

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761055Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 761055	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: Dupixent Established/Proper Name: Dupilumab Dosage Form: Injection, 150 mg/mL		Applicant: Regeneron Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A
RPM: Matthew White		Division:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☒ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - 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) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <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>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>3/29/17</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ 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):
(confirm chemical classification at time of approval)

- | | |
|--|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☒ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☒ 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 required 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)	☐ Yes ☒ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ 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)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Approval – 3/28/17
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included
❖ Proprietary Name - Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	- Conditionally acceptable: 8/31/16 - Review: 8/26/15
❖ Labeling reviews (indicate dates of reviews)	RPM: 9/13/16 DMEPA: 3/10/17 DMPP/PLT (DRISK): 12/19/16 OPDP: 12/14/16 SEALD: ☒ None CSS: ☒ None Product Quality 3/22/17 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	9/15/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	N/A
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
Applicant is on the AIP	☐ Yes ☒ No

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

- This application is on the AIP - 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>)	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC <u>11/16/16</u> If PeRC review not necessary, explain:	
❖ Breakthrough Therapy Designation	☐ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Granted: 11/18/14
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	11/17/14
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>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	9/22/16: Filing Communication 12/19/16: Review Extension – Major Amendment 1/9/17: Advice – Withdrawal of Major Amendment 2/7/17: Late-Cycle Meeting Background Package
❖ 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)	MPC minutes – 11/14/14
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	2/24/16 – CMC only 12/16/15 – Cancelled
EOP2 meeting (<i>indicate date of mtg</i>)	5/21/14 5/8/14 – CMC only
Mid-cycle Communication (<i>indicate date of mtg</i>)	11/9/16
Late-cycle Meeting (<i>indicate date of mtg</i>)	2/21/17
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	10/2/15: Type B – CMC only 6/22/15: Type B – Cancelled 8/4/14: Type A 1/23/13: Type C 5/26/10: Pre-IND

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	3/27/17
Division Director Summary Review (<i>indicate date for each review</i>)	3/27/17
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	3/27/17
PMR/PMC Development Templates (<i>indicate total number</i>)	3/27/17
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	3/24/17
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	3/24/17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	COA: 12/14/16 CBER: 1/4/17 DPMH: 1/19/17
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	N/A
• 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>)	1/13/17: No REMS required
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	2/14/17: Clinical inspection summary 2/15/17: Letter-Kolodziej 2/15/17: Letter-Regeneron 2/15/17: Letter-Sofen
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	12/7/16

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	12/19/16
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	11/2/16
• Supervisory Review(s) <i>(indicate date for each review)</i>	12/6/16
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	12/5/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	Included in P/T review, pages 18-19
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review <i>(indicate date for each review)</i>	☒ None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	☒ 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>	Executive Summary: 3/9/17 Facilities: 3/7/17 Immunogenicity: 1/27/17 Drug Product: 1/30/2017 Drug Product – Micro: 2/13/17 Drug Substance: 2/6/2017 Drug Substance – Micro: 1/31/17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	CDRH/OC/DMQ: 12/7/16, 21/21/16 CDRH/GHDB: 2/1/2017
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	2/6/17
☐ Review & FONSI <i>(indicate date of review)</i>	N/A
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable – 3/7/16 ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	N/A
Finalize 505(b)(2) assessment	N/A
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☒ Done (Send email to CDER OND IO)
❖ For products that need to be added to the flush list (generally opioids): Flush List 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	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ 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	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

MATTHEW E WHITE
03/29/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761055

GENERAL ADVICE

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Associate Director Regulatory Affairs
777 Old Saw Mill River Rd
Tarrytown, NY 10579

Dear Dr. Babilonia:

Please refer to your Biologics License Application (BLA) dated and received July 29, 2016, submitted under section 351(a) of the Public Health Service Act for Dupixent (dupilumab) injection, 150 mg/mL.

We also refer to your November 23, 2016, major amendment to this application, containing information related to the addition of (b) (4) as a (b) (4).

We also refer to our December 19, 2016, letter in which we acknowledged receipt of your major amendment and we notified you that we were extending the user fee goal date by three months to provide time for a full review of the submission.

We have received your January 6, 2017, amendment to this application, withdrawing the information related to the addition of (b) (4) as a (b) (4). Therefore, the original user fee goal date, March 29, 2017, remains in effect.

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

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

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/s/

KENDALL A MARCUS
01/09/2017



BLA 761055

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Associate Director Regulatory Affairs
777 Old Saw Mill River Rd
Tarrytown, NY 10579

Dear Dr. Babilonia:

Please refer to your Biologics License Application (BLA) dated and received July 29, 2016, submitted under section 351(a) of the Public Health Service Act for Dupixent (dupilumab) injection, 150 mg/mL.

On November 23, 2016, we received your November 23, 2016, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is June 29, 2017.

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

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

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/s/

KENDALL A MARCUS
12/19/2016

PeRC Meeting Minutes
November 16, 2016

PeRC Members Attending:

Lynne Yao
John Alexander
Meshaun Payne
Gettie Audain
Greg Reaman
Donna Snyder
Gil Burkhart
Freda Cooner
Lily Mulageta
Dionna Green
Gerri Baer
Wiley Chambers
Victor Baum
Rosemary Addy
Shrikant Pagay
Adrienne Hornatko-Munoz
Megha Kaushal

Agenda

	Non Responsive				
9:00					
9:15					
10:10					
10:20					
10:30					
					adults patients whose disease is not adequately controlled by prescription therapy, (b) (4)
10:50	BLA	Dupixent (dupilumab) Partial Waiver/Deferral (with Agreed		Matthew	(b) (4) or (b) (4) not
	Non Responsive				
11:00					
11:10					
11:20					
11:40					

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Non Responsive

Dupixent (dupilumab) Partial Waiver/Deferral (with Agreed iPSP)

- Proposed Indication: For the treatment of atopic dermatitis in adults patients whose disease is not adequately controlled with topical prescription therapy
- This product triggers PREA as a new active ingredient and has a goal March 29, 2017.
- The division indicates that there are no changes to the Agreed iPSP and the sponsors' current pediatric plan.
- The sponsor is requesting waiver in children < 6 months of age because studies are impossible or highly impracticable. Atopic dermatitis that is not adequately controlled with topical therapy is not able to be diagnosed this early because patients have generally not been proven to fail therapy during the first 6 months of life.
- The sponsor is requesting deferral in children from ages 6 months to 18 years of age.
- The PeRC reiterated their support of a staged approach to studies in pediatric patients because of the potential serious adverse events with systemic biologic therapy. However, the division noted that in all the other programs evaluating dupilumab, no malignancies attributed to the drug have been identified.
- *PeRC Recommendations:*
 - The PeRC agreed to the waiver in pediatrics less than 6 months of age, since studies are impossible and highly impracticable.
 - The PeRC agreed to the deferral of pediatrics ages 6 months to 18 years of age until adult studies are completed and ready for approval.
 - The PeRC recommends that the final PMR dates reflect dates agreed upon in the iPSP.

Non Responsive

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/s/

GETTIE AUDAIN
12/02/2016



BLA 761055

MID-CYCLE COMMUNICATION

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Associate Director Regulatory Affairs
777 Old Saw Mill River Rd
Tarrytown, NY 10579

Dear Dr. Babilonia:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Dupixent (dupilumab) injection, 150 mg/mL.

