agreed to provide these comments.

The Division suggested that Elusys look retrospectively at all the animal studies they have conducted and consider how their processes could be changed in the future so that nonhuman primates and rabbits are used in the most efficient manner. The Division stated that Elusys has conducted a tremendous number of studies and that it is very important that animal studies be done in a very careful manner in order to answer specific questions and use animals efficiently. The meeting concluded with the Division offering to work with Elusys to develop a protocol that would use animals efficiently and obtain the necessary information.

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

#### **5.0 ACTION ITEMS**

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
Meeting minutes will be provided within 30 days	FDA	August 29, 2013
A Special Protocol Assessment will be submitted	Elusys	TBD

#### **6.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUMATHI NAMBIAR  
08/28/2013



IND 012285

**MEETING MINUTES**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Executive Director, Regulatory Affairs  
25 Riverside Drive, Suite 1  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ETI-204.

We also refer to the meeting between representatives of your firm and the FDA on March 15, 2013. The meeting was an End-of-Phase 2 meeting to obtain Agency concurrence on Phase 3 development plans.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

John Farley, MD, MPH  
Acting Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** End-of-Phase 2

**Meeting Date and Time:** March 15, 2013, 11:00 am – 12:00 pm  
**Meeting Location:** Building 22, Conference Room 1419  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

**Application Number:** IND 012285  
**Product Name:** ETI-204  
**Indication:** Inhalational *Bacillus anthracis* infection  
**Sponsor/Applicant Name:** Elusys Therapeutics, Inc.

**Meeting Chair:** John Farley, MD, MPH  
**Meeting Recorder:** Jane A. Dean, RN, MSN

### **FDA ATTENDEES**

#### **Division of Anti-Infective Products (DAIP):**

John Alexander, MD, MPH	Clinical Team Leader
Lynette Berkeley, PhD	Clinical Microbiology Reviewer
Jane A. Dean, RN, MSN	Regulatory Health Project Manager
John Farley, MD, MPH	Acting Director
Karen Higgins, ScD	Statistics Team Leader
Seong Jang, PharmD	Clinical Pharmacology Reviewer
Katherine Laessig, MD	Deputy Director
Naseya Minor, MS	Regulatory Health Project Manager
Amy Nostrandt, DVM, PhD	Pharmacology/Toxicology Reviewer
Sumathi Nambiar, MD, MPH	Deputy Director For Safety
Elizabeth O'Shaughnessy, MD	Clinical Reviewer
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Kerry Snow, MS	Microbiology Team Leader
Barbara Styr, MD	Deputy Director, Medical Countermeasures, OAP
Chen Sun, PhD	Product Quality Reviewer
Trang Trinh	Pharmacy Student
Tao Xie, PhD	Product Quality Reviewer
Lan Zeng, PhD	Statistics Reviewer

#### **Office of Counterterrorism and Emergency Coordination (OCTEC):**

Susan McDermott, MD	Medical Officer
Gerald Poley, MD	Medical Officer
Andrea Vincent, PharmD, JD	Pharmacist

**SPONSOR ATTENDEES**

**Elusys Therapeutics, Inc.:**

Leslie Casey, PhD	VP Research
Robin Conrad, MS	Executive Director, Regulatory Affairs
Ariane Cutolo	Senior Manager, Regulatory Affairs
Stephen J. Haworth, MD	VP/Chief Medical Officer
Marion McGlynn, MS, MBA	Senior Director, Project Management
Christa Nagy, PhD	Director, Clinical Operations
Elizabeth Posillico, PhD	CEO
Annette Shadiack, PhD	Sr. Director, Nonclinical

(b) (4)	(b) (4)
(b) (4)	President/Chief Executive Officer Principal Scientist

**Biomedical Advanced Research and Development Authority (BARDA):**

Michael Merchlinsky, PhD	Subject Matter Expert
Chia-Wei Tsai, PhD	Project Officer
James Wangelin, MS, RAC	Senior Regulatory Advisor

(b) (4)	:
(b) (4)	Sr. Research Scientist

**1.0 BACKGROUND**

Elusys requested an End of Phase 2 meeting on January 7, 2013. The meeting was granted and scheduled for March 15, 2013. The meeting package arrived February 1, 2013. The Division prepared preliminary responses to the questions and sent them to Elusys on March 13, 2013 via email (see Attachment 1).

**2. DISCUSSION**

The meeting, which began with introductions of all attendees, was turned over to Elusys. Elusys said they would focus the discussion on Questions 3 – 7 and Question 13.

**Question 3A**

Elusys requested agreement that the proposed pivotal animal efficacy studies, AR022 and AP202, were adequately designed to support the indication of treatment of inhalational anthrax due to *Bacillus anthracis* in combination with other drugs. The Agency noted that a large number of animal studies have already been completed. The Agency also clarified that the statements in the preliminary response related to “formulation” were intended to refer to manufacturing process changes for the proposed product. Elusys is currently planning a separate

meeting to discuss the product quality studies for the comparability of the current product with the original product.

