

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125521Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 125521	BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: TALTZ Established/Proper Name: ixekizumab Dosage Form: PFS and AI		Applicant: Eli Lilly Agent for Applicant (if applicable): N/A
RPM: J. Paul Phillips		Division: Division of Dermatology and Dental 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><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <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"> Proposed action User Fee Goal Date is 03/23/2016 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		N/A
❖ Application Characteristics ³		

¹ 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.

² 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).

³ 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): N/A
 (confirm chemical classification at time of approval)

- | | |
|---|---|
| <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 type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(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 require actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ 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)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<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	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	N/A
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>01/27/2016</u> If PeRC review not necessary, explain: <u>N/A</u> 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • 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>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ 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 previous action letters, as these are located elsewhere in package</i>)	N=2
❖ 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)	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 10/29/2014
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 8/14/2015
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 12/02/2015
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	07/30/2014 CMC Guidance; 04/30/2014 Guidance; 01/28/2014 Guidance
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 03/22/2016
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 03/18/2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> (see Division summary review)
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> 03/22/2016
Clinical	
❖ Clinical Reviews	

<ul style="list-style-type: none"> Clinical Team Leader Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> 11/20/2015
<ul style="list-style-type: none"> 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>	Pg. 203- 11/20/2015 Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	06/22/2015: DEPI review #1 10/15/2015: DEPI review #2 08/25/2015: DPP review #1 10/09/2015: DPP review #2 10/02/2015: Drug Utilization 02/19/2016: DPMH review 01/07/2016: COA review
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> 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> 	N/A N/A <input checked="" type="checkbox"/> 01/22/2016
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	<input checked="" type="checkbox"/> 11/03/2015 Summary 08/26/2015 Bukhalo letter 11/03/2015 Birbara letter 11/03/2015 Blauvelt letter
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <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>	<input checked="" type="checkbox"/> 11/03/2015
Clinical Pharmacology <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>	<input checked="" type="checkbox"/> 10/30/2015
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 09/11/2015
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 11/02/2015
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 11/02/2015
❖ 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
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 02/26/2016
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 10/27/2015: Drug Product 10/27/2015: Drug Substance 10/30/2015: Immunogenicity 10/30/2015: Micro Drug Product 10/30/2015: Micro Drug Substance
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> 04/28/2015: CDRH compliance/facilities review #1 10/08/2015: CDRH compliance/facilities review #2 10/30/2015: CDRH device review
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Pg. 5- 10/27/2015 Drug Product review
<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 checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>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- 10/07/2015: Facility review 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"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	N/A
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	N/A
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	N/A
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	N/A
❖ 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

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

/s/

J P PHILLIPS
03/23/2016



BLA 125521

MID-CYCLE COMMUNICATION

Eli Lilly and Company
Attention: Brian E. Wagner, PharmD
Director, Global Regulatory Affairs - US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Wagner:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for ixekizumab.

We also refer to the teleconference between representatives of your firm and the FDA on August 14, 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 Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD, FAAD
Deputy Director (Acting)
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 14, 2015; 9:00 a.m. ET

Application Number: BLA 125521
Product Name: ixekizumab
Proposed Indication: psoriasis
Applicant Name: Eli Lilly and Company

Meeting Chair: Jill Lindstrom, MD
Meeting Recorder: Paul Phillips

FDA ATTENDEES

Jill Lindstrom, MD, Deputy Director (Acting), DDDP
Julie Beitz, MD, Director, ODE III
Amy G. Egan, MD, MPH, Deputy Director, ODE III
Jane Liedtka, MD, Clinical Team Leader, DDDP
Howard Anderson PhD, Product Quality Team Leader, OBP
Maria Cecilia Tami, PhD, Product Quality Reviewer, OBP
Xu Di, PhD, Product Quality Reviewer, OBP
Patricia Hughes, Ph.D., Branch Chief (Acting), DMA
Colleen Thomas, PhD, Product Quality Microbiology Reviewer, DMA
Bo Chi, PhD, Product Quality Microbiology Reviewer, DMA
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Lucas Kempf, MD, Clinical Team Leader, DPP
David Shih, MD, MS, Deputy Director, DEPI 1
Gabiella Anic, PhD, MPH, Epidemiology Reviewer, DEPI 1
Jamie Wilkins Parker, PharmD, Risk Management Analyst, Acting Team Leader, DRISK
Erin Hachey, PharmD, Risk Management Analyst, DRISK
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III
J. Paul Phillips, MS, Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein, Independent Assessor
Christopher Sese, Independent Assessor

APPLICANT ATTENDEES

Robin Wojcieszek, Sr. Director, Global Regulatory Affairs
Brian Wagner, Director, Global Regulatory Affairs
Allison Kennington, Sr. Director, Global Regulatory Affairs - CMC
Robert Seevers, Principle Research Scientist, Global Regulatory Affairs - CMC

Bruce Meiklejohn, Research Fellow, Global Regulatory Affairs -CMC
Wale Osuntokun, Medical Director
Dan Braun, Medical Fellow
Talia Muram, Medical Advisor
Kimberley Jackson, Research Advisor
Janelle Erickson, Research Advisor

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.

2.0 SIGNIFICANT ISSUES

Product Quality

a) Validation (b) (4)

The microbial retention study did not consider the effect of the drug product on the challenge organism (b) (4). (b) (4) the product formulation or test process should be identified and the microbial retention study should be repeated accordingly. Possible re-test strategies include reduced exposure time, modification of a test parameter (e.g., temperature), or modification of the product formulation (further pH adjustment, placebo, etc.).

Meeting Discussion:

The applicant will provide additional data from an internal report within one week to address the FDA concerns with the (b) (4) validation.

b) Drug product endotoxin testing

Low endotoxin recovery affects the drug substance, and endotoxin recovery results from three different batches of drug product were inconsistent. Endotoxin release testing strategies for the drug substance and drug product must be determined prior to approval.

Meeting Discussion:

The applicant will provide additional data within one week to address the endotoxin testing issues. The applicant referenced studies performed for other Eli Lilly products (i.e. BLA 125547—necitumumab; BLA 125469—dulaglutide) and proposed to address the endotoxin testing issues for BLA 12551 (ixekizumab) in a similar manner.

c) Bridging strategy for comparator product

With regard to the use of US-licensed Enbrel at certain study sites and EU-approved etanercept at other study sites for the active comparator arm of your two superiority clinical trials submitted in your BLA, we note that you cancelled a meeting with FDA that was scheduled for September 17, 2014 to discuss your plans to provide a bridge between US-licensed Enbrel and EU-approved etanercept. As such, FDA did not have an opportunity to discuss your plans prior to the submission of your BLA for ixekizumab or to provide FDA's recommendations to you.

Specific to your development program, we agree it may be reasonable to use US-licensed Enbrel at certain study sites and EU-approved etanercept at other study sites for the active comparator arm of your superiority clinical trials if you can establish an adequate scientific bridge to justify the relevance of data obtained with EU-approved etanercept. If you seek to use data from clinical studies comparing ixekizumab to EU-approved etanercept, to support a claim of superiority of ixekizumab to US-licensed Enbrel, you should provide adequate data or information to scientifically justify the relevance of this comparative data and establish an acceptable scientific bridge to US-licensed Enbrel. With respect to your development program, the type of bridging data that may be needed to provide adequate scientific justification for this approach would include data from direct, comparative analytical studies (e.g. structural and functional data) of US-licensed Enbrel and EU-approved etanercept, and is likely to also include bridging clinical PK study data. The comparisons should meet the pre-specified acceptance criteria for analytical and PK similarity. You may submit publicly available information regarding EU-approved etanercept to justify the extent of comparative data needed to establish a bridge to US-licensed Enbrel. The complexity of the product, particularly with respect to higher order structure, post-translational modifications (e.g., glycosylation) and the degree of heterogeneity associated with the product may impact the considerations for the scientific justification regarding the extent of bridging data. You should address any other factors that may affect the extent of bridging data to support such an approach. The adequacy of this scientific justification and bridge would be a review issue.

Based on our preliminary review of the data and information intended to support a scientific bridge between US-licensed Enbrel and EU-approved etanercept, we do not think that you have provided an adequate bridge to scientifically justify the relevance of the comparative data generated using EU-approved etanercept. However, based on our preliminary review of the data from the two superiority clinical trials, it appears that you have sufficient data from subjects administered US-licensed Enbrel to adequately assess superiority of ixekizumab to US-licensed Enbrel. Therefore, at this time, we do not think that you will need to provide a bridge to justify the relevance of the comparative data generated using EU-approved etanercept in order to support licensure of ixekizumab.

We remind you that our review is ongoing, and at this time we are providing you with notification of a review issue that has been identified. Please note, however, that the use of both US-licensed Enbrel and EU-approved etanercept as active comparators in a clinical trial may have labeling implications should the data generated using both products be necessary to support approval.

Meeting Discussion:

The applicant proposed to submit additional information, within one week, related to the proposed bridging strategy for establishing similarity between EU versus US sourced etanercept. The applicant inquired about the possibility of having a separate meeting to discuss the analytical requirements for establishing a scientific bridge. The FDA agreed to review the additional information once submitted and then determine a time to discuss further with the applicant the FDA expectations for establishing a scientific bridge.

3.0 INFORMATION REQUESTS

Product Quality

- a) We anticipate requesting information regarding the tolerance of the neutralizing antibody assay

Meeting Discussion:

The FDA noted that an information request related to the tolerance of the neutralizing antibody assay would be provided to the applicant within the next couple of weeks.

Clinical

- a) Regarding the retrospective analysis of suicidal ideation, provide the following additional information:

- Subject numbers and location of narratives for the 39 cases categorized as “not enough information”
- The magnitude of change from baseline (e.g. from 0 to 1) for subjects who experienced a worsening of response to Question #12, presented at the subject level in a table
- Description of clinical follow-up (e.g. subjects referred for psychiatric evaluation, followed more closely, etc.) that was provided to subjects who experienced a worsening of score on the QIDS or on Question #12
- Clarification regarding whether or not the reviewers for the C-CASA analysis were blinded to the segment of the study

Meeting Discussion:

The applicant noted that the numbers and locations of the narratives for the 39 cases, are contained in Appendix 2 of the Regulatory Response document submitted on 8/6/2015.

The applicant clarified that the reviewers for the C-CASA analysis were blinded to the segment of the study.

The applicant proposed to provide the remaining information for the Clinical information request within 3 weeks. The FDA agreed this timing was acceptable.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns at this time and there are currently no plans for a REMS, pending the final outcome of the suicidal ideation and behavior (SIB) analysis

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee (AC) meeting

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the Late-Cycle Meeting is Wednesday, December 2, 2015 at 11:00 a.m. ET

Meeting Discussion:

The applicant agreed that the proposed time and date for the Late Cycle meeting were acceptable. The applicant will let FDA know whether the preference is for a face-to-face meeting or a teleconference.

The applicant asked if there were any changes to the date for communicating labeling and the PDUFA action goal date for the application. The FDA confirmed that at this time there were no changes to either date; however, if the applicant were to submit a major amendment that could impact the PDUFA action goal date.

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

/s/

JILL A LINDSTROM
08/31/2015

BLA 125521 ixekizumab
Mid-Cycle Communication
Agenda

1.0 INTRODUCTION

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2.0 SIGNIFICANT ISSUES

Product Quality

a) Validation (b) (4)

The microbial retention study did not consider the effect of the drug product on the challenge organism (b) (4). (b) (4) the product formulation or test process should be identified and the microbial retention study should be repeated accordingly. Possible re-test strategies include reduced exposure time, modification of a test parameter (e.g., temperature), or modification of the product formulation (further pH adjustment, placebo, etc.).

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BLA 125521 ixekizumab
Mid-Cycle Communication
Agenda

Specific to your development program, we agree it may be reasonable to use US-licensed Enbrel at certain study sites and EU-approved etanercept at other study sites for the active comparator arm of your superiority clinical trials if you can establish an adequate scientific bridge to justify the relevance of data obtained with EU-approved etanercept. If you seek to use data from clinical studies comparing ixekizumab to EU-approved etanercept, to support a claim of superiority of ixekizumab to US-licensed Enbrel, you should provide adequate data or information to scientifically justify the relevance of this comparative data and establish an acceptable scientific bridge to US-licensed Enbrel. With respect to your development program, the type of bridging data that may be needed to provide adequate scientific justification for this approach would include data from direct, comparative analytical studies (e.g. structural and functional data) of US-licensed Enbrel and EU-approved etanercept, and is likely to also include bridging clinical PK study data. The comparisons should meet the pre-specified acceptance criteria for analytical and PK similarity. You may submit publicly available information regarding EU-approved etanercept to justify the extent of comparative data needed to establish a bridge to US-licensed Enbrel. The complexity of the product, particularly with respect to higher order structure, post-translational modifications (e.g., glycosylation) and the degree of heterogeneity associated with the product may impact the considerations for the scientific justification regarding the extent of bridging data. You should address any other factors that may affect the extent of bridging data to support such an approach. The adequacy of this scientific justification and bridge would be a review issue.