We also refer to the teleconference between representatives of your firm and the FDA on November 9, 2016. 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 Matthew White, Senior Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Snezana Trajkovic, MD
Clinical Team Leader
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: November 9, 2016 at 10:00 a.m.

Application Number: BLA 761055

Product Name: Dupixent (dupilumab) injection, 150 mg/mL

Proposed Indication: For the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical (b) (4)

Applicant Name: Regeneron Pharmaceuticals, Inc.

Meeting Chair: Snezana Trajkovic, MD

Meeting Recorder: Matthew White

FDA ATTENDEES

Amy G. Egan, MD, MPH, Deputy Director, Office of Drug Evaluation III (ODE III)
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Jill Lindstrom, MD, FAAD, Deputy Director, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Brenda Carr, MD, Clinical Reviewer, DDDP
Michele Dougherty, PhD, Review Chief, Division of Biotechnology Review and Research IV (DBRR IV)
Cristina Ausin, Ph.D. Team Leader, DBRR IV
Gunther Boekhoudt, PhD, Product Quality Reviewer, DBRR IV
Lakshmi Narasimhan, PhD, Microbiology Reviewer, Office of Process and Facilities (OPF)
Wayne Seifert, Consumer Safety Officer, Division of Inspectional Assessment (DIA)
Sapana Patel, PharmD, Lead Reviewer, Center for Devices and Radiological Health (CDRH), General Hospital Devices Branch (GHDB)
Crystal Lewis, BA, RN, Consumer Safety Officer, CDRH, Division of Manufacturing and Quality (DMQ)
Tri Bui-Nguyen, PhD, MS, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Matthew White, Regulatory Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

Peggha Khorrami, Independent Assessor, Eastern Research Group

APPLICANT ATTENDEES

Gianluca Pirozzi, MD, PhD, VP, Global Project Head, Sanofi

Nia Tatsis, PhD, Associate VP, Regulatory Affairs, Sanofi
Armi-Desiree Luthman, Senior Director, Regulatory Affairs, Sanofi
Frank Seebach, MD, Executive Director, Regulatory Affairs, Regeneron
Neil Graham, MD, VP, Program Direction, Regeneron
Elisa Babilonia, PhD, Associate Director, Regulatory Affairs, Regeneron
Ned Braunstein, MD, Senior VP, Regulatory Affairs, Regeneron
Richard Swanson, PhD, Senior Director, Regulatory Affairs, Regeneron
Bolanle Akinlade, MD, Executive Director, Clinical Sciences, Regeneron
Jennifer McNay, PhD, Executive Director, Clinical Sciences, Regeneron
Michele Lastro, PhD, Associate Director, CMC Regulatory Sciences, Regeneron
Alexandria Richart, PhD, CMC Regulatory Sciences Specialist, Regeneron
Kris Ghosh, PhD, Executive Director, CMC Regulatory Affairs, Regeneron

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

- Sanofi Winthrop Industrie FEI: 3003259844 is currently pOAI.
- We acknowledge that you may submit information supporting the introduction of (b) (4) to your BLA. Please note that this submission would require the following sections (as discussed during the February 24, 2016 CMC pre-BLA meeting):



And any additional information or data that would support [REDACTED] (b) (4)

This submission may constitute a major amendment to the Application, which would extend the goal date by three months to provide time for a full review of the submission.

- According to section 3.2.P.3.1, LeTrait is the only testing site listed for the following assays: appearance of PFS within the safety system, sterility, needle shield removal force, and activation and unlocking force. [REDACTED] (b) (4)

- We are also providing the following [REDACTED] (b) (4) comments to assist your preparation of the [REDACTED] (u) (4) for the [REDACTED] (u) (4) site. These comments expand on the advice we previously provided during the pre BLA meeting for dupilumab drug product.

[REDACTED] (b) (4)

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b.

(b) (4)

Meeting Discussion:

The sponsor provided a summary of the information to be submitted supporting (b) (4). As a consequence of this submission, some of the existing files will be updated. The sponsor confirmed that a reviewer's guide highlighting the differences in the current files will be included in the submission. This BLA submission supporting the introduction of (b) (4) will be reviewed per Agency procedures and upon its receipt a decision will be made as to whether this submission constitutes a major amendment.

The sponsor asked when the Agency would decide if the submission of the (b) (4) constitutes a major amendment. The Agency explained that once the amendment is received, the Agency will evaluate its content and notify the sponsor as soon as possible of the decision. To expedite planning needed to support decision making regarding the amendment and how it will be classified, the Agency suggested that the sponsor notifies the Agency of their planned submission timelines when possible. The sponsor agreed to submit a correspondence to the BLA notifying the Agency when they will submit the BLA sections related to the (b) (4).

(b) (4)

Post Meeting Addendum:

1.

(b) (4)

2. Provide the address and FEI# for the (b) (4) facility

3.0 INFORMATION REQUESTS

- Two information requests sent November 3, 2016
- Information request sent November 4, 2016

Meeting Discussion:

The Agency acknowledge receipt of the sponsor's response to the November 3, 2016, information request regarding the validation data for assays use to assess post-vaccination immune response. Additional information requests may be forthcoming.

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.

5.0 ADVISORY COMMITTEE MEETING

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

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The proposed date for the Late-Cycle Meeting is January 22, 2017.

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/s/

SNEZANA TRAJKOVIC
11/23/2016



BLA 761055

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Associate Director Regulatory Affairs
777 Old Saw Mill River Rd
Tarrytown, NY 10579

Dear Dr. Babilonia:

Please refer to your Biologics License Application (BLA) dated and received July 29, 2016, submitted under section 351(a) of the Public Health Service Act for Dupixent (dupilumab) injection, 150 mg/mL.

We also refer to your amendments dated March 31, April 6, and June 29, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is March 29, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 29, 2016. In addition, the planned date for our internal mid-cycle review meeting is October 28, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

We request that you submit the following information:

Biostatistics

1. Your protocols specify that your efficacy assessment tools including the Investigator's Global Assessment (IGA) scale and the Eczema Area and Severity Index (EASI) are "provided in the study reference manual"; however, your study reference manuals do not show the category descriptors for the IGA scale. Submit the IGA scale, or identify its location in the BLA.

Clinical Pharmacology

2. Provide the names of the final population PK model (NONMEM and MONOLIX) and corresponding input datasets that were used for estimation of covariate effects including effect for anti-drug antibodies (ADA). The dataset names listed in the model files differ from the names of the provided datasets.
3. Provide the output tables from the final model, including parameters (Ke, CL, V, etc.) and exposure values (observed Ctrough, individual predicted AUC, and individual predicted Ctrough at Weeks 2, 4, 8, 12 and 16). Include USUBJID in these tables to facilitate linking with the subject identifier in clinical analysis datasets.
4. Submit a dataset for evaluation of exposure-response relationships for the following safety variables: ADRs of conjunctivitis, herpes simplex, and oral herpes. The dataset needs to include all subjects (i.e., do not exclude subjects who were discontinued or rescued before Week 16). Include separate identifier flags in the dataset for subjects who were Week 16 completers, subjects who discontinued before Week 16, subjects who discontinued before Week 16 due to treatment-emergent adverse event (TEAE), and subjects who received rescue therapy before Week 16, for potential sensitivity analysis.
5. Provide time-to-event datasets for the above safety variables along with the exposure data (i.e., observed and predicted Ctrough, and predicted AUC_{tau}) and conduct exposure-response analyses for these variables. Conduct these analyses by assigning observed/predicted Ctrough and AUC_{tau} closest to the time of safety event/discontinuation/rescue for subjects with these events and Week 16 exposure values for subjects with none of these events. Report the findings as incidence rates (incidence adjusted by time of exposure, e.g. per 100 person-year) for each quartile of exposure.