The Agency suggested that Elusys consider submitting their animal efficacy studies with the animal toxicity studies in a preBLA submission as a rolling review. In that way, the reviewers would be able to start evaluating the studies and determine if they are adequate. In the meantime, Elusys could proceed with their clinical program. The application already has Fast Track designation, allowing a rolling submission, and has orphan product designation, so there would be no user fee implications. The Agency would typically expect that the modules be complete, but is willing to explore the possibility of a partial submission of the non-clinical module. The Agency suggested that a pre-BLA meeting be planned; this would give the review team the chance to provide input on the overall submission contents. The Agency noted that Elusys already has a good start with their summaries in the most recent submission which provided the status of each study. During the discussion, it was noted that datasets for the animal efficacy studies would be needed and preparation of some datasets could involve a substantial amount of work. The pre-BLA submission would need to clearly identify the product lots used in each of the animal efficacy studies.

#### Question 3B

Elusys asked about the design of their protocols. The Agency had a question about the immune status of the animals. The survival of a number of placebo-treated animals observed in the nonhuman primate studies may not be fully explained by differences in the quantity of bacteria in the blood of the animals. The possibility exists that the monkeys could have been exposed to related bacterial species that may share immunological epitopes with *B. anthracis* and the animals may not have been truly naïve even though routine screening with an ELISA to protective antigen (PA) did not demonstrate evidence of immunity to *B. anthracis*. A single assay to detect antibodies to PA might be inadequate to detect partially immune animals so additional screening is recommended. Elusys stated that they would consider the suggestion. The Agency also suggested that Elusys explore the idea of validating the assay they would use for screening of nonhuman primates. Elusys stated that unlike previous studies where subjects were randomized prior to anthrax exposure, the new pivotal trials will randomize subjects when disease symptoms occur. The Agency raised a concern about blinding in previous studies, most of which had dosing vials marked as either “X”, “Y”, or “Z”. These would essentially allow one to know if a particular animal is assigned to group “X”, “Y”, or “Z” and it is easy to separate out the three groups of animals. The Agency would not consider this completely blinded. In pivotal trials, the treatment assigned to each and every animal needs to be blinded and not labeled in any way that would distinguish one group of animals from another. Elusys stated that “blinding by group” had been in place for the past 4 years.

There was some discussion of whether Elusys intended to include both IV and IM administration of ETI-204 in their initial BLA submission. The Agency stated that proof of efficacy at a lower exposure would be supportive of efficacy at a higher exposure. However, the differences in pharmacokinetic profile for IM compared to IV administration (in animals or humans) could affect whether animal efficacy studies conducted using IV administration would support IM administration in humans. The Agency suggested that if additional animal studies are needed to

evaluate the current product, then studies of IM administration may be the most efficient use of animals. The Agency recommended that Elusys focus on completing the clinical intravenous studies first and then proceed to the intramuscular studies.

#### Question 4

Elusys asked for comment on their plan for subject selection in the planned human pharmacokinetic and safety trials. The Agency requested clarification on whether subjects with asthma or a history of allergies would be included in the trials. Elusys responded that subjects with these comorbidities will not be excluded and each subject's medical history will be recorded. Elusys clarified that they intend to monitor subjects for a full 24 hours after intravenous administration of ETI-204 in each of the three human trials.

#### Question 5

Elusys stated their reason for performing an assessment of the first 20 patients in the repeat dose study was in the interest of safety. This was acceptable to the Division. Elusys agreed to add stopping criteria to the protocol.

#### Question 6

Elusys sought further clarification regarding the design of the ciprofloxacin drug-drug interaction study. The Agency reiterated the major points in the preliminary response which was that 50 subjects would likely be more subjects than necessary for such a study. Elusys stated that the number of patients proposed in Study AH110 was calculated to show no drug interaction between ciprofloxacin and ETI-204 based on the PK variability of ETI-204. The Agency recommended that the number of patients be reduced because there is no known mechanism-based rationale to expect an interaction between ciprofloxacin and ETI-204. In addition, Study AH1-1, a drug-drug interaction study of ETI-204 114 mg and ciprofloxacin 500 mg did not demonstrate an interaction. Elusys agreed to revise the protocol accordingly.

#### Question 7a

Elusys asked about additional drug-drug interaction studies. The Agency recommended that Elusys evaluate the effect of ETI-204 on the cytokines that can affect the expression of CYP450 enzymes. The Agency recommended collecting blood samples before and after dosing for both the treatment group and the placebo group in order to evaluate the changes in cytokine concentrations. Elusys agreed to the Agency's recommendation.

#### Question 7b

Elusys asked about the effect of ETI-204 on the immunogenicity of the anthrax vaccine. If Elusys intends to include a prophylaxis indication, then such studies would be necessary.

#### Question 13

With respect to the need for additional nonclinical studies, the Agency noted that tissue studies needed to be GLP-compliant. Elusys stated they were. The last submission with the summaries of all the studies did not indicate that they were GLP-compliant. Elusys will make the necessary correction to reflect GLP-compliance.

Elusys plans to start studies in human subjects this year, late June or July. Originally, they were targeting the BLA submission for the end of 2014 but if they chose to submit as a rolling review, the timeline will be changed.