Based on our preliminary review of the data and information intended to support a scientific bridge between US-licensed Enbrel and EU-approved etanercept, we do not think that you have provided an adequate bridge to scientifically justify the relevance of the comparative data generated using EU-approved etanercept. However, based on our preliminary review of the data from the two superiority clinical trials, it appears that you have sufficient data from subjects administered US-licensed Enbrel to adequately assess superiority of ixekizumab to US-licensed Enbrel. Therefore, at this time, we do not think that you will need to provide a bridge to justify the relevance of the comparative data generated using EU-approved etanercept in order to support licensure of ixekizumab.

We remind you that our review is ongoing, and at this time we are providing you with notification of a review issue that has been identified. Please note, however, that the use of both US-licensed Enbrel and EU-approved etanercept as active comparators in a clinical trial may have labeling implications should the data generated using both products be necessary to support approval.

3.0 INFORMATION REQUESTS

Product Quality

BLA 125521 ixekizumab
Mid-Cycle Communication
Agenda

- a) We anticipate requesting information regarding the tolerance of the neutralizing antibody assay

Clinical

- a) Regarding the retrospective analysis of suicidal ideation, provide the following additional information:
- Subject numbers and location of narratives for the 39 cases categorized as “not enough information”
 - The magnitude of change from baseline (e.g. from 0 to1) for subjects who experienced a worsening of response to Question #12, presented at the subject level in a table
 - Description of clinical follow-up (e.g. subjects referred for psychiatric evaluation, followed more closely, etc.) that was provided to subjects who experienced a worsening of score on the QIDS or on Question #12
 - Clarification regarding whether or not the reviewers for the C-CASA analysis were blinded to the segment of the study

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns at this time and there are currently no plans for a REMS, pending the final outcome of the suicidal ideation and behavior (SIB) analysis

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee (AC) meeting

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the Late-Cycle Meeting is Wednesday, December 2, 2015 at 11:00 a.m. ET

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/s/

J P PHILLIPS
08/12/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125521

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

ATTENTION: Brian E. Wagner, Pharm.D.
Director, Global Regulatory Affairs - US

Dear Dr. Wagner:

Please refer to your Biologics License Application (BLA) dated and received March 23, 2015, submitted under section 351(a) of the Public Health Service Act for Ixekizumab Injection, 80 mg/mL.

We also refer to:

- Your correspondence, dated and received March 23, 2015, requesting review of your proposed proprietary name, Taltz
- Your amendment to the Request for Proprietary Name Review, dated and received, March 23, 2015

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

If any of the proposed product characteristics as stated in your March 23, 2015, submissions 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 Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Paul Phillips, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
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/

TODD D BRIDGES
06/17/2015



IND 100834

MEETING MINUTES

Eli Lilly and Company
Attention: Brian E. Wagner, PharmD
Director, Global Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Wagner:

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

We also refer to the meeting between representatives of your firm and the FDA on October 29, 2014. The purpose of the meeting was to discuss the planned submission of a Biologics License Application (BLA) for ixekizumab for the treatment of moderate to severe plaque psoriasis.

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 J. Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dentals Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: October 29, 2014; 9:00 AM
Meeting Location: FDA W.O. Bldg. 22

Application Number: IND 100834
Product Name: ixekizumab
Indication: Treatment of moderate to severe plaque psoriasis
Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Tatiana Oussova, MD
Meeting Recorder: J. Paul Phillips

FDA ATTENDEES

Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Julie Beitz, MD, Director, ODE III
David Kettl, MD, Clinical Team Leader, DDDP
Milena Lolic, MD, Clinical Reviewer, DDDP
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, DCP3
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP3
Michele Dougherty, PhD, Product Quality Team Leader, DMA
Ram Sihag, PhD, Product Quality Reviewer, DMA
Carolyn McCloskey, MD, Epidemiologist, DEPI 1
Omolara Laiyemo, PharmD, Regulatory Health Project Manager, DDDP
J. Paul Phillips, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Aarti Shah, PhD, Team Leader, Ixekizumab Product Team
Olawale Osuntokun, M.D., Medical Director, Ixekizumab Product Team
Kimberley Jackson, Ph.D., Research Advisor, PK/PD
Janelle Erickson, Ph.D., Research Advisor, Statistics
Robin Wojcieszek, R.Ph., Sr. Director, Regulatory
Brian Wagner, Pharm.D., Director, Regulatory
Allison Kennington, Ph.D., Sr. Director, CMC Regulatory
Chin Lee, M.D., Sr. Medical Director, Ixekizumab Product Team
Carl Garner, PhD, Sr. Director, Regulatory

Purpose of the Meeting:

To discuss the planned submission of a Biologics License Application (BLA) for ixekizumab for the treatment of moderate to severe plaque psoriasis

Regulatory Correspondence History

We have had the following meetings with you:

- 01/29/2008 Clinical Hold teleconference
- 06/22/2011 Guidance meeting
- 11/07/2012 Guidance meeting
- 09/04/2013 Guidance—Written Responses
- 11/01/2013 Guidance—Written Responses
- 01/28/2014 Guidance—Written Responses
- 04/30/2014 Guidance meeting
- 07/30/2014 Guidance meeting (CMC only)

We have sent you the following correspondences:

- 11/26/2007 IR letter
- 02/06/2008 Clinical Hold letter
- 02/07/2008 IR letter
- 03/18/2008 Advice/IR letter
- 04/17/2008 IR letter
- 05/02/2008 Remove Clinical Hold letter
- 04/22/2010 Advice/IR letter
- 02/07/2012 Advice/IR letter
- 05/30/2012 Advice letter
- 07/09/2012 Advice/IR letter
- 07/18/2012 Advice/IR letter
- 08/28/2012 Advice/IR letter
- 04/09/2013 Advice/IR letter
- 04/17/2013 Advice/IR letter
- 06/13/2013 Advice/IR letter
- 08/01/2013 Advice/IR letter
- 08/08/2013 Advice/IR letter
- 10/03/2013 Proprietary Name Granted letter
- 11/18/2013 Advice/IR letter
- 11/20/2013 Harmonized Annual Report Due Date Granted letter
- 03/10/2014 Advice letter
- 05/22/2014 Advice/IR letter
- 09/25/2014 Advice/IR letter

Question 1:

The preliminary efficacy and safety results from the pivotal Phase 3 trials (that is, Studies RHBA, RHBC, and RHAZ) are provided respectively in Section 6 and Section 7 of this document. The preliminary 12-week efficacy results from these trials demonstrated that both

initial ixekizumab dosing regimens (that is, 80 mg every 2 weeks [Q2W] and 80 mg every 4 weeks [Q4W]) achieved all the primary and gated secondary objectives ($p < .001$). Across all these objectives, the 80 mg Q2W initial dosing regimen allowed a higher percentage of patients to achieve a response compared to 80 mg Q4W dosing regimen, with approximately 40% of patients able to achieve resolution of their psoriasis as measured by Psoriasis Area and Severity Index (PASI) 100 or static Physician Global Assessment (sPGA) 0 by Week 12 (Section 6). With regard to the adverse event (AE) safety profile, there was little or no clinically meaningful difference in terms of types, frequency, or severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), or rates of discontinuation due to AEs between the Q2W or Q4W initial dosing regimens within each study (Section 7).

In the Maintenance Dosing Period of Study RHAZ, both dosing regimens (that is, 80 mg Q4W and 80 mg every 12 weeks [Q12W]) maintained a statistically significant higher percentage of patients at sPGA (0,1) compared to placebo; however, a higher percentage of patients on the 80 mg Q4W dosing regimen (71% to 75%) maintained response when compared to patients on the 80 mg Q12W maintenance dosing regimen at Week 60 (34% to 41%) (Table 6.10). For the defined 12-week responders, over 50% were able to achieve sPGA 0 or PASI 100 at Week 60 on 80 mg Q4W compared to between 19% and 21% for patients on the 80-mg Q12W regimen (Table 6.13). Although evaluation of the Maintenance Dosing Period safety data is ongoing, preliminary results suggest that both doses appear to have an acceptable safety profile for long term use. There did not appear to be clinically meaningful differences in the safety profile during the Maintenance Dosing Period whether the patients received 80 mg Q2W or 80 mg Q4W as an induction dose.

Lilly's approach to determine the optimal dosing regimen will be based on the integrated summary and analysis of critical data that pertain to the dose-response relationship of efficacy (that is, complete resolution and achieving skin clearance above PASI 75), and the safety profile (for example, types, rates, and severity of events). Lilly will evaluate the dose-exposure-response and dose-exposure-toxicity relationships in order to determine the optimal dosage regimen for the initial 12-week dosing period and the Maintenance Dosing Period. Recent literature has reported an incremental benefit on quality of life for patients achieving skin clearance above PASI 75 (Takeshita et al. 2014); thus, many patients and health care providers may seek higher levels of skin clearance. With regard to Lilly's pivotal Phase 3 psoriasis studies and achieving skin clearance above PASI 75, preliminary results demonstrate that the ixekizumab 80 mg Q2W dosing regimen during the initial 12 weeks of treatment allowed a greater percentage of patients to achieve higher levels of skin clearance (Table 6.10). For patients who do achieve at least sPGA (0,1) at 12 weeks, the ixekizumab 80 mg Q4W maintenance dosing regimen allowed over 50% of such patients to achieve complete resolution of their psoriasis at Week 60.

Does FDA have any comments or recommendations on Lilly's approach to determining the dosing recommendations?

Response:

We agree with your approach to explore the dose-exposure-response and dose-exposure-toxicity relationships in order to determine the optimal dosage regimen for the initial 12-week dosing

period and the Maintenance Dosing Period. The regimen that has the most favorable benefit/risk should be selected.

Historically, the Agency's recommendation has been that achieving a $\geq 75\%$ improvement in PASI from baseline was an acceptable co-primary endpoint.

Whether higher PASI score of one regimen warrants higher dose selection needs to be carefully balanced with safety profile of the same, higher dose regimen and will be a review issue.

Advisory Committee input will be recommended, as currently there are no approved products with this pathway target and your product is a new molecular entity (NME) for the treatment of moderate to severe plaque psoriasis.

Question 2:

Based on current information from the ongoing evaluation of the clinical safety of ixekizumab (Section 7), Lilly believes that labeling will adequately communicate safety risks to prescribers. Therefore, Lilly does not propose to submit a Risk Evaluation and Mitigation Strategy (REMS)—that is, a risk mitigation beyond labeling—at the time of the initial BLA submission, but Lilly will include a Risk Management Plan (RMP). Lilly intends to prepare a patient medication guide to ensure patient education about the potential risk of serious or opportunistic infections for patients taking ixekizumab, given that the safety profile and infection risk from ixekizumab may differ from other marketed immunosuppressive agents, including biologics presently used for treatment of psoriasis. Lilly will continue to evaluate incoming clinical trial data for ixekizumab and will consider the need for a REMS based on any new important risks.

As part of a pharmacovigilance plan, Lilly

(b) (4)

(b) (4)

(b) (4)

Lilly plans to conduct a prospective observational pregnancy exposure registry. The registry will be used to compare women exposed to ixekizumab during pregnancy to an unexposed control population with respect to pregnancy and fetal/neonatal outcomes.

Details regarding the observational, postmarketing (b) (4) pregnancy registry will be provided at the time of the submission.

Does FDA have any preliminary comments on Lilly's approach to address any potential postmarketing risk management actions?

Response:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine 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. We will make a final determination for the need for a REMS during the review of your application. The elements of your proposed post-marketing plan appear appropriate; however the Agency may have additional comments on your registry proposals when the complete protocols are submitted for review.