General Hospital Devices

6. In Module 3.2.P.2.4, it is stated a risk management plan is designed prior to a risk assessment; however, a risk analysis could not be located for the device constituent.

7. In Section 3.2.P.2, a biocompatibility summary of the applicable device components was provided; provide the location of the full biocompatibility tests performed which include cytotoxicity, sensitivity and irritation testing.
8. A description of the needle safety feature was provided; however, please provide the location within the DMF file for the specifications to the constituents.
9. You state the (b) (4) Needle Guard is cleared under (b) (4); however, a letter of authorization could not be located from the 510k holder. Please provide a letter of authorization so that we can review the safety and efficacy data within the associated 510k submission. Without the letter of authorization, we will not be able to leverage any data associated in the associated 510k to support your combination product.
10. In section, 3.2.P.8.3 long-term storage stability data to support shelf life will include testing of needle safety feature at end of shelf life; however, accelerated aging stability data does not include testing of the needle safety feature as an endpoint to support the end of shelf life performance. Include this as an endpoint to support performance at end of shelf life prior to approval of the BLA.
11. In section 3.2.P.5.6, release testing does not include activation of safety system or safety system unlocking force. Ensure that release testing includes testing to verify the safety system performs as intended after the manufacturing process.

PRESCRIBING INFORMATION

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

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

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

PROMOTIONAL MATERIAL

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We reference the partial waiver granted on November 10, 2015, for the pediatric study requirement for this application for pediatric patients preterm and term neonate (0 to 27 days) and infants from 1 to 5 months old, inclusive.

We reference the partial deferral granted on November 10, 2015, for the pediatric study requirement for this application for pediatric patients 6 months to less than 18 years of age.

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

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/s/

JILL A LINDSTROM
09/22/2016



BLA 761055

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Regeneron Pharmaceuticals, Inc
777 Old Saw Mill River Rd
Tarrytown, NY 10579

ATTENTION: Elisa Babilonia, Ph.D.
Associate Director, Regulatory Affairs

Dear Dr. Babilonia:

Please refer to your Biologics License Application (BLA) dated and received July 29, 2016, submitted under section 351(a) of the Public Health Service Act, for Dupilumab (b) (4) 300 mg.

We also refer to your correspondence, dated and received August 2, 2016, requesting review of your proposed proprietary name, Dupixent.

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

If any of the proposed product characteristics as stated in your August 2, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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 Tri M. Bui-Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. For any other information regarding this application, contact Matthew E. White, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4997.

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/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
08/31/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125104

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Viswanathan (Seenu) Srinivasan, Ph.D.
Director, CMC Regulatory Affairs
81 Columbia Turnpike
Rensselaer, NY 12144

Dear Dr. Srinivasan:

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

We also refer to the meeting between representatives of your firm and the FDA on February 24, 2016.

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 please contact the RBPM, Andrew Shiber at 301-796-4798.

Sincerely,

Cristina Ausin, Ph.D.
Acting Team Leader
Division of Biotechnology Review and Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Biotechnology Products (OBP)/Division of Biotechnology Review and Research I

Michele Dougherty, Ph.D.	Review Chief
Cristina Ausin, Ph.D.	Team Leader
Gunther Boekhoudt, Ph.D.	Product Quality

Office of Process and Facilities

Lakshmi Narasimhan, Ph.D.	Microbiology
Reyes Candau-Chacon, Ph.D.	Microbiology
Patricia Hughes, Ph.D.	Branch Chief

Office of New Drugs/Division of Dermatology and Dental Products

Snezana Trajkovic, M.D.	Clinical Lead
Brenda Carr, M.D.	Medical Officer

Office of Program and Regulatory Operations

Steven Kinsley, Ph.D.	Regulatory Business Project Manager
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SPONSOR ATTENDEES

Regeneron Pharmaceuticals

Ned Braunstein, M.D.	Senior Vice President, Regulatory Affairs
Jennifer McNay, Ph.D.	Executive Director, Process Sciences
Seenu Srinivasan, Ph. D.	Director, CMC Regulatory Affairs
Paul Vescio, Ph. D.	Manager, CMC Regulatory Affairs
Alexandria Richart, Ph.D.	CMC Regulatory Sciences Specialist, IOPS
Bernard Schilling, Ph.D.	Senior Director, Process Sciences, IOPS
Bola Akinlade, M.D.	Executive Director, Clinical Sciences
Frank Seebach, M.D.	Executive Director, Regulatory Affairs
Hanne Bak, Ph.D.	Vice President, Pre-Clinical Mfg & Process Development
Neil Graham, M.D.	Vice President, Program Direction
Paul Bigwarfe, Ph.D.	Director, Analytical Sciences, IOPS
Thomas Daly, Ph.D.	Vice President, Pre-Clinical Development & Protein Chemistry

Sanofi-Aventis

Antonella Lozito, Pharm.D.	Director, Global Regulatory Affairs
Christopher Homan, Ph.D.	Manager, New Product Quality
Estelle Chouin, M.S.	IDSL/PSO le Trait Duplilumab Project Leader
Gianluca Pirozzi, M.D., Ph.D.	Vice President, Global Project Lead
Brad Goering, Ph.D.	Director, Regulatory CMC Biologics
Nia Tatsis, Ph.D.	Vice President, Global Regulatory Affairs

MEETING MINUTES

Meeting Type: B
Category: CMC Only

Date: February 24, 2016
Time: 12:00PM Eastern Standard Time

Location: FDA White Oak
10903 New Hampshire Avenue
White Oak Building 21, Conference Room: 1537
Silver Spring, Maryland 20903

Application Number: IND 107969
Product Name: dupilumab

2.0 DISCUSSION

Drug Substance

Question 1:

Does the Agency agree with the future WCB lot qualification procedure and its annual reportable approach as outlined below?

FDA Response to Question 1:

Regarding the qualification of cell banks (WCB), you indicated your intention to include WCB (b) (4) this should be clarified in the BLA.

In general, qualification of a new WCB should include an assessment of in-process parameters and quality attributes for a defined number of DS lots manufactured with the new WCB. The WCB qualification protocol submitted to the BLA should include, in addition to the listed tests, a determination of gene copy number and a defined WCB stability testing frequency that takes into account the planned usage of the WCB lots and any extended interruption in manufacturing of the product. Be aware that all corresponding qualification results are required to support the approval of any new WCB.

The adequacy of the WCB qualification procedure will be a review issue. In the absence of an approved WCP qualification protocol or if the qualification protocol is deemed inadequate the qualification of a new WCB will have to be reported in a supplement as per 21CFR601.12.