**Post-meeting note:** On March 20, 2013, a brief, informal teleconference took place between John Alexander, Jane Dean and Robin Conrad. The purpose of the call was to determine if there was still a need to have the added benefit teleconference scheduled for March 29, 2013 after Elusys received the suggestion for submitting the BLA as a rolling submission. Dr. Alexander explained the Agency's rationale for Elusys to submit their BLA as a rolling submission. The Agency would need to review the rest of the studies to make a determination if an added benefit study would be required. The intent of such a study would be to assess the lack of interference of ETI-204 with other antibacterial drugs. Should Elusys decide to submit the BLA as a rolling submission, the Agency would provide comments that might determine the need for an added benefit study as quickly as possible. The concern of Elusys was that it takes one and a half years to set up another study using nonhuman primates. These issues could be worked out in a preBLA meeting. Elusys stated they were hoping to submit information in the BLA on both the IV and IM administration of the drug. However, they do not have the data yet on how to translate this to humans. (b) (4)

They would not have to provide nonclinical summaries with final study reports but they will need to include datasets for all of the efficacy studies which they would have to obtain from NIH. The Agency recommended that Elusys request a preBLA meeting. Elusys withdrew their request for the telecon scheduled for March 29, 2013.

### 3.0 ISSUES REQUIRING FURTHER DISCUSSION

Additional issues that require discussion are: how a rolling submission will be conducted and what would be required within the module(s) submitted.

### 4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Minutes will be sent to Elusys	FDA	April 14, 2013
Elusys will explore the option of submitting the application as a rolling submission.	Elusys	To be determined
Elusys will request a pre BLA meeting with the Agency	Elusys	To be determined
Review study reports submitted to date and provide feedback to Elusys based on that review	FDA	To be determined
Elusys will have an End-of-Phase 2 meeting with the product quality team	Elusys	May 7, 2013

## **5.0 ATTACHMENTS AND HANDOUTS**

Attachment 1: Preliminary responses to meeting questions sent on March 13, 2013.

**From:** Dean, Jane  
**Sent:** Wednesday, March 13, 2013 2:17 PM  
**To:** 'Robin Conrad'  
**Cc:** Cindi Dillon; Ariane Cutolo  
**Subject:** IND 012285 (ETI-204) - revised preliminary comments to 3/15/13 meeting questions

**Importance:** High

Robin, below are the revised responses to your meeting questions. Please be advised that any new information or data not contained in your meeting package and presented in response to these comments will not be considered for official comment at the scheduled meeting. The information may be very briefly presented, but must be provided as a submission to the application subsequent to this meeting to allow an opportunity for appropriate review and comment.

In preparation for our upcoming meeting, please be advised that the official advice and recommendations of this division will be communicated during the formal dialogue of our upcoming meeting. Any conversations before or after the official meeting will not reflect the decisions or agreements of the division and thus will not be reflected in the official meeting minutes. If follow-up or clarification on a particular issue is required, those issues should be discussed during the meeting or can be pursued through the formal meetings process in a subsequent meeting or teleconference.

If you wish to change this meeting to a telecon, please contact your Project Manager. If you wish to cancel this meeting, the following responses will become part of the administrative record. Submit your cancellation by letter to your application and contact your Project Manager.

If you wish to discuss another application, the official meeting process should be followed as outlined in the May 2009 "*Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*".

### **1.1. ETI-204 Dose Selection**

#### **Question 1**

Based on the results of a survival model to describe the dose-response and exposure-response for ETI-204 in anthrax-infected rabbits and monkeys, Elusys is proposing to evaluate an ETI-204 dose of 16 mg/kg IV in the pivotal nonclinical efficacy studies. Does FDA agree with the dose selection for the Phase 3 nonclinical studies?

**FDA Response to Question 1:** Yes, we agree with your dose selection (i.e.16 mg/kg IV).

## Question 2

A dose of 16 mg/kg is proposed for the clinical studies based on a bridged human population PK model that was used as a simulation tool to derive a human dose with exposure that meets or exceeds the predicted efficacious dose in monkeys. Does FDA agree with the dose selection for the Phase 3 clinical studies?

**FDA Response to Question 2:** Yes, we agree with your dose selection. However, it should be noted that a human dose that yields exposure that exceeds (rather than meets) the predicted exposures with the effective dose in animals is preferred (as long as it has acceptable safety profile in humans) in order to ensure efficacy in humans.

## 1.2. Pivotal Efficacy Studies

### Question 3

A. Does the FDA agree that Studies AR022 and AP202 are adequately designed to support the following indication:

ETI-204 is indicated for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs.

**FDA Response to Question 3A:** The designs of Study AR022 (efficacy study in New Zealand White rabbits) and Study AP202 (efficacy study in Cynomolgus monkeys) appear adequate and we agree with the proposed indication. However, we believe that these studies are premature, especially if you do not yet have a final formulation for your product. Additionally, depending on the CMC review for comparability between the final formulation and the formulation conducted in previous trials, it might be possible to rely on some of the previously conducted trials to support the efficacy of the product. At our meeting, you should be prepared to discuss the extent of the differences in the product used in the previous studies reported in tables submitted to the Agency on 3/6/13 and the product that you are proposing to use in the additional studies.