Question 3:

This briefing document includes a summary of key development changes, actions, or approaches taken by Lilly to address FDA feedback, as well as a summary of the Chemistry, Manufacturing, and Control (CMC) development, device development, and nonclinical and clinical development plans. Lilly understands that as a new molecular entity (NME), the ixekizumab BLA submission will be subject to “The Program” under Prescription Drug User Fee Act (PDUFA) V, and hence, at the pre-BLA meeting, FDA and Lilly should come to an agreement on the content of a complete application for filing of the proposed indication for ixekizumab. Therefore, Lilly will be seeking agreement from FDA that the Phase 3 efficacy and safety data to be submitted in the BLA, together with the information presented in the draft table of contents (TOC) for the BLA (Attachment 2) and the contents of the 4-month safety update (Section 14), provide a complete application in support of filing and registration of use of ixekizumab for the treatment of patients with moderate-to-severe plaque psoriasis.

Does FDA agree that the proposed content provides a complete application?

Response:

Overall your application appears adequate for filing. The adequacy of the information to support registration will be the focus of the BLA review.

From a technical standpoint (not content related), the proposed format for the planned BLA is acceptable. Please see the following comments:

- 1.6.3 Correspondence regarding meetings – a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.
- Summary of Clinical Efficacy should reside in m2.7.3 (not m2.7.2)
- Summary of Clinical Pharmacology should reside in m2.7.2. (not m2.7.3.)
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 (tabular format), should be linked to the referenced studies in m5.
- Do not create additional nodes in the eCTD structure beyond what is in the specifications (e.g. 5.3.5.3.1).

The options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section m1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non- eCTD) that is being referenced by the current

application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m1.14.1.1– Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document along with a hypertext link to the location of the information, when possible.

2. To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g. NDA, IND). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to NDA 123456). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application and the application number that is being referenced.

Prior to using cross application linking in an application, it is recommended that sponsor submit an "eCTD cross application links" sample, to ensure successful use of cross application linking.

To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov.

For more information on eCTD sample, please refer to the Sample Process web page which is located at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

From the product quality perspective, the draft table of contents for module 3 provided in Attachment 2, which represents a high level overview of the proposed module 3 content, appears acceptable to constitute a complete application. However, we have additional Microbiology Product Quality comments to assist with the preparation of your BLA.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden samples should be collected (b) (4). Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale should be provided. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5). Bioburden samples should be collected (b) (4).
- Data demonstrating microbial control (b) (4) (3.2.S.2.5).

- Bioburden and endotoxin data obtained during manufacture of the three process qualification batches (3.2.S.2.5).
- Summary of shipping validation studies and data (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4). The bioburden limit should be (b) (4).
- Summary report with summary results from bioburden and endotoxin test method qualification performed for in-process intermediates and drug substance (3.4.S.4).

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the aseptic process and sterility assurance. For guidance on the type of data and information that should be submitted, refer to the FDA guidance for industry, *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*. Provide information and validation data summaries in Section 3.2.P.3.5 for the following:

- (b) (4) study report (b) (4).
- (b) (4) e (b) (4) Provide summary data for the three most recent (b) (4) studies and describe the (b) (4) program.
- Identify any step in the process (b) (4) and submit validation summary data. Bioburden and endotoxin levels before and after the maximum hold time should be monitored and bioburden and endotoxin limits provided.
- (b) (4).
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.
- A description of the routine environmental monitoring program.
- Summary of shipping validation studies and data.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated initially to qualify the container closure system and process and during stability. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) and at expiry (3.2.P.8.2).
- Qualification data for bioburden, sterility and endotoxin test methods performed for in-process intermediates and buffers (where applicable) and the drug product, as appropriate (3.2.P.5).
- Rabbit Pyrogen Test results from three lots of drug product in accordance with 21 CFR 610.13(b).
- (b) (4) (b) (4) The effect of hold time on endotoxin recovery should be assessed (b) (4)

(b) (4) The studies should be conducted using containers of similar composition as those used for drug product during hold.

Inspection Readiness:

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers. An updated manufacturing schedule for the bulk drug substance and drug product fill finish sites should be included in Module 1 of the BLA.

Question 4:

Given that biologic agents often have been discussed at an FDA Advisory Committee, Lilly is interested in FDA's thoughts on whether such a meeting will be necessary.

Does FDA currently foresee that an Advisory Committee meeting will be needed for ixekizumab?

Response:

Ixekizumab is a novel anti IL-17 monoclonal antibody for psoriasis treatment and an Advisory Committee meeting will be recommended. See also response to Q1.

Question 5:

Because the prefilled syringe and auto-injector delivery devices (described in Attachment 11, "Delivery Devices: Auto-Injector and Prefilled Syringe") are platform delivery systems that will be used for other drug products in addition to ixekizumab, Lilly plans to submit Medical Device Master Files (MAFs) to the Center for Devices and Radiological Health (CDRH) that will describe the 2 delivery devices. Lilly believes that access to the MAF documents for reviewers from the Center for Drug Evaluation and Research (CDER) will be managed within FDA.

Does Lilly need to make special provisions for CDER reviewers to access the CDRH MAFs for the prefilled syringe and the auto-injector?

Response:

Prior to the meeting, the sponsor notified the FDA that their plans for submission of the BLA had changed and they would no longer be submitting a MAF to CDRH, but would instead be submitting all information to the BLA. Therefore, a response to Question 5 is no longer needed.

Question 6:

Lilly has previously described to FDA a plan for integration of the clinical study data (SN0185), and FDA responded that the plan was acceptable. An updated Program Safety Analysis Plan (PSAP), Version 4, was submitted to FDA on 27 May 2014 (SN0208), and an updated Integrated Efficacy Analysis Plan (IEAP), Version 3, was submitted to FDA on 27 May 2014 (SN0208). Section 9 of this briefing document describes additional updates to Lilly's plan for integration and analysis of clinical safety data. Section 7 provides a preliminary summary of the available study-level safety data.

Does FDA have any additional comments regarding the integrated analysis plan for safety, in light of the study-level safety data summarized in this document?

Response:

We do not have any additional comments regarding the integrated analysis plan for safety at this time.

Question 7:

In the draft guidance *Providing Submissions in Electronic Format—Summary Level Clinical Site Data for CDER's Inspection Planning*, FDA requests that sponsors provide a summary-level clinical site dataset for the Office of Scientific Investigations (OSI). Section 13 of this briefing document lists the studies for which Lilly plans to provide these datasets. Lilly is seeking confirmation that its plan for submitting summary-level clinical site data from pivotal studies will be sufficient to facilitate CDER's inspection planning.

Does FDA agree with Lilly's plan?

Response:

Your plan to submit summary-level clinical data from the pivotal studies appears adequate. Also, please see the OSI site inspection information below under administrative comments.

Clinical Pharmacology

You did not submit any Clinical Pharmacology specific questions; however, we have the following comments:

- We noted that you plan to analyze the immunogenicity samples for ixekizumab concentrations in subjects who are positive for anti-drug antibodies (ADA) in Studies RHBC and RHBA. We recommend that you measure ixekizumab concentrations in all the immunogenicity samples regardless ADA status in Studies RHBC and RHBA, which will facilitate the interpretation of the immunogenicity data. These ixekizumab concentrations data from the two studies (RHBC and RHBA) will be important for within-study comparisons to evaluate the impact of immunogenicity on PK and safety/efficacy.

As separate PK samples were not collected in Study RHBC or Study RHBA, the drug concentration data from the immunogenicity samples will provide additional PK data for your Phase 3 trials and you should consider including these PK data into your population PK/PD analyses for evaluation of the exposure-response relationships for efficacy and safety.

- We noted that you have conducted two *in vitro* studies that evaluated the effect of IL-17A on CYP enzyme mRNA expression and/or activities. However, recent studies have indicated that *in vitro* or animal studies have limited value in the qualitative and quantitative projection of clinical drug interactions for cytokine modulators and translation of *in vitro* to *in vivo* and animal to human results to date has been inconsistent. Therefore, we recommend that you conduct a clinical trial to assess whether ixekizumab alters the metabolism or pharmacokinetics of CYP substrates in the target psoriasis patient population treated with ixekizumab. The recommended drug-drug interaction (DDI) clinical study is based on the

current understanding that subjects with psoriasis have elevated levels of proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon the disease improvement following biological treatment. As a result, the exposure of CYP substrates could be reduced when the psoriasis disease condition is improved and the proinflammatory cytokines are normalized.

We are open to further discussion regarding the clinical study design to evaluate the DDI for your product. We understand that the DDI data from the recommended clinical study may not be available at the time of your BLA submission; as such, the recommended DDI study could be conducted as a post approval study if the BLA is approved. Refer to the following guidance for more information:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

Meeting Discussion:

The sponsor clarified their plan for population pharmacokinetic (PK) analyses and exposure response analyses using the PK data from the Phase 3 trial RHAZ and Phase 2 trial RHAI. The FDA provided additional clarification regarding the previous request to analyze drug concentration in the immunogenicity samples from Phase 3 trials RHBC and RHBA. These additional PK data would be useful for exposure response analysis for efficacy and safety based on the observed PK concentrations and should be available at the time of submission. The PK data would also facilitate the interpretation of whether the drug concentration in the immunogenicity samples would interfere with the performance of the immunogenicity assays.

The sponsor anticipates BLA submission in the first half of 2015.

CDRH Devices

The briefing package did not specify whether the prefilled syringe configuration of the combination product will have a staked or luer lok needle and anti-needlestick prevention feature. As applicable to your device design, consult the following guidance documents:

- *Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4* (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM346181.pdf>) regarding what the FDA expects in terms of overall performance testing for a glass syringe, and
- *Medical Devices with Sharps Injury Prevention Features* (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>) if your device also has an anti-needle stick feature.

You should also test the final-finished combination product as a whole (with drug/biologic loaded into the glass syringe and assembled with the needle with its (b) (4) shield) in its final to-be-marketed configuration. Note the *Sharps Injury Prevention* guidance Section 10 (Simulated Clinical Use Testing) which details that all intended user populations/subpopulations should be recruited/represented to perform the activation testing of 500 safety devices with zero failure tolerated.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or BLA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
5. You should provide the Agency with SAS transport files in electronic form. The sponsor might refer to the Analysis Data model (ADaM) Examples in Commonly Used Statistical Analysis Methods for guidance:
http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_examples_final.pdf. The FDA prefers that the sponsor arrange a test submission, prior to actual submission. Please refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at esub@fda.hhs.gov, or for standardized data submission questions, contact edata@fda.hhs.gov.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The sponsor and the FDA agreed that there would not be any late submission components for this BLA.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held. See FDA's response to Question 2 above.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms 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, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) SITE INSPECTIONS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

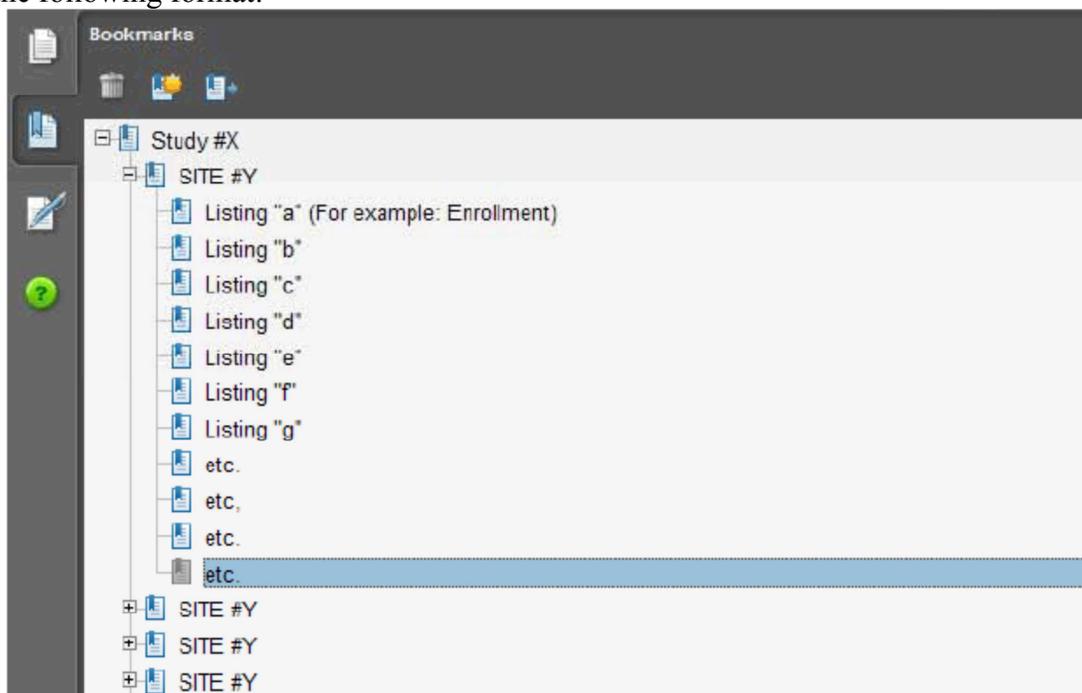
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

I. Attachment 1

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA request document for a full description of requested data files

References:

1. eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)
2. FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)
3. For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

TATIANA OUSSOVA
11/05/2014



IND 100834

MEETING MINUTES

Eli Lilly and Company
Attention: Brian E. Wagner, Pharm.D.
Director, Global Regulatory Affairs
Lilly Corporate Center/ Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wagner:

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

We also refer to the meeting between representatives of your firm and the FDA on July 30, 2014. The purpose of the meeting is to discuss and gain alignment with the FDA on Lilly's platform approach to ADA and NAb assay development and definitions for immunogenicity related terms.