Sponsor Responses:

We appreciate your advice. We will have production data in the BLA on WCB (b) (4). It will be important for us to have an approved qualification protocol in the BLA so that we may introduce the other WCBs into manufacturing as annual reportable changes. Considering the reproducibility of our processes, robust cell line technologies, and the

strength of our IPC program, we propose that (b) (4) is sufficient to qualify a new WCB. Does the Agency agree?

For production under the BLA, the WCBs would be used (b) (4)
We will clarify this in the BLA. An annual WCB stability testing program is in place (b) (4)
(b) (4) This is the same approach we are using for the Praluent BLA 125559.

Discussion: *Regeneron Pharmaceuticals discussed the rational of using (b) (4) to qualify a new WCB. FDA agrees with this approach provided that the manufacturing process for the WCB does not change. If the sponsor introduces changes in the current WCB manufacturing process, (b) (4) may be required to qualify the new WCB (b) (4)*
(b) (4)
egeneron also stated that the protocol for qualification of WCB and manufacturing process would be included in the BLA.

Question 2:

Does the Agency agree with the proposed approach to determining Drug Product (DP) Time Out of Refrigeration (ToR) for patients to be included in the product labeling?

FDA Response to Question 2:

The planned storage conditions appear appropriate. Testing should be sufficient to demonstrate that there are no changes to the purity, potency or microbiological attributes of dupilumab upon storage at 25°C.

In addition, the product label should specify that the ToR applies only to the intact container closure (i.e. prior to removing the needle guard).

Sponsor Response:

The Sponsor agrees with the Agency's comments. No further discussion needed.

No Meeting Discussion.

QUESTION 3:

The Sponsor has completed a drug product (prefilled syringe (PFS) manufacturing process validation campaign from material produced from the C2P1 manufacturing process. The campaign consisted of 3 lots produced at 100% of the intended commercial batch size, followed by 3 lots at approximately 30% of the intended commercial batch size. Data from the first 3 lots provide evidence that the process is able to produce material that meets its pre-determined specifications and quality attributes. A detailed data analysis and review of (b) (4) identified an issue (b) (4) and a need for optimization (b) (4)
(b) (4) This resulted in a refinement to the operating parameters during (b) (4) which necessitated the execution of 3 additional lots to supplement the initial validation. Data from the six validation batches produced from the initial and supplementary validation campaigns provides sufficient objective and scientific evidence that the process is capable of consistently delivering quality product.

Stability will be monitored for all six validation batches at real-time and accelerated storage conditions (5 °C and 25 °C, respectively). Stability under stress storage conditions (45 °C) will also be monitored. The Sponsor will provide 12 months of real-time stability data at the time of BLA submission from the three batches manufactured from the first validation campaign. Six months of stability data from the supplementary validation will also be provided at the time of BLA submission. The Sponsor will provide updated stability data (simple stability updates) during the review for all drug product batches and proposes to set shelf-life of the commercial product based on the cumulative real-time stability data from the three batches manufactured in the initial validation campaign. Does the Agency concur with the proposed approach to set shelf life for the Dupilumab drug product?

FDA Response to Question 3:

In general we agree with the proposed approach to set shelf life for the dupilumab drug product. However a final decision regarding the adequacy of the data to support licensure will be a review issue. Furthermore, the suitability of the stability data from dupilumab DP lots manufactured during PV1 campaign to support the product's shelf life will need to be confirmed comparing it with stability data from drug product lots manufactured using (b) (4)

(b) (4)

Sponsor Response:

Lots manufactured during the PV2 campaign will be used to demonstrate that (b) (4) does not compromise sterility of the drug product.

Discussion: Regeneron Pharmaceuticals discussed that the PV2 campaign was undertaken to show that (b) (4) did not affect the sterility of the product. The sponsor said that they planned to release the lots manufactured during the PV2 campaign, but they were not planning to release the lots manufactured during the PV1 campaign. FDA agreed with the strategy.

QUESTION 4:

The Sponsor has identified a (b) (4) the C2P1 process. (b) (4) which over time, result in the formation of particulates when the samples are stored at the long-term storage condition of 5 °C. Dupilumab drug product (DP) produced from C2P1 material has been used throughout Phase 3 pivotal clinical studies, and approximately 3,000 patients have been exposed to dupilumab manufactured with the C2P1 process, with no significant safety concerns observed. The Sponsor intends to commercialize the C2P1 manufacturing process based on demonstrated safety and efficacy data comparing DP derived from C2P1 (b) (4) and an earlier manufacturing process, C1P2 (b) (4).

Currently the Sponsor has limited the shelf life of C2P1-derived drug product based on the increase of particulates during long-term storage as determined by the USP <788> microscopic particle count test. The Sponsor intends to set end of shelf life specifications for particulate matter content using Micro-Flow Imaging (MFI). Does the Agency agree with the proposed control strategy for monitoring sub-visible particulates (b) (4) for commercialization of C2P1-derived drug product? Does the Agency agree that C2P1 shelf life could be extended beyond the current 15 months assigned to clinical material, assuming acceptable stability results are obtained for the lead stability lots using the proposed particulate matter control strategy?

FDA Response to Question 4:

In general we agree with the proposed control strategy which includes the following:

- *Setting a (b) (4) specification for DS.*
- *Monitoring sub-visible particulates in DP by MFI.*
- *Including PS80 content as part of DP release and stability specifications.*
- *Developing a method to quantify (b) (4)*

These control strategies are sufficient for monitoring sub-visible particulates (b) (4) for commercialization of C2P1-derived drug product; however, a final decision regarding the adequacy of the data and the assays to support licensure will be a review issue.

Regarding the proposal to extend the C2P1 shelf life beyond the current 15 months assigned to clinical material, the determination of the product's shelf-life will be based on all the available stability data. Therefore, it is premature to make a determination at this time

Sponsor Response:

The Sponsor thanks the Agency for their response.

No Meeting Discussion.

QUESTION 5:

The Sponsor proposes to implement an optimized DS manufacturing process designated as C2P2 (b) (4)

The Sponsor intends to include both C2P1 and C2P2 processes in the original BLA. To support registration of C2P2, the Sponsor proposes to perform an analytical comparability assessment of DS samples derived from both C2P1 and C2P2 manufacturing processes. Does the Agency agree that the proposed validation and analytical comparability studies are adequate to support registration of the C2P2 process, assuming drug substance from both C2P1 and C2P2 manufacturing processes are determined to be analytically comparable? Moreover, the Sponsor intends to provide the Agency with the Analytic Comparability Report around the time of the pre-BLA meeting. We ask that, as a post-meeting note, the Agency include in the meeting minutes its conclusion on whether the analytic comparability data will be sufficient to license the C2P2 process.

FDA Response to Question 5:

In general we agree that the proposed validation and analytical comparability studies are sufficient to support registration of the C2P2 process, however a final decision regarding the adequacy of the data to support licensure will be a review issue.

Please clarify whether [REDACTED] (b) (4) would be in operation during the pre-license inspection.

Sponsor Response:

[REDACTED] (b) (4)
[REDACTED] We will provide the Agency with our manufacturing schedule to help the Agency plan the pre-license inspection.