We would like to have a discussion with you regarding your entire development plan in order to determine how best to utilize resources prior to you conducting your proposed two large pivotal monotherapy animal studies and an additional added-benefit study in

rabbits. Please note that we support the full implementation of the Animal Welfare Act and in particular the three R's of reduce, refine and replace. We believe that it might be possible either to rely on information from previously conducted studies and/or to reduce the planned size of your future studies.

We would like to ask for additional information about how the rabbit study, AR022, will differ from studies AR021 and AR033 and how the monkey study, AP202, will differ from study AP204. Those three previously conducted studies showed significant results of the 16 mg/kg dose compared to placebo. Studies 1030, AP201, and 1056 also provide supportive evidence of a lower dose. What information will be obtained from studies AR022 and AP202 that was not obtained from the previous studies? For instance, was there a problem with the study conduct in the previous trials, were the studies randomized and blinded, did the previous studies use the final formulation of ETI-204, was adequate histopathology obtained, and was the timing of the treatment trigger different?

- B. Does the FDA have any comments regarding the design of Studies AR022 and AP202? Specifically, can FDA comment on the following:
- Primary and additional efficacy endpoints
  - Randomization and blinding
  - Sample size calculations
  - Statistical analyses and populations
  - Safety monitoring

Does the Agency agree that Studies AR022 and AP202 qualify for and can be submitted for SPA following this meeting?

**FDA Response to Question 3B:** The following are some specific comments for these planned protocols. However, prior to implementation, we believe additional information is needed.

We note that you screened all animals in your completed studies for the presence of antibodies to PA to evaluate for prior immunity to *B. anthracis*. This may not be sufficient to guarantee that all animals are naive based on the survival rate in the placebo arm in Study AP203 and AP204. The immune status of the animals prior to exposure to the challenge agent is likely to influence the progression of disease and response to treatment. These alterations in immune responses may have been initiated by pre-exposure to the causative agent, or cross-reactive antigens, as well as alterations in microbiota by prior treatment with antibiotics. To adequately detect animals with a pre-existing specific or nonspecific immunological reaction to the challenge agent requires evaluation of both humoral and cellular immune responses to as many epitopes as

possible. Sensitive assays are available to measure both T-cell and B-cell immune responses and should be validated. We would like ask for your perspective on the feasibility of performing additional screening for both T-cell and B-cell immune responses to *B. anthracis* in Studies AR022 and AP202.

- We would also like to discuss the number of animals in Study AP202 and AR022. We note that there are 30 monkeys in the placebo arm in Study AP202. We recommend that you consider an alternate (such as 2:1) randomization scheme in order to reduce the number of monkeys in the placebo arm and possibly in the overall study.
- To reduce the chance of inadvertently revealing treatment assignment for some animals, we recommend that you consider larger block sizes or the use of random block sizes to randomize the order of the treatment vials.
- Please note that we will be interested in any parameter that might affect survival, such as the LD50 dose of aerosolized inhaled *B. anthracis*, quantitative bacteremia, protective antigen (PA) levels, and/or other signs and symptoms.
- You state that since the frequency of measurement for treatment triggers is different, i.e., SIBT (hourly) and PA-ECL (every six-hour), the order of treatment will be the following in attempt to balance the disease state in both treatment groups.
  - The chronological order animals trigger for treatment (e.g. positive PAECL or SIBT).
  - In the case where animals trigger for treatment at the same time point, the treatment order will be determined by the trigger type, animal triggered by ECL positive will be treated first.
  - In the case where animals trigger for treatment at the same time point by the same type of trigger, then the treatment order will be determined by the challenge order.

It is not clear how these steps will balance disease state by treatment group. Please clarify.

C. Besides the protocol, does the Agency need additional information for the SPA?

**FDA Response to Question 3C:** We agree to a SPA for your pivotal efficacy protocols, however it is important that we discuss your clinical development plan prior to submission of a SPA. Please note that a SPA submission should contain specific questions for the Division on the aspects of the protocol requiring agreement. Your statistical analysis plan should be finalized and submitted along with the protocol for the SPA.

### 1.3. Clinical Studies

#### Question 4

Elusys proposes to conduct the Phase 3 safety program with a consistent approach to subject selection, study procedures, assessments, and restrictions for the planned clinical studies AH104, AH109, and AH110.

- a. Does the FDA have any comments on the subject selection criteria?

**FDA Response to Question 4a:** We note that you plan to enroll patients with stable comorbid diseases. Please clarify if you plan include patients with asthma and/or a history of atopy?

- b. Does the FDA consider the proposed safety and tolerability assessments appropriate?

**FDA Response to Question 4b:** The proposed safety and tolerability assessments, in general, appear appropriate. Please clarify if patients will be monitored for a full 24 hours after administration of ETI-204 IV in each of the three protocols.

### Question 5

Does the FDA have any comments regarding the design of the proposed repeat-dose study AH109? Specifically, can FDA comment on the following:

- Timing of the repeat dose
- Sample size and analysis plan as specified in the protocol
- Planned blinded safety review

**FDA Response to Question 5:** The timing of the repeat dose of ETI-204 at 14 days and 120 days is acceptable. Please provide more detail on how you plan to conduct the blinded safety review and include a rationale for pausing after the initial 20 patients, so that we can provide comments. Please include stopping criteria in the protocol.