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

If you have any questions, contact me.

Sincerely,

{See appended electronic signature page}

Susan Kirshner, Ph.D.
Review Chief
Division of Therapeutic Proteins
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: CMC Only

Meeting Date and Time: July 30, 2014 at 1:00PM
Meeting Format: Face to Face

Application Number: 100834
Product Name: Ixekizumab.
Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Susan Kirshner, Ph.D.
Meeting Recorders: Andrew Shiber, Pharm.D.

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Biotechnology Products (OBP)

Daniela Verthelyi, M.D., Ph.D.	Laboratory Chief, Division of Therapeutic Proteins (DTP)
Susan Kirshner, Ph.D.	Review Chief, DTP
Cecilia Tami, Ph.D.	Team Leader, DTP
Sarah Kennett, Ph.D.	Review Chief, Division of Monoclonal Antibodies (DMA)
Chana Fuchs, Ph.D.	Team Leader, DMA
Michele Dougherty, Ph.D.	Team Leader, DMA
Ram Sihag, Ph.D.	Quality Reviewer, DMA
Andrew Shiber, Pharm.D.	Regulatory Project Manager, OBP

SPONSOR ATTENDEES

Eli Lilly and Company

Michael P. Heffernan, M.D.	Medical Fellow, Bio-Medicines Business Unit
Richard Higgs, M.S.	Research Fellow, Statistics
Allison Kennington, Ph.D.	Senior Director, CMC Regulatory Affairs
(b) (4)	Medical Fellow, Tailored Therapeutics
Bruce Meiklejohn, Ph.D.	Fellow, CMC Regulatory Affairs
Robert Metcalf, Ph.D.	Vice President, Regulatory Affairs
Talia Muram, M.D.	Medical Advisor, Tailored Therapeutics
Robin Pitts Wojcieszek, R.Ph.	Senior Advisor, Regulatory Affairs

1.0 BACKGROUND

Name of drug: Ixekizumab

Indication: For the treatment of psoriasis.

Objectives: The purpose of this Type C meeting is to discuss the following points:

1. The sponsor's approach and interpretation of minimum required dilution (MRD) data.
2. Approaches to cut point determination including using baseline Phase 2 and/or Phase data to set a cut point.
3. Eli Lilly's focus on assay sensitivity and drug tolerance with their current format versus alternative/competitor formats.
4. The sponsor's approach to determining treatment emergence.

2.0 DISCUSSION

The Sponsor submitted a slide presentation before the meeting to facilitate discussion which is attached to this meeting minutes.

Question 1: Question 1: Does our approach for MRD determination seem adequate and sufficient?

FDA Response to Question 1:

For this specific assay format (ACE), your approach to MRD determination is adequate because detection of ADAs is performed in the absence of matrix components and excess drug. However, for other assay formats in which matrix components might contribute to high background signal and interfere with the detection of ADAs, this approach is inadequate. For other assay formats we recommend that the Minimum Required Dilution be established using a panel of individual samples from untreated patient population or healthy donors. Samples should be serially diluted and tested in the selected assay format together with the assay diluent. The MRD is the lowest sample dilution that yields a signal close to that of the assay diluent. Selection of the MRD should minimize assay background while ensure adequate assay sensitivity. Therefore, it is recommended that MRD do not exceed 1:100.

Meeting Discussion: The Sponsor clarified (slide 2 of the presentation) that MRD is evaluated using 10 NHS samples and plotted as mean + SEM. The Sponsor asked for recommendations on how to evaluate MRD when positive control material performs better in matrix than buffer. In general, the highest binding is obtained in buffer alone and decreases in the presence of matrix. However, the Sponsor claimed that for some assays the signal of the positive control antibody is higher in matrix than in buffer. The FDA has not observed this phenomena occurring with other products/assays. The buffer used in the assay as well as the positive control antibody were some of the factors that were discussed as possible causes. The Sponsor mentioned that this behavior is not related to a specific buffer or positive control antibody and has been seen across a range of buffers and positive control antibodies. The FDA would like to see the data submitted to assist in the review process.

Question 2: Does the FDA have general recommendations for instances in which recovery in human serum is much different than that of buffer—for instance, when hyperimmune monkey serum or affinity-purified antibody contains a large amount of anti-Fc reactivity that will be reactive in buffer but suppressed by the high amount of IgG Fc present even in diluted human serum?

FDA Response to Question 2:

Our interpretation of the question is that you are concerned about the presence of anti Fc antibodies in the positive control antiserum. If the positive control antibody is expected to contain high anti Fc reactivity, we recommend that a more suitable positive control be developed (e.g rabbit) and optimized.

Meeting Discussion: FDA responded that we had not encountered that scenario, perhaps because sponsors don't submit such data to FDA.

Question 3: With regard to the tier 1 cut point, does FDA believe that our approach to set a disease state specific cut point based on a 95th percentile threshold from baseline patient data is sufficient?

FDA Response to Question 3:

The adequacy of your approach to establish the assay cut point for ixekizumab depends on the specific data you obtained during the validation exercise for your specific assay. As a general approach, a screening cut point should be established using at least 50 normal human serum samples. This sample size allows statistical determination of the variability of the study population and the assay. Outliers should be identified using an adequate statistical method and removed from the cut point calculation. Samples that are true positives at baseline should also be removed from the cut point calculation. Once statistical outliers and true positive samples are removed from the data set, the data should be analyzed using a suitable statistical approach that takes into account the distribution of the data. Regardless of the approach selected to analyze the cut point data, the screening cut point should be set using a 5% false positive rate to maximize the possibility to detect all ADA positive samples. Once established, the assay cut point should be confirmed using treatment naïve samples from the target population.

Samples with pre-existing antibodies are most frequently identified by comparing the results of the cut point samples tested in the presence and absence of drug. Samples with pre-existing antibodies generally demonstrate a large decrease in signal in the presence of drug.

Meeting Discussion: The Sponsor's strategy for establishing ADA assay cut points was discussed based on slides 3-5 of the sponsor's slide presentation. Specifically, the Sponsor requested input on how to analyze cut point data with skewed (not normal) distribution. The Agency explained that skewed data often occur due to the presence of true positive samples in the cut point data set. Statistical outliers and baseline true positive samples should be removed from the cut point calculation. Inclusion of outlier and true positive data points result in the calculation of a higher cut point. The main concern with an inflated cut point is the risk of false negatives as the assay may fail to detect low positive samples. If the data are not normally distributed after removal of outliers then the sponsor should use non-parametric statistical approaches to set the cut point. Whether parametric or non-parametric statistical methods are used the screening cut point should be established using a 5% false positive rate with a 90% confidence level.

Question 4: Does this approach seem reasonable to generally apply to other assays?

FDA Response to Question 4:

The adequacy of the approach to establish the cut point of an assay depends on different factors like assay format, matrix components, target population, among others and should be selected based on the data obtained during the assay validation exercise. For many assay formats, calculating the cut point based on the variability of the response of treatment naïve serum

samples is appropriate.

Meeting Discussion: See discussion in question 3.

Question 5: With regard to the tier 2 cut point, what advice does FDA have for instances such as this when the calculated value is so high, and does our choice of a more conservative 50% threshold to minimize missing true positives seem prudent?

FDA Response to Question 5:

Like the screening cut point, the confirmatory cut point should be established based on assay variability. The most common approach to confirming the specificity of an ADA response is to use unlabeled drug to inhibit the binding of ADA to labeled drug. Therefore, the most common approach to establishing the specificity cut point is to determine the assay variability of treatment naive patient samples tested in the presence of unlabeled drug, to account for the impact of unlabeled drug on the assay. In such cases, the confirmatory cut point will be the % inhibition just above the assay variability. The confirmatory cut point should be established using appropriate statistical methods.

Meeting Discussion: The Sponsor proposes to implement a tier 2 (confirmatory) cut point of >50% inhibition for those assays where the confirmatory cut point calculated statistically results in a % inhibition higher than 50%. Assay variability, assay platform and inclusion of outliers and baseline positive samples in the cut point calculation were discussed during the meeting as possible causes for tier 2 cut points >50% inhibition. Most frequently, tier 2 cut points around 30% inhibitions are seen for most of the assays. Tier 2 cut points of >50% inhibitions are generally not acceptable and the reasons for such high values should be understood and overcome to the extent possible. This may require using different approaches to setting the cut point, such as evaluating assay variability and inhibition using a positive control antibody. The sponsor may want to discuss alternative approaches with FDA.

Question 6: Sensitivity was determined using affinity-purified antibody from monkeys hyperimmunized with ixekizumab spiked into normal human serum samples and then analyzing those samples at the MRD (1:5) of the ACE assay. Does this approach seem reasonable?

FDA Response to Question 6:

The approach to assessing the sensitivity of your assay is adequate.

Question 7: What recommendations does FDA have for instances in which affinity-purified antibody contains a large amount of anti-Fc reactivity that will be suppressed by IgG Fc present in diluted human serum? In this case, would it be considered acceptable to use monoclonal antibodies against the complementarity determining regions (CDRs) of the therapeutic antibody to determine sensitivity?

FDA Response to Question 7:

In the case you positive control is not adequate for your assay format, a new positive control antibody should be developed.

Meeting Discussion: The Sponsor asked about the adequacy of using affinity purification against the Fab portion or variable regions only as an acceptable approach to developing a new positive control antibody. The FDA stated that the approach could be acceptable for some molecules. Anti-idiotypic antibodies have been used as controls. The FDA stated that the antibody used needs to be a relevant positive control.

Question 8: Our approach to determine drug tolerance of our assay consisted of using 500 ng/ml affinity-purified antibody from monkeys hyperimmunized with ixekizumab spiked into normal human serum samples containing 0.1-500 µg/ml of ixekizumab, and then analyzing those samples at the MRD (1:5) of the ACE assay. Does this approach seem acceptable?

FDA Response to Question 8: *Your proposed study design is used by some companies. However, drug tolerance is highly dependent on both the concentration of drug and the concentration of ADA in the sample. Therefore, we recommend assessing samples with different concentrations of the positive control antibody including a low concentration that gives signals near the cut point of the assay and different concentrations of drug. This approach will provide a better understanding of the overall assay tolerance.*

Meeting Discussion: The idea of testing drug tolerance at different concentrations of the positive control (low, medium and high) is to understand the how the assay performs at a wide range of ADA and drug concentrations. The sponsor requested clarification regarding the utility of assessing drug tolerance at low drug concentrations. The Agency responded that testing drug tolerance at low concentrations provided additional information on assay performance. In addition to testing drug tolerance in range of 250-500 ng/ml, both higher and lower ranges should be assessed to characterize the drug tolerance of the assay.

Question 9: In light of recent feedback regarding the drug tolerance of other screening immunogenicity assays, we have begun to assess drug tolerance at 250, 375, and 500 ng/ml ADA. Is this consistent with FDA expectations?

FDA Response to Question 9:

Please, see response to question 8.

Question 10: Does our definition of treatment-emergence as a 4-fold or greater increase in titer compared to baseline seem reasonable? And can this definition be broadly applicable across other molecules?

FDA Response to Question 10: *A four-fold increase in titer compared to baseline is reasonable to define a sample as treatment emergent when a two fold dilution scheme is used. However, there are different methods for reporting titer and consequently other valid methods for defining a method as treatment emergent. For example, treatment emergent responses may be defined by increases in titer above assay variability when titers are calculated by extrapolating the dilution to the cut point.*

Meeting Discussion: An alternative method for determining titer is to interpolate the linear portion of the curve to the cut point. When that method is used assay variance can be determined and used to define treatment emergent responses.

Additional comments:

FDA noted that ADA assays are reviewed by the product quality divisions. FDA's expectation is that the assays will undergo thorough development and validation similar to assays used in a GMP or CLIA environment.