The Sponsor proposes that, given the similarity of the C2P1 and C2P2 manufacturing processes, the inspection of the C2P2 manufacturing process should be representative of the C2P1 process. Does the Agency agree?

We provided the Agency with an interim comparability report on the 18th of February, 2016. This report contains final data on release and characterization of DS and [REDACTED] (b) (4). The BLA will include DP release data and stability data for DS, [REDACTED] (b) (4) and DP. With respect to the data provided to date, would the Agency be able to provide, in their official meeting minutes, their assessment of the data to support comparability and approval of the C2P2 process?

Discussion: *FDA agreed that the inspection of the C2P2 process could be representative of the C2P1 process. The Sponsor asked for information on the potential timing of the PAI inspection. FDA stated that the inspection will be scheduled between filing and mid-cycle.*

[REDACTED] (b) (4)
[REDACTED] he Sponsor will determine the manufacturing schedule and give that information to FDA to assist in the scheduling of the facility inspection.

The Sponsor asked if the Agency had any comments on the analytic comparability report submitted on February 18, 2016. The FDA informed Regeneron that in the context of this meeting we are unable to discuss the comparability protocol. In addition, the FDA suggested for Regeneron re-submit the package as an amendment to the IND for review. The Agency will expedite the review of the amendment according to timelines defined for the review of products with a breakthrough therapy designation. Comments to the sponsor regarding the comparability data provided for the C2P2 process will be provided in a timely fashion to support the continued, rapid product development. The Sponsor agreed to resubmit the comparability report to the IND as an amendment for review.

QUESTION 6:

Does the Agency agree with the proposed contents and organization of the Module 3.2 Body of Data to support registration of material manufactured using both the C2P1 and C2P2

FDA Response to Question 6:

In general, we agree with the proposed contents and organization of the Module 3.2. However, we have some additional comments.

In the meeting package you indicate your intention to propose (b) (4) according to a protocol. However, table 31 does not include a protocol in section 3.2.P.8.3.

You indicate that section 3.2.P.5.4 will include tabulated summaries for (b) (4); however, according to table 31 you do not intend to provide validation information regarding the (b) (4). Validation is required for all intended commercial devices.

Regarding shipping validation, you have stated that you plan (b) (4). This approach is not acceptable. The simulated shipping validation information and data and the actual shipping validation protocol should be provided in the initial BLA submission.

The following items were not included in the Module 3 Table of Contents. These items should be provided in the BLA submission.

- (b) (4)
- (b) (4) data for the PFS during air transportation demonstrating maintenance of the sterile barrier.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).
- Endotoxin recovery data. (b) (4)

Sponsor Response:

The Sponsor thanks the Agency for their response. The simulated shipping validation results will be provided as part of the rolling submission.

Discussion: FDA agreed that the simulated shipping validation results could be provided in the latter stages of the rolling submission.

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/s/

CRISTINA AUSIN-MORENO
03/07/2016

PREMEETING COMMUNICATION**IND: 107969****Product:** Dupilumab**Regulatory Path:** §351 of the Public Health Service Act**Sponsor:** Regeneron Pharmaceuticals, Inc.

Proposed Indication: For the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapy, (b) (4), or (b) (4) not advisable. (b) (4)

Type of Meeting: Type B**Meeting Date:** December 16, 2015**Introductory Comment:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 16, 2015, at 8:30 a.m. in White Oak Building 22 between Regeneron Pharmaceuticals, Inc. and the Division of Dermatology and Dental Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Matthew White). 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 telecom). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions.

Purpose of the Meeting:

The purpose of this meeting is to discuss the development program for dupilumab.

Regulatory Correspondence History

We have had the following meeting(s)/teleconference(s) with you:

- 11/4/2015: Type B (guidance) meeting
- 10/2/2015: Type B (guidance) meeting
- 7/22/2015: Informal teleconference to discuss the pediatric study plan (PSP)

- 46 • 8/4/2014: Type A (guidance) meeting
- 47 • 5/21/2014: Type B (End-of-Phase 2) meeting
- 48 • 5/8/2014: Type B (CMC End-of-Phase 2) meeting
- 49 • 3/31/2014: Teleconference to discuss the pediatric study plan (PSP)
- 50 • 1/23/2013: Type C (guidance) meeting
- 51 • 11/22/2011: Teleconference to discuss Grade 4 adverse events (elevated CPK) which
- 52 occurred during Study R668-AD-0914
- 53 • 5/26/2010: Type B (pre-IND) meeting
- 54

55 We have sent the following correspondences:

- 56 • 11/18/2015: Grant rolling review letter
- 57 • 11/10/2015: Initial pediatric study plan (iPSP) – agreement letter
- 58 • 11/10/2015: Advice letter
- 59 • 10/20/2015: Advice letter
- 60 • 9/28/2015: Revised iPSP with Division comments
- 61 • 7/2/2015: Information request letter
- 62 • 6/15/2015: Draft preliminary responses for a type B meeting (cancelled)
- 63 • 6/12/2015: Advice letter
- 64 • 4/30/2015: Advice letter
- 65 • 4/13/2015: Advice letter
- 66 • 4/2/2015: Advice letter
- 67 • 4/2/2015: Advice/information request letter
- 68 • 2/19/2015: Advice letter
- 69 • 2/4/2015: Advice letter
- 70 • 1/30/2015: Advice letter
- 71 • 11/18/2014: Grant breakthrough therapy designation request letter
- 72 • 11/10/2014: Advice letter
- 73 • 10/27/2014: Advice letter
- 74 • 10/23/2014: Advice/information request letter
- 75 • 10/21/2014: Information request letter
- 76 • 10/7/2014: Information request letter
- 77 • 10/6/2014: Acknowledge breakthrough therapy designation request letter
- 78 • 8/27/2014: Advice letter
- 79 • 12/20/2013: iPSP advice letter
- 80 • 11/14/2013: Advice letter
- 81 • 10/4/2013: IRB waiver granted letter
- 82 • 8/21/2010: Study may proceed letter
- 83 • 7/12/2010: Acknowledge IND letter
- 84 • 7/12/2010: Advice letter
- 85

87 **Regulatory:**

88

89 **Question 10:**

90 Does the Agency agree with the Sponsor's proposal for studies to be considered "covered
91 clinical studies" for the purposes of providing financial disclosures and summary level
92 clinical site data for BIMO requirements?

93

94 **Response:**

95 The proposal is acceptable

96

97 You propose to submit BIMO data only for Studies 1334, 1416, 1224, and 1021 even
98 though there are 11 different studies listed for subjects with atopic dermatitis. Please note
99 that if clinical sites from one or more of the remaining seven studies are selected, then
100 BIMO data for those sites may be requested.

101

102 **Question 11:**

103 The Sponsor plans to submit a request for priority review at the time of submission of the
104 BLA. Does the Agency have any comments on this plan?

105

106 **Response:**

107 The decision on whether priority review will be granted will be based on the information
108 and data available at the time your complete BLA is submitted. If it is determined that
109 dupilumab, if approved, would provide a significant improvement in the safety or
110 effectiveness of the treatment of moderate-to-severe atopic dermatitis in adult patients
111 who are not adequately controlled with (b) (4) topical prescription therapy, or
112 (b) (4) not advisable, we will designate the review of BLA
113 as a priority review. If priority review designation is granted, we will inform you in
114 writing by Day 60 of the review.