### Question 6

Does the FDA have any comments regarding the design of the ciprofloxacin drug-drug interaction study AH110? Specifically, can FDA comment on the following:

- Sample size and analysis plan as specified in the protocol
- Ciprofloxacin dosing regimen

Can the agency confirm that no other ETI-204 antibiotic interaction studies are required?

**FDA Response to Question 6:** We recommend that you reduce the number of patients in the drug interaction trial to approximately 20 patients and consider increasing the number of patients in the single-dose, safety and tolerability and pharmacokinetic study, AH104. We do not agree with the proposed dose of [REDACTED] (b) (4). The recommended dose for severe complicated lower respiratory tract infections is 750 mg PO q12 hours and this dose is equivalent to 400 mg IV q 8 hours based on an equivalent AUC. The potential adverse effects of ciprofloxacin (and quinolones in general) and the possibility of antibiotic-associated diarrhea should be explained in the informed consent form. The protocol should include a strategy to manage patients who develop antibiotic-associated diarrhea. Please also include stopping criteria in the protocol.

#### **Question 7**

a. Except for Study AH110, Elusys has no plans for additional clinical drug-drug interaction studies. Can the Agency confirm that no additional clinical drug interaction studies are required to support the following indication?

ETI-204 is indicated for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs.

**FDA Response to Question 7a:** Yes, we agree. However, we suggest you evaluate the effect of ETI-204 on the cytokines (e.g., interleukins) that can affect the expression of CYP450 enzymes.

b. Can the Agency confirm whether a study examining the effect of ETI-204 on the immunogenicity of the anthrax vaccine is required at time of filing to support the following indication?

ETI-204 is also indicated for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

**FDA Response to Question 7b:** We do not require a study at time of filing. However, you will be required to conduct a study of the effect of ETI-204 on the immunogenicity of the anthrax vaccine if ETI-204 receives approval for a prophylaxis indication.

### **Question 8**

Does the FDA have any comments regarding the design of study AH104? Specifically, can the FDA comment on the sample size and analysis plan?

**FDA Response to Question 8:** The general design of Study 104 (single-dose, safety and tolerability and pharmacokinetic study in healthy human subjects), appears appropriate. Please see the response to Question 6; we recommend increasing the sample size for this safety study, while reducing the sample size for study AH 110.

### **Question 9**

Does the FDA agree that the clinical studies (AH104, AH109, and AH110) are sufficient in design and size to support the following indication and inclusion of the data in the Clinical Trials section of the Prescribing Information?

ETI-204 is indicated for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs.

**FDA Response to Question 9:** We do not agree with the planned size of Study AH110. Please refer to the responses to questions 4 through 6.

The Clinical Studies section of the Prescribing Information for ETI-204 will not contain data from these human safety and tolerability/pharmacokinetic studies. Data from these studies will be included in the *Warnings and Precautions*, *Adverse Reactions*, and *Clinical Pharmacology* sections of the label. The *Clinical Studies* section will contain a

summary of the pivotal efficacy studies in animals. As an example, please refer to the Prescribing Information for raxibacumab injection.

**Question 10**

Does the Agency have any comments regarding the proposed approach to address pediatric dosing recommendations at the time of BLA filing?

**FDA Response to Question 10:** We do not have any comments at this time. Your approach to address a pediatric dosing regimen is acceptable.

**1.4. Safety Database for Registration**

**Question 11**

Does the FDA agree that the proposed size and scope of the clinical safety database is adequate for registration?

**FDA Response to Question 11:** We generally recommend a minimum safety database of 300-500 human subjects at the intended therapeutic dose; therefore, your proposal for a safety database of 350 human subjects at the proposed dose of 16 mg/kg ETI-204 is sufficient for submission in an NDA for the proposed indication. We note that there is additional safety information for 150 human subjects who received a range of doses of ETI-204 in the safety database.

Please be aware that if unexpected adverse reactions occur during the planned human studies, additional safety evaluations may be warranted.

**1.5. Nonclinical Safety Pharmacology and Toxicology**

**Question 12**

Elusys proposes that the neuropathological assessments conducted to date demonstrate that the acute inflammatory reaction observed in nonsurvivors treated with ETI-204 is

due to the presence of extravascular bacteria and the lack of findings in survivors or uninfected animals suggest no deleterious effect of ETI-204. Therefore, additional neuropathological analysis of brains from future nonclinical studies would not be informative. Does the Agency agree that additional neuropathological assessments aren't necessary?

**FDA Response to Question 12:** It is advised that tissues continue to be collected for detailed neuropathological analysis in the event that further special neuropathological examination (above and beyond standard histopathology examination) is needed in the future.

It is unclear why the majority of non-survivors have pathological signs consistent with hemorrhagic meningo-encephalitis while a lower percentage of non-surviving control animals are similarly affected. Unless further neuropathology assessment could explore reasons to explain this increased incidence and/or severity of neuropathological findings, it does not seem necessary to continue with these detailed assessments at this time. However, routine post-mortem histopathology should be performed to monitor the incidence of CNS involvement in ongoing and future studies.