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/s/

SUSAN L KIRSHNER
09/08/2014



IND 100834

MEETING PRELIMINARY COMMENTS

Eli Lilly and Company
Attention: Brian E. Wagner, Pharm.D.
Director, Global Regulatory Affairs
Lilly Corporate Center/ Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wagner:

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

We also refer to your May 30, 2014, correspondence, requesting a meeting to discuss and gain alignment with the FDA on Lilly's platform approach to ADA and NAb assay development and definitions for immunogenicity related terms.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call Andrew Shiber, at (301) 796-4798.

Sincerely,

{See appended electronic signature page}

Susan Kirshner, Ph.D.
Review Chief
Division of Therapeutic Proteins
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: C
Meeting Category: CMC

Meeting Date and Time: July 30, 2014 1:00 PM - 2:00 PM Eastern Daylight Savings
Meeting Location: FDA White Oak
10903 New Hampshire Avenue
White Oak Building 71, Conference Room: 2244
Silver Spring, Maryland 20903

Application Number: IND 100834
Product Name: Ixekizumab.
Sponsor/Applicant Name: Eli Lilly and Company

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for July 30, 2014 1:00 PM - 2:00 PM Eastern Daylight Savings between Eli Lilly and Company and the Office of Biotechnology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Purpose of meeting: The purpose is to discuss the following points:

1. The sponsor's approach and interpretation of minimum required dilution (MRD) data.
2. Approaches to cut point determination including using baseline Phase 2 and/or Phase data to set a cut point.
3. Eli Lilly's focus on assay sensitivity and drug tolerance with our current format versus alternative/competitor formats.
4. The sponsor's approach to determining treatment emergence.

Names of drug: Ixekizumab.

Indication: For the treatment of psoriasis.

2.0 DISCUSSION

General Comments:

There are many assay formats and platforms available to detect anti-drug antibodies (ADA). Each assay format has advantages and limitations and therefore, no single assay format will fit all products. During assay development multiple assay formats may be evaluated and the most promising format further developed and validated for clinical studies. Consequently, a single approach to assay validation is unlikely to adequately address all assay parameters. Irrespective of the format and platform, assays should be suitable for their intended purpose that is: sensitive, specific, precise, able to detect relevant immunoglobulin isotypes and optimized to address potential interference of the sample matrix.

The purpose of ADA assays is to allow for a more complete understanding of the safety and efficacy of the drug. Therefore, it is critical to accurately classify samples as positive or negative so that the impact of ADA on adverse events and changes in efficacy or PK can be established.

Minimal REQUIRED Dilution (MRD)

Discussion Points

Question 1: Does our approach for MRD determination seem adequate and sufficient?

FDA Response to Question 1:

For this specific assay format (ACE), your approach to MRD determination is adequate because detection of ADAs is performed in the absence of matrix components and excess drug. However, for other assay formats in which matrix components might contribute to high background signal and interfere with the detection of ADAs, this approach is inadequate. For other assay formats we recommend that the Minimum Required Dilution be established using a panel of individual samples from untreated patient population or healthy donors. Samples should be serially diluted and tested in the selected assay format together with the assay diluent. The MRD is the lowest sample dilution that yields a signal close to that of the assay diluent. Selection of the MRD should minimize assay background while ensure adequate assay sensitivity. Therefore, it is recommended that MRD do not exceed 1:100.

Question 2: Does the FDA have general recommendations for instances in which recovery in human serum is much different than that of buffer—for instance, when hyperimmune monkey serum or affinity-purified antibody contains a large amount of anti-Fc reactivity that will be reactive in buffer but suppressed by the high amount of IgG Fc present even in diluted human serum?

FDA Response to Question 2:

Our interpretation of the question is that you are concerned about the presence of anti Fc antibodies in the positive control antiserum. If the positive control antibody is expected to contain high anti Fc reactivity, we recommend that a more suitable positive control be developed (e.g rabbit) and optimized.

Determination of Cut Point

Discussion Points

Question 3: With regard to the tier 1 cut point, does FDA believe that our approach to set a disease state specific cut point based on a 95th percentile threshold from baseline patient data is sufficient?

FDA Response to Question 3:

The adequacy of your approach to establish the assay cut point for ixekizumab depends on the specific data you obtained during the validation exercise for your specific assay. As a general approach, a screening cut point should be established using at least 50 normal human serum samples. This sample size allows statistical determination of the variability of study population and the assay. Outliers should be identified using an adequate statistical method and removed from the cut point calculation. Samples that are true positives at baseline should also be removed from the cut point calculation. Once statistical outliers and true positive samples are

removed from the data set, the data should be analyzed using a suitable statistical approach that takes into account the distribution of the data. Regardless of the approach selected to analyze the cut point data, the screening cut point should be set using a 5% false positive rate to maximize the possibility to detect all ADA positive samples. Once established, the assay cut point should be confirmed using treatment naïve samples from the target population.

Samples with pre-existing antibodies are most frequently identified by comparing the results of the cut point samples tested in the presence and absence of drug. Samples with pre-existing antibodies generally demonstrate a large decrease in signal in the presence of drug.

Question 4: Does this approach seem reasonable to generally apply to other assays?

FDA Response to Question 4:

The adequacy of the approach to establish the cut point of an assay depends on different factors like assay format, matrix components, target population, among others and should be selected based on the data obtained during the assay validation exercise. For many assay formats, calculating the cut point based on the variability of the response of treatment naïve serum samples is appropriate.

Question 5: With regard to the tier 2 cut point, what advice does FDA have for instances such as this when the calculated value is so high, and does our choice of a more conservative 50% threshold to minimize missing true positives seem prudent?

FDA Response to Question 5:

Like the screening cut point, the confirmatory cut point should be established based on assay variability. The most common approach to confirming the specificity of an ADA response is to use unlabeled drug to inhibit the binding of ADA to labeled drug. Therefore, the most common approach to establishing the specificity cut point is to determine the assay variability of treatment naïve patient samples tested in the presence of unlabeled drug, to account for the impact of unlabeled drug on the assay. In such cases, the confirmatory cut point will be the % inhibition just above the assay variability. The confirmatory cut point should be established using appropriate statistical methods.

Determination of Sensitivity

Discussion Points

Question 6: Sensitivity was determined using affinity-purified antibody from monkeys hyperimmunized with ixekizumab spiked into normal human serum samples and then analyzing those samples at the MRD (1:5) of the ACE assay. Does this approach seem reasonable?

FDA Response to Question 6:

The approach to assessing the sensitivity of your assay is adequate.

Question 7: What recommendations does FDA have for instances in which affinity-purified antibody contains a large amount of anti-Fc reactivity that will be suppressed by IgG Fc present in diluted human serum? In this case, would it be considered acceptable to use monoclonal antibodies against the complementarity determining regions (CDRs) of the therapeutic antibody to determine sensitivity?

FDA Response to Question 7:

In the case you positive control is not adequate for your assay format, a new positive control antibody should be developed.

Assessment of Drug Tolerance

Discussion Points

Question 8: Our approach to determine drug tolerance of our assay consisted of using 500 ng/ml affinity-purified antibody from monkeys hyperimmunized with ixekizumab spiked into normal human serum samples containing 0.1-500 µg/ml of ixekizumab, and then analyzing those samples at the MRD (1:5) of the ACE assay. Does this approach seem acceptable?

FDA Response to Question 8:

Your proposed study design is used by some companies. However, drug tolerance is highly dependent on both the concentration of drug and the concentration of ADA in the sample. Therefore, we recommend assessing samples with different concentrations of the positive control antibody including a low concentration that gives signals near the cut point of the assay and different concentrations of drug. This approach will provide a better understanding of the overall assay tolerance.

Question 9: In light of recent feedback regarding the drug tolerance of other screening immunogenicity assays, we have begun to assess drug tolerance at 250, 375, and 500 ng/ml ADA. Is this consistent with FDA expectations?

FDA Response to Question 9:

Please, see response to question 8.

Definition of Treatment-Emergent Immunogenicity and Selection of Samples to Test in the Neutralizing Assay

Discussion Points

Question 10: Does our definition of treatment-emergence as a 4-fold or greater increase in titer compared to baseline seem reasonable? And can this definition be broadly applicable across other molecules?

FDA Response to Question 10:

A four-fold increase in titer compared to baseline is reasonable to define a sample as treatment emergent when a two fold dilution scheme is used. However, there are different methods for reporting titer and consequently other valid methods for defining a method as treatment emergent. For example, treatment emergent responses may be defined by increases in titer above assay variability when titers are calculated by extrapolating the dilution to the cut point.

Question 11: What is FDA's current recommendation with regard to which samples should be analyzed in the neutralizing assay – treatment emergent samples only, or all confirmed positive samples (including baseline) from the screening assay?

FDA Response to Question 11:

All confirmed positive samples should be analyzed in the neutralizing antibody assay. This allows for a more complete understanding of the impact of pre-existing antibodies on safety and efficacy.

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/s/

SUSAN L KIRSHNER
07/29/2014



IND 100834

MEETING MINUTES

Eli Lilly and Company
Attention: Brian E. Wagner, PharmD
Director, US Regulatory Affairs
Lilly Corporate Center/ Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wagner:

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

We also refer to the teleconference between representatives of your firm and the FDA on April 30, 2014. The purpose of the meeting was to discuss the development program for (ixekizumab).

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

If you have any questions, call Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance meeting

Meeting Date and Time: April 30, 2014; 9:00 a.m. ET
Meeting Format: Teleconference

Application Number: IND 100834
Product Name: (ixekizumab)
Proposed Indication: Treatment of plaque psoriasis
Sponsor Name: Eli Lilly and Company

Meeting Chair: David Kettl, MD
Meeting Recorder: J. Paul Phillips

FDA ATTENDEES

Stanka Kukich, MD, Deputy Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Milena Lolic, MD, Clinical reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Carin Kim, PhD, Biostatistics Reviewer, DB III
Michele Daugherty, PhD, Product Quality Team Leader, DMA
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP III
Elektra Papadopoulos, MD, Study End Points Team Leader, SEALD
Yasmin Choudhry, MD, Study End Points Reviewer, SEALD
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
J. Paul Phillips, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Carlos Garner, PhD, Sr. Director, US Regulatory Affairs
Kimberly Sterling, PharmD, Director, Health Outcomes
Janelle Erickson, PhD, Principle Research Scientist, Statistics
Debbie Guttman-Carlisle, Research Scientist, US Regulatory Affairs
Robin Wojcieszek, RPh, Sr. Director, US Regulatory Affairs
Michael Heffernan, MD, Sr. Medical Director
Brian Wagner, PharmD, Director, US Regulatory Affairs
April Naegeli, PhD, Sr. Research Scientist, Global Health Outcomes
Enkeleida Nikai, MBA, Sr. Research Scientist, Global Health Outcomes
Baojin Zhu, PhD, Sr. Research Scientist, Statistics
Dana Hardin, MD, Director, US Regulatory Affairs

Purpose of the Meeting:

Discuss the Itch NRS responder definition and strategy for analyzing and reporting Itch NRS data in the (ixekizumab) Phase 3 psoriasis clinical program

Regulatory History

We have had the following meetings/teleconferences with you:

- 01/29/2008 Clinical Hold teleconference
- 06/22/2011 Guidance meeting
- 11/07/2012 Guidance meeting
- 09/04/2013 Guidance—Written Responses
- 11/01/2013 Guidance—Written Responses
- 01/28/2014 Guidance—Written Responses

We have sent the following correspondences:

- 11/26/2007 IR letter
- 02/06/2008 Clinical Hold letter
- 02/07/2008 IR letter
- 03/18/2008 Advice/IR letter
- 04/17/2008 IR letter
- 05/02/2008 Remove Clinical Hold letter
- 04/22/2010 Advice/IR letter
- 02/07/2012 Advice/IR letter
- 05/30/2012 Advice letter
- 07/09/2012 Advice/IR letter
- 07/18/2012 Advice/IR letter
- 08/28/2012 Advice/IR letter
- 04/09/2013 Advice/IR letter
- 04/17/2013 Advice/IR letter
- 06/13/2013 Advice/IR letter
- 08/01/2013 Advice/IR letter
- 08/08/2013 Advice/IR letter
- 10/03/2013 Proprietary Name Granted letter
- 11/18/2013 Advice/IR letter
- 11/20/2013 Harmonized Annual Report Due Date Granted letter
- 03/10/2014 Advice letter

Preliminary Agency Comments

As previously communicated, itching severity is a clinically relevant concept for patients with moderate to severe plaque type psoriasis. The Agency also previously communicated that information about the ability of an instrument to measure a PRO and satisfaction of elements or the PRO guidance does not necessarily imply that particular patient outcomes are appropriate for eventual product labeling. Responder definitions related to itch were not provided when the relevant protocols were reviewed by the Agency in 2011 and 2012.