115

116 If your application is granted priority review designation and the review team determines
117 that a first cycle approval is likely, we will consider an expedited review of your
118 marketing application.

119

120 Please be advised that not every marketing application for a breakthrough therapy-
121 designated drug will receive an expedited review. Each marketing application will be
122 evaluated on a case-by-case basis, taking all relevant factors into account, to determine if
123 an expedited review is appropriate. Below are examples of factors that may influence the
124 decision to conduct an expedited review even if other criteria for an expedited review are
125 met (although they do not necessarily rule out an expedited review):

126

- 127 • Resources to expedite the review are not available because of competing public
- 128 health priorities
- 129 • An advisory committee (AC) meeting is needed for reasons such as clinical trial
- 130 results or safety issues

- 131 • An unanticipated safety issue is identified that requires a risk evaluation and
- 132 mitigation strategy (REMS) with elements to ensure safe use
- 133 • Manufacturing issues are identified

134

135 Please note that designation of an expedited review of a marketing application for a
136 breakthrough therapy-designated drug will not change the PDUFA review performance
137 goals.

138

139 **Question 12:**

140 Based on the data from nonclinical and clinical studies conducted to date, as well as an
141 evaluation of the mechanism of action of dupilumab, there is no evidence of CNS activity
142 or signs associated with drugs of abuse. Does the FDA agree that Drug Abuse Liability
143 Assessment (DALA) studies for dupilumab are not required?

144

145 **Response:**

146 Yes.

147

148 **Product Quality Microbiology**

149

150 We are providing additional product quality microbiology comments for you to consider
151 during development of your commercial manufacturing process and preparation of your
152 351(k) BLA submission.

153

154 All facilities should be registered with FDA at the time of the 351(k) BLA submission
155 and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The
156 facility should be in operation and manufacturing the product during the inspection. A
157 preliminary manufacturing schedule for both the drug substance and drug product should
158 be provided in the Module 1 of the BLA to facilitate the planning of the pre-license
159 inspections during the review cycle. Please include in the BLA submission a complete list
160 of the manufacturing and testing sites with their corresponding FEI numbers.

161

162 The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information
163 and data summaries for microbial and endotoxin control. The provided information
164 should include, but not be limited to the following:

165

- 166 • Bioburden and endotoxin levels at critical manufacturing steps should be
- 167 monitored using qualified bioburden and endotoxin tests. Bioburden samples
- 168 should be collected (b) (4). The pre-established
- 169 bioburden and endotoxin limits should be provided (3.2.S.2.4).

170

171

172

173

174

175

- 176
177 • (b) (4)
178
179
180
181
182 • Bioburden and endotoxin data obtained during manufacture of at least three
183 conformance lots (3.2.S.2.5).
184
185 • Information and summary results from the shipping validation studies (3.2.S.2.5).
186
187 • Drug substance bioburden and endotoxin release specifications (3.2.S.4). Please
188 note that DS specification for bioburden should be (b) (4)
189 (b) (4).
190
191 • Summary report and results from bioburden and endotoxin test methods
192 qualification performed for (b) (4) the drug substance
193 (3.2.S.4).
194
195 • (b) (4)
196
197
198
199
200
201
202 The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation
203 data summaries to support the aseptic process and sterility assurance. For guidance on
204 the type of data and information that should be submitted, refer to the 1994 FDA
205 guidance for industry *Submission Documentation for Sterilization Process Validation in*
206 *Applications for Human and Veterinary Drug Products* at
207 [http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidanc](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf)
208 [es/ucm072171.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf).
209
210 The following study protocols and validation data summaries should be included in
211 Section 3.2.P.3.5:
212
213 • (b) (4)
214
215 •
216
217
218
219 •
220

- 221 (b) (4)
222
223
224 • (b) (4)
225
226 (b) (4)
227 • (b) (4) if applicable.
228
229 • Three successful consecutive media fill runs, including summary environmental
230 monitoring data obtained during the runs.
231
232 • A description of the routine environmental monitoring program.
233
234 • Shipping validation studies, including container closure integrity data.
235 Additionally for PFS, the difference in air pressures during air shipment may
236 cause movement of the plunger which may breach the sterility of PFS. Include
237 results to demonstrate that the PFS plunger movement during air transportation
238 does not impact product sterility.
239
240 • (b) (4) validation summary data and information, if applicable.
241

242 The following method validation information should be provided:
243

- 244 • Container closure integrity testing (3.2.P.2.5). System integrity (including
245 maintenance of the microbial barrier) should be demonstrated initially and during
246 stability. Container closure integrity methods validation should demonstrate that
247 the assay is sensitive enough to detect breaches that could allow microbial
248 ingress. We recommend that container closure integrity testing be performed in
249 lieu of sterility testing for stability samples at the initial time point and every 12
250 months (annually) until expiry (3.2.P.8.2).
251
252 • Summary report and results for qualification of the bioburden, sterility and
253 endotoxin test methods performed for (b) (4) (if applicable) and
254 the drug product, as appropriate.
255
256 • Summary report and results of the Rabbit Pyrogen Test conducted on three
257 batches of drug product in accordance with 21CFR 610.13 (b).
258
259 • Formulations with certain excipient and polysorbate combinations have been
260 reported to interfere with endotoxin recoverability in the USP LAL test methods
261 over time. The effect of hold time on endotoxin recovery should be assessed by
262 spiking a known amount of standard endotoxin (CSE or RSE) into undiluted in-
263 process samples (if applicable) and the drug product and then testing for
264 recoverable endotoxin over time. These studies should be conducted in the
265 containers in which the product and samples are held prior to endotoxin testing.

266
267 **Pharmacology/Toxicology**
268

269 No Pharmacology/Toxicology questions were included in the briefing document.
270 However, we have the following nonclinical comment.
271

272 Provide an updated comprehensive carcinogenicity risk assessment for your biologic
273 product when you submit the nonclinical data for your BLA and incorporate this
274 information into the label for your biologic product.
275

276 **Clinical Pharmacology:**
277

278 **Question 7:**

279 Does the Agency agree on the content and format of the Module 2.7.2?
280

281 **Response:**

282 Yes, based on the information provided in the briefing package, we agree that the content
283 and format of Module 2.7.2 would be in general acceptable to support our review of the
284 Clinical Pharmacology section of the BLA.
285

286 We acknowledge that you plan to conduct analyses to assess the impact of
287 immunogenicity on efficacy and safety based on subjects' anti-drug antibodies (ADA)
288 status. In addition to your planned pooling strategy for the integrated efficacy and safety
289 analysis, we recommend that you also assess the immunogenicity incidence and its
290 clinical impacts stratified by monotherapy and combination therapy. Clarify if longer
291 term immunogenicity data, e.g., up to 52-week data in study R668-AD-1225, will be
292 included in the overall immunogenicity assessment plan.
293

294 Your briefing package did not provide detailed information regarding the evaluation of
295 the impact of immunogenicity on PK of dupilumab. We have the following general
296 recommendations regarding the assessment of the immunogenicity impact on PK:
297

- 298 • We recommend that you include between-subject comparison (i.e., between ADA
299 positive subjects and ADA negative subjects) as well as within-subject
300 comparison (i.e., before ADA positive and after ADA positive) of PK data.
301
- 302 • We acknowledge that you will include subjects ADA status as a covariate in the
303 population PK analysis on an exploratory basis to evaluate the impact of ADA on
304 dupilumab PK. In the population PK analysis, further explore the necessity of
305 treating the subject ADA status as a time-varying variable for ADA status.
306
- 307 • You may consider exploring the use of ADA titer data in addition to the ADA
308 status in the analyses.
309

311 **Question 8:**

312 Does the Agency agree that the population PK and PK/PD analysis plans and the
313 proposed data sets for inclusion in these analyses will provide sufficient evidence to
314 enable FDA's Pharmacometric team review?