### **Question 13**

a. Does the FDA agree that no additional ETI-204 nonclinical safety pharmacology or toxicology studies are needed to support registration for the following proposed indication?

ETI-204 is indicated for the treatment of adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs.

**FDA Response to Question 13a:** We refer you to ICH M3 (R2) and ICH S6 for information regarding the types of studies needed to support a marketing application.

Tissue cross-reactivity studies should be GLP-compliant. If these show no binding to human or test animal tissues, then it is possible that the general toxicology studies performed to date may be sufficient, providing that the dose and dosing regimen in the toxicology studies cover the proposed clinical dose and dosing regimen with an acceptable margin of safety.

It should be noted that the standard core battery of safety pharmacology studies normally should include CNS and respiratory evaluation. When you file your NDA, you should include a justification why these studies were not performed or were not needed.

If significant levels of impurities are present, these may need to be characterized in GLP toxicology studies.

b. Does the FDA agree that no additional nonclinical safety pharmacology or toxicology studies are required to support the following prophylaxis indication?

ETI-204 is also indicated for prophylaxis of inhalational anthrax when alternative therapies are not available or are not appropriate.

**FDA Response to Question 13b:** See response to question 13a above.

#### **Question 14**

Elusys has developed appropriate bioanalytical methods to support the planned Phase 3 program. Does the Agency have any questions or concerns with the planned methods?

**FDA Response to Question 14:** In general, your approach and methodology are appropriate. However, we would like to emphasize the following:

- It is important to use appropriate quality controls (QC)s.
- QC values must fall within previously chosen acceptable limits.
- QC results must be submitted to the Agency along with the test results.

In addition, you have previously provided partial validation data for the immunoassay used for the detection of anti-ETI-204 antibodies in normal human serum (SN95; August 02, 2012). However, the complete validation of the ECL immunoassay for the detection of anti-ETI-204 antibodies has not yet been provided to us for review. In addition, you have not provided information regarding an assay to detect the neutralizing capacity of

immunogenic responses in humans. These data should be provided in advance of the licensure application.

Jane

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Jane A. Dean, RN, MSN  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
FDA/CDER

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/s/  
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JOHN J FARLEY  
04/12/2013

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 125509

**MEETING MINUTES**

Elusys Therapeutics, Inc.  
Attention: Robin L. Conrad  
Vice President, Regulatory Affairs  
25 Riverside Drive  
Pine Brook, NJ 07058

Dear Ms. Conrad:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Anthim (obiltoxaximab), 600 mg/6 mL, injection.

We also refer to the meeting between representatives of your firm and the FDA on December 11, 2015. The purpose of the meeting was to discuss the status of the review.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jane A. Dean RN, MSN, Regulatory Health Project Manager at (301) 796-1202.

Sincerely,

*{See appended electronic signature page}*

John Alexander, MD, MPH  
Cross Discipline Team Leader  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



## MEMORANDUM OF LATE-CYCLE MEETING MINUTES

**Meeting Date and Time:** December 11, 2015, 2:00 pm  
**Meeting Location:** Building 22, Conference Room 1415  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

**Application Number:** BLA 125509  
**Product Name:** Anthem  
**Applicant Name:** Elusys Therapeutics, Inc.

**Meeting Chair:** John Alexander, MD, MPH  
**Meeting Recorder:** Jane A. Dean, RN, MSN

### **FDA ATTENDEES**

#### **Division of Anti-Infective Products:**

Abimbola Adebawale, PhD	Associate Director of Labeling
John Alexander, MD, MPH	Cross Discipline Team Leader
Shukal Bala, PhD	Clinical Microbiology Reviewer
Kimberly Bergman, PharmD	Clinical Pharmacology Team Leader
Lynette Berkeley, PhD, MT, (ASCP)	Clinical Microbiology Reviewer
Edward Cox, MD, MPH	Director, Office of Antimicrobial Products (OAP)
Jane A. Dean, RN, MSN	Regulatory Health Project Manager
Jeffrey Florian, PhD	Pharmacometrics Reviewer
Ramya Gopinath, MD	Clinical Reviewer
Karen Higgins, ScD	Statistical Team Leader
Fang Li, PhD	Pharmacometrics Reviewer
Ling Lan, PhD	Statistical Reviewer
Xianbin Li, PhD	Statistical Reviewer
Sumathi Nambiar, MD, MPH	Director
Amy Nostrandt, DVM, PhD	Pharmacology/Toxicology Reviewer
Elizabeth O'Shaughnessy, MD	Clinical Reviewer
Wendelyn Schmidt, PhD	Pharmacology/Toxicology Team Leader
Joseph Toerner, MD, MPH	Deputy Director for Safety
Zhixia (Grace) Yan, PhD	Clinical Pharmacology Reviewer

#### **Office of Biotechnology Products:**

LT Jibril Abdus-Samad, PharmD	Labeling Reviewer
David Frucht, MD	Acting Director/DBRR II
Rashmi Rawat, PhD	Product Quality Team Leader
Tao Xie, PhD	Product Quality Reviewer