The Agency cannot concur at this time with your proposed responder definition for the Itch NRS. Additional information will be necessary to evaluate who might be clinically meaningful responders for this patient reported outcome, particularly since you did not establish inclusion criteria with respect to the Itch NRS in the phase 3 protocols. We will need to consider information such as the number of subjects with reported itching at baseline and the number of suggested itch responders, as well as evaluation of the itch response data for subjects who received placebo treatment. Additional discussion of the clinical meaningfulness of your proposed responder definition(s) should be presented in your application. The selection of clinically meaningful responders needs to take into consideration that, for example, the clinical implications of a subject with a baseline Itch NRS of 4 who would be a “responder” might be different than subjects who have a baseline Itch NRS of 10 and demonstrate the same numerical decrease on the Itch NRS.

You should also provide a scientific rationale that data from study JADP for baricitinib has relevance for the proposed PRO itch claims for ixekizumab.

Specific aspects of eventual product labeling cannot be addressed at this time, and will be considered during review of the complete BLA application.

Question 1:

Based upon the methodological approach and evidence presented, does the FDA agree that the proposed Itch NRS responder definition is sufficient to demonstrate a clinically meaningful treatment benefit in the target population and therefore is acceptable as a target for a labeling claim of improvement in itching severity? If the FDA does not agree, what alternative approach would the Division advise Lilly to take in order to establish an Itch NRS responder definition that is sufficient?

Response:

Using the optimal ROC cutoff point for which the Youden Index (YI) is maximized, you stated that a “3 point reduction range is optimal in predicting sPGA change from baseline ≤ -2 ”. You then stated that “these data suggest a ≥ 3 point reduction in itch NRS score is a clinically meaningful responder definition” (page 15). However, the Agency has the following comments regarding your approach in selecting a “clinically meaningful” point reduction on the itch NRS.

- Note that the success criterion for the sPGA endpoint is achieving clear (0) or almost clear (1), which is a stricter criterion than a ≤ -2 change from baseline to Week 12.
- The proposed criterion of ≤ -3 change on the itch NRS corresponds to a smaller criterion for success than that on the sPGA scale, assuming the categories in the two scales are equally spaced. Therefore, you should propose a higher cutoff point for the success criterion on the itch NRS scale.
- Your Table 6.3 shows that the sPGA change from baseline ≤ -2 group (i.e., sPGA score was improved from baseline by 2 or more points) had -5.27 itch NRS (with a median of 6) change from baseline, and the sPGA change from baseline ≥ -1 group (i.e., the sPGA score was reduced from baseline score by < 2 points, did not change or worsened) had -2.45 mean itch NRS change from baseline to Week 12. With only a -3 change reduction required on the itch NRS to be considered a “responder”, the itch NRS change of 3 point

or more could easily be obtained for those in the sPGA change from baseline ≥ -1 group as well.

- Your conclusion for clinically meaningful responder definition is based on pooled data from 5-arm study JADP. Placebo success rates for PRO are often high and responder cut-off of 3 points on itch NRS is difficult to accept as clinically meaningful in the absence of placebo data for comparison. Furthermore, while 3 grade improvement might be clinically meaningful for someone with baseline score of 5, the same may not apply for subject with baseline score of 10.
- Your YI findings (Table 6.5) show that the YI is maximized at 36.97 for “-3 change” on the itch NRS; however, note that your YI at “-4 change” on itch NRS is very close to that of the “-3 change” at 36.67. You might consider calculating the predicted probabilities for success on the sPGA for different cutoff points of change on the itch NRS.
- Furthermore, subjects who are “clear” on the sPGA are expected to have no itch. You might consider an approach based on the subset of subjects who were clear on the sPGA scale.

Question 2:

Does the FDA agree that Lilly’s SAPs regarding the Itch NRS are acceptable to support inclusion of the labeling concept of improvement in itching severity? If the FDA does not agree, what alternative approach would the Division advise Lilly to take in order to analyze Itch NRS data to support a label claim of treatment benefit?

Response:

You have proposed to analyze the results of the itch NRS as a continuous variable as the major secondary endpoint with an analysis of proportions using a responder definition (i.e., ≥ 3 point reduction on the NRS) as a supportive analysis. Provide a rationale for this approach instead of specifying the analysis of proportions as the major secondary endpoint.

Using the responder definition above (i.e., ≥ 3 point reduction in itch NRS score from baseline to Week 12), you proposed to compare treatment groups using pseudo-likelihood-based mixed-effect model of repeated measures (MMRM). It should be noted that such an approach that incorporates information from each visit might not be clinically meaningful yet the analysis might yield statistically significant overall treatment effect by considering the overall data. The Agency recommends that you consider a responder definition at each time point. Also, for a labeling claim, results from two trials should be presented for replication of study findings.

Question 3:

Does the FDA agree that if ixekizumab were to show an improvement in itching severity versus placebo based on the revised responder definition, this benefit could be described in labeling and in promotional materials? If the FDA does not agree, what alternative approach would the Division advise Lilly to take to describe the benefit of improvement in itching severity?

Response:

The evidence you submitted demonstrates that the Itch NRS is an appropriate measure of the severity of Itch in the proposed context of use. However, we have comments concerning their responder definition and proposed statistical analysis plan (see response to questions 1 and 2).

It is important to note that a similar level of evidence is needed to support promotional claims as for labeling claims. The decision on acceptance of itch severity improvement for the labeling of your product will be made in the context of review of the overall BLA application.

Meeting Discussion:

In response to the FDA comments, the sponsor stated that they would conduct additional analyses as recommended by the FDA, including the analysis of responders on the itch NRS scale for the subset of sPGA responders (sPGA score of 0). In addition, the sponsor proposed to change the responder definition on the PRO scale from 3 to 4 point reduction. The FDA responded that we cannot make any agreement on the responder definition in the absence of reviewing the pertinent data. The sponsor agreed to submit the findings of their additional analyses to the FDA.

The FDA also noted that for the itch endpoint to be considered in the labeling, not only is the definition (i.e., success criteria) of a responder on the itch NRS a critical element, but the proportion of subjects who are responders would also be an important factor. In addition, such endpoint should be prespecified and controlled for multiplicity along with the other secondary endpoints.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](#).

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/s/

DAVID L KETTL
05/01/2014



IND 100834

**MEETING REQUEST-
WRITTEN RESPONSES**

Eli Lilly and Company
Attention: Brian E. Wagner, PharmD
Director, Global Regulatory Affairs
Lilly Corporate Center/ Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Wagner:

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

We also refer to your submission dated November 14, 2013, containing a Type C meeting request. The purpose of the requested meeting was to obtain input on the guidance on the logistical and formatting aspects of the planned BLA prior to the pre-BLA meeting.

Further reference is made to our Meeting Granted letter dated November 26, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your November 14, 2013 background package.

If you have any questions, call Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Guidance

Application Number: IND 100834
Product Name: ixekizumab
Proposed Indication: psoriasis
Sponsor Name: Eli Lilly and Company
Regulatory Pathway: §351 of the Public Health Service Act

Purpose:

To obtain input on the guidance on the logistical and formatting aspects of the planned BLA prior to the pre-BLA meeting

Preliminary Comment:

We note that Phase 3 trials are still ongoing and blinded, and our responses are based on the information provided in the briefing document. No preliminary Phase 3 safety and efficacy information has been provided. We acknowledge that you intend to request a pre-BLA meeting once the results of Phase 3 are available later this year. We may have additional recommendations and requests for information when the Phase 3 trial data is evaluated.

Question 1:

Does FDA have any comments or questions about the content and organization of the TOC?

Response:

It appears that your proposed electronic BLA submission is organized according to general Agency recommendations and from a technical standpoint seems appropriate.

A linked Note to Reviewer (section 1.2) needs to briefly describe where information can be found throughout the application.

We note that the proposed table of contents for Module 3, Quality, appears to reflect information that would normally be submitted to support a new drug application. Refer to the “ICH Harmonised Tripartite Guideline; The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality –M4Q(R1), Quality Overall Summary of Module 2 and Module 3: Quality” regarding information relevant to include in the eCTD structure for a biologics licensing application. For example, 3.2.S.2.3 should include information related to the source and starting materials of biological origin; the source, history, and generation of the cell substrate; and cell banking system, characterization, and testing.

Question 2:

Does FDA agree with the list of studies identified by Lilly as requiring financial disclosure information on its investigators and when this information will be collected?

Response:

Based on our understanding of your eventual application, your proposal appears to be consistent with the Agency's requirement that financial disclosure information should be submitted for all clinical investigators who conducted clinical studies for which you intend to rely on to establish efficacy and any study which makes a significant contribution to the safety of the product. You should refer to the discussion of these requirements in the February 2013 Agency guidance, Financial Disclosure by Clinical Investigators.

The proposed timing for collection of individual financial disclosure information is acceptable.

Question 3:

Does FDA agree with Lilly's proposal to use a QBR template and to provide this information as an appendix to Module 1.2? If FDA agrees with the use of the QBR template, would FDA please provide Lilly with the current version of the QBR template?

Response:

We have no objection to your proposal of providing additional Clinical Pharmacology information using a QBR template to aid the review of your application at the time of BLA submission.

We have attached a QBR template that includes a list of general questions applicable for most biological products. However, we remind you that additional questions may be added to the general template when we review your application for ixekizumab.

It is acceptable to place the QBR guide in m1.2 section. Be sure to provide a clear leaf title so reviewers can quickly identify sections of the document.

Question 4:

Does FDA agree with the proposed criteria for notable events, including which events will include individual patient narratives as outlined in Table 5.2?

Response:

The criteria for events listed in Table 5.2 are generally acceptable. We note again that phase 3 trial data has not been presented for evaluation as trials remain ongoing and blinded.

You have recently identified allergy/hypersensitivity as potential risk associated with ixekizumab administration. In order to fully understand the spectrum and nature of these reactions, we recommend that events for allergic reactions/hypersensitivities include both moderate and severe reactions.

Question 5:

Does FDA agree with the proposed format for the patient narratives for each category of notable patients (see Appendix 5)?

Response:

The proposed format for the patient narratives is acceptable; however, we recommend that all narratives contain a medical summary.

We agree with your proposal that all patients for whom a narrative is created will be listed in tables (line listings) called “Tables of Significant and Notable Patients”. The “Tables of Significant Notable Patients” should provide electronic links to individual narratives and corresponding CRFs.

Question 6:

Does FDA agree with Lilly’s plan for submitting patient CRFs described above and outlined in Table 5.2?

Response:

Your plan for submitting CRFs for each patient listed in the Table 5.2 is acceptable. A study's CRFs should be placed in a CRF folder under the applicable trial with a file tag of "case-report-forms." CRFs for additional patients should be readily available during the review of your BLA should we need to request them.

Question 7:

Does FDA agree that Lilly’s plan for the 4-month safety update is acceptable?

Response:

Your plan is acceptable.

To facilitate the review, in addition to proposed updated integrated analysis sets containing initial submission data and the 4-month safety update data, provide integrated safety analysis set containing 4-month safety update data from the ongoing studies RHAI, RHAT, RHAZ, RHBA, RHBC, and RHBL.

It is acceptable to separate safety analysis from study RHAP (in patients with psoriatic arthritis) from ongoing studies in patients with psoriasis.

Question 8:

Does FDA agree with the report types for submission?

Response:

Your proposal to include full CSRs for all studies conducted in psoriasis population studies in the BLA submission is appropriate.

You proposed to submit two population PK/PD reports specifically for Study RHAZ and Study RHAI (Table 5.1). Include in your BLA submission an integrated population PK/PD analysis with data from all appropriate clinical studies to describe the exposure-response relationship of your product in subjects with psoriasis.

Question 9:

Does FDA agree with the planned sensitivity analysis for handling missing data for binary outcomes?

Response:

The Agency has commented on the statistical analysis plan concerning the methods for handling missing data in the Advice Letter sent on 4/17/2013. You are now proposing a new sensitivity analysis for handling missing data (i.e. placebo multiple imputation). It would be difficult to concur with your proposed approach as it is difficult to make judgments based on your assumptions and methodology. Provide a scientific justification for your proposed sensitivity analysis or propose other simpler approaches as a sensitivity analysis for handling missing data.

Question 10:

Does FDA agree with Lilly's plan for integrating (safety) data?