315

316 **Response:**

317 While the population PK and PK/PD analysis plans and the proposed data sets for
318 inclusion in these analyses may be sufficient to support our Pharmacometric review of
319 the BLA, we have the following comments:

320

321 Based on the information provided in the briefing package, we noted that at the proposed
322 time of BLA data cut-off (April 2016), the two monotherapy Phase 3 trials (R668-AD-
323 1334 and R688-AD-1416) would have been completed. We also noted that you currently
324 propose to include PK data at Week 16 or later from only approximately 50% of the
325 subjects in these two Phase 3 trials for the planned population PK and PK/PD analysis.
326 The Week 16 PK data could be critical for the analysis of dose-/exposure-response
327 relationship for efficacy to determine the optimal dosing regimen because the primary
328 and key secondary efficacy variables are evaluated at Week 16 of the two monotherapy
329 Phase 3 trials; therefore, we recommend that you include complete PK data up to Week
330 16 of the two monotherapy Phase 3 trials (R668-AD-1334 and R688-AD-1416) in the
331 population PK and PK/PD analysis at the time the clinical portion of the BLA is
332 submitted.

333

334 In addition to the dose-/exposure-response analysis for efficacy, conduct dose-/exposure-
335 response analysis for safety (e.g., adverse events of interests). The dose-exposure-
336 response analyses for both efficacy and safety would help the selection of the dosing
337 regimen that has the most favorable benefit-risk.

338

339 We have the following additional recommendations regarding your population PK and
340 PK/PD analyses and datasets submission:

341

- 342 • Submit NONMEM control streams of the base and final model for the population
343 PK analysis.
- 344
- 345 • Submit model codes or control streams and output listings for all major model
346 building steps, e.g., base structural model, covariates models, final model, and
347 validation model. These files should be submitted as ASCII text files with *.txt
348 extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- 349
- 350 • Submit a model development decision tree and/or table which gives an overview
351 of modeling steps.
- 352

354 **Biostatistics**

355

356 **Question 9:**

357 Does the Agency agree with the content and format of the electronic datasets to be
358 provided in the AD BLA for AD studies as well as supportive Asthma and NP studies?

359

360 **Response:**

361 Your proposal to submit both SDTM and ADaM datasets in SAS transport (xpt) format
362 along with define documents for all Phase 2 and 3 AD trials, and to submit the SAS
363 programs used to produce the derived datasets and the summary tables and figures for the
364 two monotherapy studies is acceptable. For ease of printing by reviewers, a define.pdf is
365 also recommended.

366

367 For endpoints that include imputations, include and clearly identify or flag both observed
368 and imputed outcomes. Note that the analysis dataset documentation file should include
369 sufficient detail, such as definitions or descriptions of each variable in the dataset,
370 algorithms for derived variables (including source variables used), and descriptions of the
371 codes used in factor variables. For all Phase 3 trials, include statistical programs for all
372 non-standard or model-based analyses (e.g., multiple imputation, MMRM, as applicable).
373 Include the study protocol, all protocol amendments, the statistical analysis plan, an
374 annotated copy of the case report form, generated treatment assignment lists, and the
375 actual treatment allocations (along with the date of enrollment).

376

377 **Clinical**

378

379 **Question 1:**

380

381 A) Does the Agency agree that the patient exposure including the safety database
382 planned to be included in the BLA is adequate to support the review for the
383 proposed indication?

384

385 B) Does the Agency agree with the proposal for the data cut-off and outputs to be
386 included in the BLA?

387

388 **Response:**

389 The table below displays your estimate of the number of subjects exposed to Dupilumab
390 at the time of the 120 day safety update to your BLA. At the time of submission of the
391 initial BLA, you will provide data from ~615 patients with AD that have been exposed
392 for ≥ 1 year to dupilumab 300 mg qw (b) (4)

393

395 **Table 2: Anticipated Exposure Database for the BLA**
 396

<i>Total AD patients exposed to dupilumab</i>				
	300 mg qw AD-1225 (Open Label)	300 mg qw AD-1224 (Placebo- controlled)	Day 120 safety update	Total Exposure at the Time of the Day 120 Safety update (300 mg qw)
≥6 months*	652	295	--	947
≥ 12 months**	388	228	165	781
≥ 18 months	33	0	---	33

397 * assumes 7% drop-out rate R668-AD-1224 and 10% drop out rate for R668-AD-1225

398 ** assumes 14% drop-out rate R668-AD-1224 and 10% drop out rate for R668-AD-1225

399

400 This database appears acceptable assuming no unanticipated safety signals emerge during
 401 review.

402

403 The planned data cut-off and outputs to be included in the BLA appear to be acceptable at
 404 this time.

405

406 **Question 2:**

407 Does the Agency agree with the proposed approach to the Day 120 safety update report?

408

409 **Response:**

410 The BLA cut-off date will be 27 April 2016, and the BLA submission is currently
 411 targeted for August 2016. Accordingly, for the Day 120 safety update report (SUR), the
 412 cut-off is planned for August 2016. This report will include remaining treatment data
 413 from the long term treatment study, R668-AD-1224 (i.e., safety data from April 2016 to
 414 August 2016) and additional safety data from the open label extension study (R668-AD-
 415 1225).

416

417 This will include the following tables and listing: treatment emergent adverse event
 418 (TEAE) profile table, TEAEs by system organ class (SOC), high level term (HLT) and
 419 preferred term (PT), SAEs by SOC and PT, discontinuations due to TEAEs by SOC and
 420 PT, deaths and exposure data.

421

422 Narratives for the following events will be provided: SAEs with onset during the SUR
 423 period, deaths that occurred during the SUR period, discontinuations due to an AE during
 424 the SUR period, adverse events of special interest during the SUR period, SAEs,
 425 treatment discontinuations provided in the initial submission for which there is new
 426 information and patients who experienced treatment emergent pregnancy during the SUR
 427 period.

428

429 This proposal is acceptable at this time.

430

431 **Question 3:**

432 Does the Agency agree with the proposed location of the efficacy results in the BLA?

433

434 **Response:**

435 The Sponsor proposes to present the efficacy data usually provided in the Integrated
436 Summary of Effectiveness (ISE) within the Summary of Clinical Efficacy (SCE)
437 (Module 2.7.3) and Module 5.3.5.3. The narrative portion of the ISE, together with key
438 tables and figures, will be concise enough to be included in the SCE. Supportive tables,
439 figures, listings, and any additional information will be provided in the ISE located in
440 Module 5.3.5.3.