**Office of Process and Facilities:**

Bo Chi, PhD	Product Quality Microbiology Reviewer
John Metcalfe, PhD	Product Quality Microbiology Reviewer

**Counter-Terrorism and Emergency Coordination Staff:**

Gerald Poley, MD	Medical Officer
Rosemary Roberts, MD	Director (via phone)

**Eastern Research Group:**

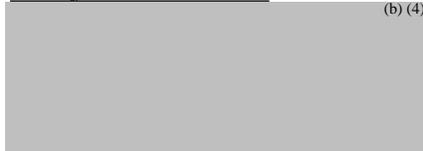
Marc Goldstein	Independent Assessor
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**SPONSOR ATTENDEES**

**Elusys:**

Greg Birrer, PhD	Sr. Director Quality Affairs
Robin Conrad, MS	VP Regulatory Affairs
Cynthia Dillon	Sr. Director Regulatory Affairs
Marion McGlynn, MS, MBA	Executive Director Project Management
Christa Nagy, PhD	Director Clinical Operations
James Porter, MS	VP Manufacturing and Development
Natalya Serbina, PhD	Senior Scientist, Nonclinical Development
Pamela Wright, PhD	Executive Director Manufacturing

**Elusys Consultants:**

 (b) (4)	Statistical Consultant
	Sr. Consultant DMPK
	Clinical and Pharmacovigilance Consultant
	Clinical Consultant and Medical Monitor (via phone)

**Biomedical Advanced Research and Development Authority:**

Drew Albright	Project Officer
Michael Merchlinsky	Subject Matter Expert
Chia-Wei Tsai	Project Officer
 (b) (4)	Contractor

**1.0 BACKGROUND**

BLA 125509 was submitted on March 20, 2015 for Anthim (obilttoximaximab) injection.

Proposed indication(s): 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.

PDUFA goal date: March 20, 2016

FDA issued a Background Package in preparation for this meeting on November 25, 2015.

## **DISCUSSION**

1. Introductory Comments – 5 minutes (John Alexander)

Welcome, Introductions, Objectives of the meeting

2. Discussion of Substantive Review Issues

Each issue was introduced by FDA and followed by a discussion.

- Hypersensitivity Reactions
- Intramuscular Administration
- Endotoxin Testing Methods
- Facilities

**Discussion:** The Division provided the following information on the assessment of hypersensitivity reactions:

- The symptoms and signs of infusion-related hypersensitivity were listed by the Applicant as Preferred Terms (PTs). However, the Division felt that an integrated assessment of all clinical manifestations in each subject with hypersensitivity presented a more accurate clinical picture than individual PTs, particularly in those subjects in whom the infusion of obiltoxaximab was stopped due to hypersensitivity (8 subjects), or who were discontinued from the study to avoid repeat administration of obiltoxaximab (2 subjects). Serious hypersensitivity or anaphylaxis occurs on a clinical continuum; thus, based on the information presented in the application, the Division's assessment is that 7 subjects met criteria for anaphylaxis.
- The Division also noted that the discontinuation of obiltoxaximab infusions by on-site investigators in 8 subjects, in addition to the need for administration of concomitant medications were significant interventions in and of themselves; this has significant potential negative implications for widespread administration of obiltoxaximab in a bioterrorism event.

Elusys countered with the following explanation:

- Criteria for clinical diagnosis of anaphylaxis include skin and/or mucosal involvement, respiratory findings such as bronchospasm and dyspnea, and cardiovascular manifestations such as hypotension.
- Elusys agreed with the Division that anaphylaxis is a continuum and they deferred to the investigator's decision on whether a subject had anaphylaxis or a hypersensitivity reaction.

- They felt that the signs and symptoms in the study subjects in whom obiltoxaximab infusion was discontinued had reactions that did not rise to the level of anaphylaxis, but did represent hypersensitivity, and are consistent with reactions to other monoclonal antibodies.

Elusys felt that the term anaphylaxis implies the need for treatment with reverse Trendelenburg, intravenous fluids, crash cart, epinephrine, etc. and that most cases of hypersensitivity with obiltoxaximab did not require these treatments.

The Division stated that they had the following concerns:

- Some of the 10 subjects with serious hypersensitivity/anaphylaxis had rash and urticaria, dyspnea, and cough and throat irritation (suggestive of angioedema) among other manifestations. However, it was not possible to comment on other manifestations of anaphylaxis such as bronchospasm or mucosal involvement, because it did not appear that physical examinations were recorded at the time of discontinuation of the infusion.
- Given the rate of serious hypersensitivity or anaphylaxis in a controlled setting, the foremost concern was whether obiltoxaximab could be safely administered for prophylaxis in a mass casualty setting, as close clinical monitoring of patients may not be possible at that time. This concern needs to be adequately communicated in labeling.
- Although the mechanism of hypersensitivity was uncertain, premedication with diphenhydramine did appear to reduce the incidence of some manifestations of hypersensitivity.
- Elusys said that because all study subjects were healthy volunteers, there may have been a lower threshold to stop the infusion in the event of hypersensitivity, in view of the lack of benefit and potential risk, to the subject. Elusys will submit case narratives which contain additional information on the subjects who experienced infusion-related reactions. They noted that the Division's analysis of benefit with diphenhydramine premedication was useful.