Response:

You propose five integrated analysis datasets for safety:

1. Integrated RHAZ, RHBA, and RHBC dataset (Induction Dosing Period)
2. Integrated RHBA and RHBC dataset (Induction Dosing Period)
3. Integrated RHAZ and RHBA dataset (Maintenance Dosing Period)
4. Integrated RHAG, RHAJ, RHAZ, RHBA, RHBC, RHAT, and RHBL dataset (All Study Periods)
5. All Rheumatoid Arthritis (RA) Ixekizumab Exposures Integrated Analysis Set

Your proposal is acceptable.

Question 11:

Does FDA agree with the proposed integrated efficacy analyses?

Response:

For the integrated efficacy analysis, you plan to use the MMRM model with missing data imputed using modified baseline observation carried forward. The Agency recommends that the approach for handling the missing data in the integrated efficacy summary to be the same as that for the primary analysis for the individual clinical trials. Also, while you may conduct modeling approach for the integrated efficacy, the Agency recommends a simple approach based on pooling dataset from the relevant clinical trials, as this makes it easier to interpret study findings at the time of efficacy evaluation.

Question 12:

Does FDA agree with Lilly's plan to evaluate the ixekizumab dose-response relationship?

Response:

Yes.

Question 13:

Does FDA agree on the choice of subgroups for integrated efficacy analyses?

Response:

Yes.

Question 14:

Does FDA agree with the choice of subgroups for assessing the impact of weight and BMI on the sPGA and PASI?

Response:

For BMI subgroups we recommend that you use commonly used Body Mass Index Table (http://www.nhlbi.nih.gov/guidelines/obesity/bmi_tbl.pdf) to define categories.

You proposed to use different thresholds as the cut-off points for the same variable defining the subgroups in your subgroup analysis. It would be difficult to interpret the findings of such analysis with overlapping threshold. However, your analysis could be considered exploratory for choosing a certain cut-off point for each variable to define the subgroups.

The impact of weight should be assessed according to earlier recommended weight categories for RHBL study: <80 kg, 80 to 100 kg and >100 kg.

Question 15:

Does FDA agree with the proposed safety analyses?

Response:

Your overall safety analysis plan appears reasonable. However, see the preliminary comment at the beginning of these meeting responses. We are provided recommendations based on our understanding of your development program to date but have not had an opportunity to consider the Phase 3 trial experience.

Question 16:

Does FDA agree with the definition for identifying “common” TEAEs?

Response:

You defined common TEAEs as TEAEs that occur in $\geq 1\%$ (before rounding) of total ixekizumab-treated patients. That approach is reasonable.

Question 17:

Does FDA agree with the proposed approach for the analysis of laboratory evaluations?

Question 18:

Does FDA agree with the proposed analyses of blood pressure and pulse?

Question 19:

Does FDA agree with these categorical threshold definitions?

Question 20:

Does FDA agree with the proposed analyses of ECGs?

Question 21:

Does FDA agree with the categorical threshold definitions?

Response for questions 17-21:

In principal, the general elements of the proposed evaluations are acceptable.

Question 22:

Does FDA agree with the choice of subgroups for safety analyses?

Response:

The proposed 5 subgroups (demographic, geographic, concomitant topical therapy, allergy pre-medication and anti-drug antibody group) and additional subgroups if warranted are reasonable choices for safety analysis.

Question 23:

Does FDA agree with the proposed integrated safety analyses to evaluate the ixekizumab dose-response relationship?

Response:

The choice of safety population, treatment periods and comparator arms appears adequate for safety analysis of the ixekizumab dose-response relationship.

Question 24:

Does FDA agree with the criteria being used for selection of cerebrocardiovascular events for adjudication?

Response:

The criteria for selection of cerebrocardiovascular events for adjudication are acceptable.

Question 25:

Does FDA agree with the categories of adjudicated events to be used for analysis of cerebrocardiovascular events?

Response:

The proposed CV categories are acceptable. We recommend that you include TIA as a separate category considering that some TIAs may be reclassified as strokes after independent adjudication.

Question 26:

Does FDA agree with the planned analyses for infections, allergic reactions/hypersensitivities, and injection site reactions as outlined in Sections 5.6.3, 5.6.5, and 5.6.6 of the PSAP (Appendix 3)?

Question 27:

Does FDA agree with the MedDRA PTs used to search for TEAEs of infections and allergic reactions/hypersensitivities as provided in Attachments 5 to 8 (infections) and 9 to 10 (allergic reactions/hypersensitivities) of the PSAP (Appendix 3), and for injection site reactions as provided in Section 5.6.6 of the PSAP?

Response for questions 26 and 27:

The selection of MedDRA PTs and planned analysis for TEAEs for infections, allergic reactions/hypersensitivities, and injection site reactions is acceptable.

Question 28:

Does FDA agree with the proposed AE listing for the other AESIs?

Response:

In addition to infections, allergic reactions/hypersensitivities, and injection site reactions you have identified hepatic AEs, cytopenias, CV AEs, malignancies and depression as AESIs. Based upon our current understanding of ixekizumab safety profile, the listing is adequate.

Question 29:

Does FDA agree with Lilly's plan to submit the formats listed in Table 5.5 (acknowledging that a conversion strategy from the observed data was used to create SDTM using SDTM, Version 1.2, and SDTM Implementation Guide, Version 3.1.2 [IG v3.1.2], including Amendment 1 for all Phase 2 and Phase 3 studies)?

Response:

For submission of biopharmaceutics and clinical pharmacology analysis data sets, we noted that Section 5.7.1 of the meeting package contains your plan which is in part similar to our general recommendations shown below.

- Submit NONMEM control streams of the base and final model for population PK analysis.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). Submit a model development decision tree and/or table which gives an overview of modeling steps.
- In data sets for pharmacokinetic (PK), pharmacodynamic (PD), and exposure-response relationship analysis, any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Separately the reasons for subject removal should be provided for each subject in a separate file linked to their individual case report form.
- All analysis datasets used in non-model-based analysis should be submitted in the xpt format.

For Phase 3 Studies RHAZ, RHBA, and RHBC you plan to submit SDTM and ADaM datasets and note that the tables, figures, and listings in the study reports are based on these ADaM datasets. As these files were used in your analysis, the approach is acceptable.

Include in your BLA submission any statistical programs for complex or nonstandard analyses (e.g. multiple imputation, MMRM).

Additional comments for electronic data submission:

The Agency prefers Sponsor to submit datasets based on the [Study Data Specifications](#) (currently 2.0). However, in general, the Agency accepts datasets, which comply, within a reasonable timeframe, with previous versions of the Study Data Specifications and other related guidance; based on the timing of protocol design, protocol initiation, and data collection.

The Agency expects Sponsor to evaluate the risk involved converting study data collected to standardized data, if applicable. The Agency prefers Sponsor to submit study data conversion explanation and rationale. The study data conversion rationale and explanation should address either scenario; decision rationale for not converting or decision rationale for converting. The Agency expects Sponsor's evaluation and rationale include study data scientifically relevant to the application's safety and efficacy representation. As such, the evaluation and explanation may include rationale based on the pooling/integrating of data from multiple studies.

The [PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017](#) guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. Sponsor should design and implement data standardization in all research protocols to be included in regulatory submissions, as required based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. Sponsor should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization ([CDASH](#)) standard for design and implementation of data collection instruments.

The Agency's methodology and submission structure supports research study design, as indicated in the [Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications](#) and the [Study Data Specifications](#). The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. Sponsor should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See [SEND](#), [SDTM](#) and [ADaM](#) as referenced in [Study Data Specifications](#)). Study analyses datasets should be traceable to the tabulations datasets.

In addition, please reference the [CDER Common Data Standards Issues Document](#) for further information on data standardization in submissions.

Additional Links:

[Electronic Regulatory Submissions and Review Helpful Links](#)

We prefer that you arrange a test submission prior to actual submission. Refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at esub@fda.hhs.gov, or for standardized data submission questions, contact edata@fda.hhs.gov.

Question 30:

Does FDA agree that submitting 2 IDBs in the CDISC SDTM and ADaM formats is acceptable (that is, IDB-SDTM and IDB-ADaM)?

Response:

See above responses. According to Table 5.5, the IDB-ADaM will include integrated datasets from 11 studies. However, in Section 5.4 you describe plans for five integrated analysis sets (that will integrate 2 to 7 studies depending on the objective of the integrated dataset); notably, none of the proposed integrated databases will include all 11 studies. Thus the rationale for creating the IDB-ADaM based on 11 studies is not clear.

Question 31:

Does FDA agree with Lilly's plan to submit define.pdf and define.xml for individual study SDTM, IDB-SDTM, individual ADaM (Phase 3 studies only), and IDB-ADaM datasets?

Response:

You should also include the define.pdf and define.xml files for the analysis datasets for any Phase 2 psoriasis studies.

Question 32:

Does FDA agree that the device-specific information (as described in Section 5.8) is appropriate for inclusion in an MAF? If not, what device-specific information needs to be included in the BLA, in addition to being included in the MAF?

Response:

The list of documents from Table 5.6 you propose to put into a Device Master File is acceptable for the device-only testing. However, the final finished product of the drug-device combination product testing should be placed in the BLA to demonstrate the safety and efficacy of the product as a whole.

You are reminded of the November 12, 2012 meeting discussion regarding the device aspects of the development program.

Additional CMC Microbiology Quality comments:

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- Monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Column resin and UF/DF membrane sanitization and storage validation data and information (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications. The bioburden limit should be (b) (4) (3.2.S.4).
- Qualification data for bioburden and endotoxin test methods performed (b) (4) (3.4.S.4).
- The effect of hold time on endotoxin recovery should be assessed (b) (4) (b) (4) (b) (4). The studies should be conducted using containers of similar composition as those used for drug substance during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the aseptic process and sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- (b) (4) retention study (b) (4).
- Sterilization and depyrogenation of (b) (4) drug product. (b) (4) should be described.
- (b) (4) microbial controls and hold times. Hold times should be validated at manufacturing scale.
- (b) (4)

- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Media fill and environmental monitoring procedures should be described.
- A description of the routine environmental monitoring program.
- Shipping validation studies.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the microbial barrier) should be demonstrated for the complete manufacturing process. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress and should include routine manufacturing process defects as controls. We recommend that container closure integrity testing be performed *in lieu* of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).
 - Qualification data for bioburden, sterility and endotoxin test methods performed (b) (4) (where applicable) and the drug product, as appropriate (3.2.P.5).
 - Perform the Rabbit Pyrogen Test on three batches of drug product in accordance with 21 CFR 610(b).
 - The effect of hold time on endotoxin recovery should be assessed (b) (4) (b) (4)
- (b) (4) The studies should be conducted using containers of similar composition as those used for drug product during hold. Effects of sampling containers on endotoxin recovery should also be evaluated.

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

We note that you have submitted an initial PSP (iPSP) and are now considering the FDA advice provided to you in response to your iPSP in a letter dated November 18, 2013.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

Appendix

CLINICAL PHARMACOLOGY SUMMARY

1. Goal

In addition to summarizing the relevant findings the goal of the Clinical Pharmacology Summary is to focus sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions a generic questionnaire is provided that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address.

The Summary generated by sponsors is a **stand-alone word document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple dose, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths,

quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 GENERAL CLINICAL PHARMACOLOGY

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology, dose-ranging, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal $t_{1/2}$ and AUC.

2.4 Exposure-Response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship. Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g.

age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-effectiveness relationship. Provide point estimate as well as a measure of the inter-subject variability for continuous and categorical endpoints. Indicate proportion of responders, if applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C_{max} or C_{min} is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Of major interest are safety endpoints determining the therapeutic range. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, C_{max} or C_{min} is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) C_{max} and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of

the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the exposure-response relationship for both efficacy and safety of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C_{max} , t_{max} , AUC, $C_{max,ss}$, $C_{min,ss}$, $C_{max,ss}/C_{min,ss}$, $t_{max,ss}$, AUC $_{0-\tau}$, CL/F, V/F and $t_{1/2}$ (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C_{max} , C_{min} , CL/F and $t_{1/2}$ of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute bioavailability of drug of parent drug and relative bioavailability, lag time, t_{max} , $t_{max,ss}$, C_{max} , $C_{max,ss}$ and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 What are the characteristics of drug metabolism?