The Division agreed that the benefit of obiltoxaximab would likely outweigh its risks for treatment of inhalational anthrax when used along with other medications, especially since these patients would be closely monitored.

[REDACTED] (b) (4)

Regarding the endotoxin testing methods, Elusys will provide the endotoxin spiking and hold study data at the end of January.

Regarding the facility, the Division noted that the review of Lonza's responses to the form 483 observations issued during the pre-license inspection has been completed and the drug substance facility is currently in compliance.

3. Discussion of Minor Review Issues

- Incidence of Infections of the Upper Respiratory Tract in healthy humans who received obiltoxaximab versus placebo.
- A Letter of Authorization for the (b) (4) DMF for (b) (4).

**Discussion:** Elusys suggested that the respiratory tract infections seen during the trials could have been seasonal, especially with the prolonged follow up. The Division agreed that this could be the case, but pointed out that when all infections related to the upper respiratory tract – for example, sinusitis, pharyngitis, bronchitis, upper respiratory tract infections - were taken together, they were more frequent in the subjects who received obiltoxaximab than those who received placebo. Further, this finding was consistent across all the human safety studies. Elusys said they would look into this further.

4. Additional Applicant Data – 10 minutes (Applicant)

**Discussion:** No discussion was needed.

5. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

Postmarket Clinical Studies:

- a. A protocol should be submitted for a clinical study to evaluate the safety profile, clinical response, and pharmacokinetics of obiltoxaximab used in the treatment of suspected or confirmed cases of inhalational anthrax. As stated in 21CFR 601.91, applicants must conduct postmarket studies, such as field studies, to verify and describe the biological product's clinical benefit and its safety when used as indicated when such studies are feasible and ethical.
- b. A study of the effect of concomitant administration of anthrax vaccine adsorbed (AVA) and obiltoxaximab may be required; this is similar to an existing PMR evaluating administration of raxibacumab with AVA.  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2012/125349Orig1s000ltr\(r\).pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/125349Orig1s000ltr(r).pdf)

**Discussion:** Elusys is working on the protocol for the field study postmarketing requirement. They intend to use a historical control and are considering enrolling 108 subjects who would be stratified by whether or not they had prodromal symptoms versus after the prodromal period. Further discussion will have to take place between Elusys and the Agency for the Postmarketing Clinical Study on the concomitant administration of anthrax vaccine adsorbed (AVA) and obiltoxaximab which is similar to the study required for raxibacumab.

The Agency will need the timeline for submitting the final protocol, study completion and final report submission for all the postmarketing requirements/commitments. For the field study, study completion and final report submission would be dependent on the occurrence of an attack.

Postmarket Commitments for Product Quality:

- c. Develop reduced and non-reduced SDS-based assays that are 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.
- d. Conduct validation studies to confirm acceptable product quality and shipper performance during shipping of obiltoxaximab drug product. This should include consideration for worst case shipping routes including routes to testing sites. The study will include monitoring of temperature during the shipment, as well as testing of pre- and post-shipment samples of obiltoxaximab for 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) and confirmation that the commercial shipping configuration minimizes physical damage to the drug product containers.
- e. 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. The final report should be submitted as a prior approval supplement.
- f. Conduct a study to support the worst case cumulative hold times in obiltoxaximab drug substance manufacturing process to demonstrate that the worst case cumulative hold time will not adversely affect the product quality of obiltoxaximab DS. These data are expected to demonstrate that there is no adverse impact to product quality when the manufacturing of a DS batch involves (b) (4). The final reports should be submitted in the BLA annual report.
- g. Re-evaluate obiltoxaximab 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. Proposed changes to the specifications should be provided in the final report.
- h. Re-evaluate obiltoxaximab 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. Proposed changes to the specifications should be provided in the final report.

- i. Establish a permanent control limit for (b) (4), of production (b) (4) and 'step (b) (4) of (b) (4) unit operations after (b) (4) points have been analyzed. The (b) (4) limits and supportive data should be submitted in the annual report.
- j. (b) (4)
- k. Conduct a study to qualify the bioburden test for the primary recovery samples using the increased sample volume (10 mL).
- l. Re-evaluate and establish final (b) (4) bioburden and endotoxin limits for all the sampling points after ten commercial lots have been manufactured.

**Discussion:** No further discussion was needed.

7. Review Plans, Wrap-up and Action Items – 5 minutes

Labeling and PMR/PMC – Teleconference planned for mid-January 2016  
Action Goal Date – by March 18, 2016

**Discussion:** No further discussion was needed.

8. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

## 5.0 ACTION ITEMS

<b>Action Item/Description</b>	<b>Owner</b>	<b>Due Date</b>
The Agency will provide the meeting minutes within 30 days	FDA	January 10, 12016
Narratives will be provided to the Agency for the seven patients that experienced a hypersensitivity reaction at the time of infusion of Anthem	Elusys	Early January, 2016
Synopsis for the proposed field study and time line for submitting to the Agency	Elusys	End of January 2016
Information for endotoxin testing	Elusys	End of January 2016

## 6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts used for this meeting.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JOHN J ALEXANDER  
01/08/2016