2.5.7 What are the characteristics of drug elimination in urine?

2.5.8 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C_{max} and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.9 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC_{0-τ} at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.6 INTRINSIC FACTORS

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate

intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C_{max}, clearance, volume of distribution and t_{1/2} for pairs studied: elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity x vs. race/ethnicity y, mild vs. severe target disease

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (dose or interval) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Body Weight

2.6.2.3 Elderly

2.6.2.4 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.5 Race/Ethnicity

2.6.2.6 Renal Impairment

2.6.2.7 Hepatic Impairment

2.6.2.8 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug

metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?
Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.2 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report the 90% confidence intervals about the geometric mean ratio for AUC and C_{max} for the drug of interest in the presence and absence of each of the co-administered drugs. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report 90% confidence intervals about the geometric mean ratio for AUC and C_{max} of each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.3 Does the label specify co-administration of another drug?

2.7.4 What other co-medications are likely to be administered to the target population?

2.7.5 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

2.8.1 *Was the manufacturing process changed during the development program? (Include a table listing all the products used throughout the clinical development programs.)*

2.8.2 *Was the proposed to-be-marketed formulation comparable to the formulation used in the pivotal clinical trials with respect to pharmacokinetics and/or pharmacodynamics?*

2.9 Analytical Section

2.9.1 What bioanalytical methods are used to assess therapeutic protein concentrations?

Briefly describe the methods and summarize the assay performance. Please provide tables for each assay to address the below questions

2.9.1.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.1.2 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.1.3 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.1.4 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20^{\circ}\text{C}$.

2.9.1.5 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.2 What bioanalytical methods are used to assess the pharmacodynamic markers?

Briefly describe the methods and summarize the assay performance.

2.9.3 What bioanalytical methods are used to assess the immunogenicity?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference (including drug interference) and matrix, etc.

2.9.3.1 What is the performance of the binding anti-product antibody assay(s)?

2.9.3.2 What is the performance of the neutralizing assay(s)?

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

/s/

SUSAN J WALKER
01/28/2014

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 125521

LATE-CYCLE MEETING MINUTES

Eli Lilly and Company
Attention: Brian E. Wagner, PharmD
Director, Global Regulatory Affairs, US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Wagner:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for ixekizumab.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 2, 2015.

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

If you have any questions, call Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 2, 2015; 11:00 a.m. ET

Meeting Format: Teleconference

Application Number: BLA 125521

Product Name: ixekizumab

Applicant Name: Eli Lilly and Company

Meeting Chair: Jill Lindstrom, MD

Meeting Recorder: Paul Phillips

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III

Amy Egan, MD, MPH, Deputy Director, ODE III

Kendall Marcus, MD, Director, DDDP

Jill Lindstrom, MD, Deputy Director, DDDP

Tatiana Oussova, MD, Deputy Director for Safety, DDDP

Nancy Xu, MD, Acting Associate Director for Labeling, DDDP

Jane Liedkta, MD, Clinical Reviewer, DDDP

Matthew Guerra, PhD, Biostatistics Reviewer, DBIII

Howard Anderson, PhD, Product Quality Team Lead, OBP

Michael Di, PhD, Product Quality Reviewer, OBP

Colleen Thomas, PhD, Quality Microbiology Reviewer, DMA

Bo Chi, PhD, Quality Microbiology Reviewer, DMA

LT Jibril Abdus-Samad, PharmD, Labeling Reviewer, OBP

Wayne Seifert, MS, Consumer Safety Officer, DIA

Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP3

Dhananjay Marathe, PhD, Senior Pharmacometrics Reviewer, OCP

Yasmin Choudhry, MD, Medical Officer, COA

Leyla Sahin, MD, Medical Officer, DPMH

Ida-Lina Diak, PharmD, MS, Safety Evaluator Team Leader, DPV

Jessica Weintraub, PharmD, Safety Evaluator, DPV

Carlos Mena-Grillasca, RPh, Safety Evaluator, DMEPA

LCDR David Shih, MD, MS, Deputy Director, DEPI

Sukhminder Sandhu, PhD, Team Leader, DEPI

Andrew Mosholder, MD, MPH, Medical Officer, DEPI

Gabriella Anic, PhD, Epidemiology Reviewer, DEPI

Jamie Wilkins-Parker, PharmD, Team Leader, DRISK

Erin Hachey, PharmD, Risk Management Analyst, DRISK

Jasminder Kumar, PharmD, Risk Management Analyst, DRISK

Maria Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III

Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
CDR Lydia Springs, RN, MSHS, CPMH, Senior Regulatory Health Project Manager, DDDP
Felecia Wilson, MS, Regulatory Health Project Manager, DDDP
J. Paul Phillips, MS, Lead Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEE

Pegah Khorrami, Independent Assessor

APPLICANT ATTENDEES

Aarti Shah, PhD, Team Leader
Allison Kennington, PhD, Sr. Director, CM&C Regulatory
Robert Seevers, PhD, CM&C Regulatory
Carl Garner, PhD, Sr. Director, Regulatory Affairs
Robin Wojcieszek, RPh, Sr. Director, Regulatory Affairs
Brian Wagner, PharmD, Director, Regulatory Affairs
Olawale Osuntokun, MD, Medical Director
Dana Hardin, MD, Medical
Dan Braun, MD, Global Patient Safety
Jeff Baxter, MS, Clinical Project Management
Janelle Erickson, PhD, Statistics
(b) (4) Consultant—Tailored Therapeutics

1.0 BACKGROUND

BLA 125521 was submitted on March 23, 2015 for ixekizumab.

Proposed indication: treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

PDUFA goal date: March 23, 2016

FDA issued a Background Package in preparation for this meeting on November 18, 2015.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

Clinical

Change in Approach Regarding the Timing of Pediatric Studies

Agency thinking regarding the timing for development of systemic agents for the pediatric population for the treatment of serious conditions such as moderate to severe psoriasis has evolved since this agreement was made. In light of the positive risk-benefit profile relative to other currently available treatments (MTX, CSA, TNF inhibitors), the Agency would like to accelerate the timeline for initiating pediatric studies for ixekizumab. A revised pediatric development plan should be submitted that includes a PK study and a study assessing safety and activity in all relevant pediatric populations. The relevant age should be subjects ages (b) (4) 17 years as was previously negotiated in the PSP dated March 30, 2014.

Suicidal Behavior Concern

A potential signal for a safety concern regarding suicidal behavior in subjects with moderate to severe plaque psoriasis treated with ixekizumab is being evaluated at this time.

Meeting Discussion:

The applicant proposed removing language in the product labeling (b) (4)
(b) (4)
(b) (4). The Agency requested that the applicant submit their rationale in writing and propose alternative language for labeling.

3. Information Requests

Chemistry, Manufacturing and Controls

Endotoxin spiking and hold study data for drug substance and drug product are pending.

Meeting Discussion:

The Agency acknowledged that the applicant will be providing the requested information for endotoxin spiking in January 2016.

Clinical

A clinical information request was sent on 12 November 2015. A response was requested by 19 November 2015.

Meeting Discussion:

The Agency acknowledged that the applicant had provided the requested clinical information.

4. Postmarketing Requirements/Postmarketing Commitments

Chemistry, Manufacturing and Controls

- Perform a repeat microbial retention study (b) (4) using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation, or a reduced exposure time for the challenge organism. Provide the

summary data, the associated report, and justification for any modifications to the study. If any (b) (4) parameters are changed as a result of the study, update the BLA file accordingly.

- Provide data from two additional commercial drug product batches to support the maximum hold time for pooled drug substance. The hold time study should include the maximum hold time a (b) (4) followed by the maximum hold time under ambient conditions. Provide data from two additional commercial drug product batches to support the maximum hold time for drug product (b) (4). The supporting data should include bioburden and endotoxin testing results from samples (b) (4). (b) (4). Data from process simulations (b) (4) may be provided *in lieu* of data from drug product batches.

Meeting Discussion:

The applicant agreed to the CMC postmarketing commitments and did not have any further questions regarding these.

Clinical

PK study and a study assessing safety and activity in all relevant pediatric populations

Meeting Discussion:

The Agency stated that the applicant could consider harmonization with international regulatory bodies in terms of the timing for addressing PREA requirements for ixekizumab. The Agency requested that the applicant provide a high level pediatric plan to address PREA and submit the plan and proposed timelines by the end of 2015. The detailed protocol could be submitted and discussed at a later time.

The Agency stated that a postmarketing requirement to address pregnancy exposure is being considered; however, the optimal study design is still under discussion.

Meeting Discussion:

The Agency provided clarification regarding the presentation of clinical trial adverse reactions data in section 6 of labeling. For infections and cytopenias, the Agency requested that the applicant provide the following exposure adjusted incidence rates:

- 1) Induction period for ixekizumab Q2W (n=1167)
- 2) Induction period for placebo (n=791)
- 3) Maintenance period for ixekizumab Q4W (received ixekizumab Q2W during induction; n=332)
- 4) Maintenance period for placebo (received placebo during induction; n=19)
- 5) Overall for ixekizumab (all Q2W exposure during induction [n=1167] plus Q4W exposure during maintenance [received Q2W during induction; n=332])
- 6) Overall for placebo (all placebo exposure during induction [n=791] plus placebo exposure during maintenance [received placebo during induction; n=19])

Addendum:

In addition to the exposure adjusted incidence rates listed above, the Agency requests the unadjusted incidence rates.

5. Review Plans

- Labeling discussions
- Continue to investigate suicidal behavior concern
- Internal wrap-up meeting
- Complete Division and Office level signatory reviews
- Take action on BLA application

6. 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.

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/s/

JILL A LINDSTROM
12/11/2015



BLA 125521

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Eli Lilly and Company
Attention: Brian E. Wagner, PharmD
Director, Global Regulatory Affairs, US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Wagner:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for ixekizumab.

We also refer to the Late-Cycle Meeting (LCM) scheduled for December 2, 2015.
Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: December 2, 2015; 11:00 a.m. ET
Meeting Location: FDA WO22/Room 1313

Application Number: BLA 125521
Product Name: ixekizumab
Indication: treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Applicant Name: Eli Lilly and Company

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

- **Discipline Review Letters**

No Discipline Review letters have been issued to date.

- **Substantive Review Issues**

The following substantive review issues have been identified to date:

Clinical

Change in Approach Regarding the Timing of Pediatric Studies

Agency thinking regarding the timing for development of systemic agents for the pediatric population for the treatment of serious conditions such as moderate to severe psoriasis has evolved since this agreement was made. In light of the positive risk-benefit profile relative to other currently available treatments (MTX, CSA, TNF inhibitors), the Agency would like to accelerate the timeline for initiating pediatric studies for ixekizumab. A revised pediatric development plan should be submitted that includes a PK study and a study assessing safety and activity in all relevant pediatric populations. The relevant age should be subjects ages ^(b)₍₄₎ 17 years as was previously negotiated in the PSP dated March 30, 2014.

Suicidal Behavior Concern

A potential signal for a safety concern regarding suicidal behavior in subjects with moderate to severe plaque psoriasis treated with ixekizumab is being evaluated at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

LCM AGENDA

1. Introductory Comments – (RPM/ CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – (Clinical)

Each issue will be introduced by FDA and followed by a discussion.

Clinical

- Change in approach to timing of PREA studies
- Suicidal behavior concern

3. Information Requests – (CMC/ Clinical)

Chemistry, Manufacturing and Controls

- Endotoxin spiking and hold study data for drug substance and drug product are pending.

Clinical

- A clinical information request was sent on 12 November 2015. A response was requested by 19 November 2015.

4. Postmarketing Requirements/Postmarketing Commitments – (CMC/ Clinical)

Chemistry, Manufacturing and Controls

- Perform a repeat microbial retention study (b) (4) using a suitable surrogate solution. Alternatively, perform the study using a modified process, a modified formulation, or a reduced exposure time for the challenge organism. Provide the summary data, the associated report, and justification for any modifications to the study. If any (b) (4) parameters are changed as a result of the study, update the BLA file accordingly.
- Provide data from two additional commercial drug product batches to support the maximum hold time for pooled drug substance. The hold time study should include the maximum hold time a (b) (4) followed by the maximum hold time under ambient conditions. Provide data from two additional commercial drug product batches to support the maximum hold time for drug product (b) (4). The supporting data should include bioburden and endotoxin testing results from samples (b) (4). Data from process simulations performed with media may be provided *in lieu* of data from drug product batches.

Clinical

- PK study and a study assessing safety and activity in all relevant pediatric populations

5. Review Plans – (RPM)

- Labeling discussions
- Continue to investigate suicidal behavior concern
- Internal wrap-up meeting
- Complete CDTL and Division Director reviews
- Complete signatory review
- Take action on BLA application

6. Wrap-up and Action Items – (RPM)

- Wrap-up: (see above review plans summary)
- Action items: TBD

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/s/

KENDALL A MARCUS
11/18/2015