441

442 Your plan appears reasonable. Note that the ISE should include comprehensive in-depth
443 analysis of the individual study results in addition to pooled efficacy results, and should
444 discuss the extent to which the results of the relevant studies reinforce or do not reinforce
445 each other. This may require additional discussion beyond individual study summaries
446 and a pooled analysis. For additional information on the content of the ISE refer to
447 guidance for industry *Integrated Summary of Effectiveness*
448 (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf>).

449

451 **Question 4:**

452

453 A) Does the Agency agree with the proposed pooling strategy for efficacy?

454

455 B) Does the Agency agree with the proposed subgroups to be analyzed for efficacy?

456

457 **Response:**

458 For the integrated summary of efficacy, you propose to conduct only one analysis of
459 pooled data for efficacy: Placebo-Controlled Monotherapy Phase 3 AD studies (Pool 1):
460 Includes the two (2) monotherapy, placebo-controlled studies, (R668-AD-1334 [SOLO1]
461 and R668-AD-1416 [SOLO2]). These 2 studies are replicate, confirmatory 16-week
462 treatment studies in adult patients with moderate-to-severe AD whose disease is not
463 adequately controlled with, or who are intolerant to, topical prescription therapy. In each
464 of these studies, approximately 600 patients were randomized to 1:1:1 to dupilumab 300
465 mg q2w: dupilumab 300 mg qw: placebo. The main objective of pooling these ~1,200
466 patients is to provide a larger sample size for subgroup analyses.

467

468 You propose to present efficacy data by gender, age and racial subgroup, as well as other
469 subgroups appropriate to the AD population.

470

471 The proposed subgroups for the integrated analyses of efficacy are as follows:

472

- 473 • Age (≥ 18 - < 40 years, ≥ 40 - ≤ 65 years, > 65 years)
- 474 • Sex (Male, Female)

- 475 • Race: White, Black or African American, Asian, other Ethnicity: Hispanic or
- 476 Latino (no/yes)
- 477 • Duration of AD (< 26 years, >=26 years)
- 478 • Baseline weight group (<70 kg, >= 70-<100 kg, >=100 kg)
- 479 • BMI (<15, [15-25], [25-30], ≥30)
- 480 • Region 1: Asia Pacific, Eastern Europe, North and South America, Western
- 481 Europe
- 482 • Region 2: Japan, Rest of world
- 483 • Baseline disease severity [moderate (IGA = 3) and severe (IGA = 4)]
- 484 • Baseline EASI (<25, >=25)
- 485 • Baseline peak NRS (<7, >= 7)
- 486 • Body Surface Area (BSA) (10%-29%, 30%-50%, > 50%)
- 487 • Previous use of systemic immunosuppressants for AD (Yes, No)
- 488 • History of asthma (Yes, No)
- 489 • History of nasal polyps (Yes, No)

490
491 Please also include subgroup analyses classified by a history of allergic rhinitis (Yes, No)

492 and a history of food allergies (Yes, No).

493

494 This proposal is otherwise acceptable at this time.

495

496 **Question 5:**

497 Does the Agency agree with the Sponsor's proposal for narratives and CRFs?

498

499 **Response:**

500 For all studies, the Sponsor will provide narratives and CRFs for all deaths, SAEs,

501 adverse events of special interest, adverse events leading to permanent treatment

502 discontinuation and patients who experienced treatment emergent pregnancy.

503

504 This proposal is acceptable at this time.

505

506 **Question 6:**

507

508 A) Does the Agency agree with the proposed pooling strategy for safety?

509

510 B) Does the Agency agree with the proposed subgroups to be analyzed for safety?

511

512 **Response:**

513 To characterize the safety profile of dupilumab, you plan to summarize adverse events

514 and drug exposure from three different pools of the data (described below).

515

516 Pool #1

517

518 2 phase 3 monotherapy trials 1334 and 1416

519 ≈ 1200 subjects (800 on dupilumab, 400 on 300mg q wk and 400 on 300mg q2W)

520

521 Pool#2

522

523 12-16 week monotherapy phase 2 and 3 trials

524 Pool #1 plus the first 12-16 weeks of trials 1117, 1021, 1314 and 1307

525

526 Pool #3

527

528 Overall exposure to dupilumab by subcutaneous injection for AD

529 Pool #2 plus trials 0914, 1121, 1026, 1224 and 1225

530

531 DDDP recommends that the primary safety pool for your product include placebo-
532 controlled trials at the proposed labeled dose and duration (include both 300mg q week
533 and 300 mg qow but present these as separate arms). This would include the following
534 trials: 1334, 1416, 1021 (just the 300 mg q w and qow arms) and 1314.

535

536 You propose the following subgroups to be analyzed for safety:

537

- 538 • Age (≥ 18 -< 40 years, ≥ 40 -<65 years, ≥ 65 years)
- 539 • Sex (Male, Female)
- 540 • Ethnicity: Hispanic or Latino (no/yes)
- 541 • Race: White, Black or African American, Asian, Other
- 542 • Ethnicity: Hispanic or Latino (no/yes)
- 543 • Duration of AD (< 26 years, ≥ 26 years)
- 544 • Baseline weight group (<70 kg, ≥ 70 -<100 kg, ≥ 100 kg)

545

546 The proposed subgroups appear acceptable at this time.

547

548

549

550

551 submitted as a supplement.

552

553 For the adverse events, provide raw incidence rates as well as the exposure-adjusted rates
554 (in patient-years) for the induction period, the “follow-up period”, as well as the overall
555 (consisting of both periods) by treatment group. For the classification of the treatment
556 group in the “follow-up” period, the dose received in the induction period should be
557 taken into account (i.e., subjects in the placebo treatment group should have received
558 placebo in the induction as well as the follow-up period to be eligible to be considered in
559 the “placebo” group).

560

561 Add suicidal behavior (suicidal ideation, suicide attempt and completed suicide) to the
562 adverse events of special interest.

563

(b) (4)

(b) (4) will be

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).
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
4. Please request a submission tracking number (STN) assignment prior to the submission of your BLA.
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

As stated in our October 29, 2015 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be

611 expected to materially impact the ability of the review team to begin its review. All
612 major components of the application are expected to be included in the original
613 application and are not subject to agreement for late submission.
614
615 Discussions and agreements will be summarized at the conclusion of the meeting and
616 reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not
617 have agreement with FDA on the content of a complete application or late submission of
618 any minor application components, your application is expected to be complete at the
619 time of original submission.
620
621 In addition, we remind you that the application is expected to include a comprehensive
622 and readily located list of all clinical sites and manufacturing facilities.
623
624 Finally, in accordance with the PDUFA V agreement, FDA has contracted with an
625 independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment
626 of the Program. ERG will be in attendance at this meeting as silent observers to evaluate
627 the meeting and will not participate in the discussion. Please note that ERG has signed a
628 non-disclosure agreement.
629
630 Information on PDUFA V and the Program is available at
631 <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.
632
633 In addition, we note that a chemistry pre-submission meeting is planned. A summary of
634 agreements reached at that meeting will be documented in the respective meeting
635 minutes.
636
637 **PREA REQUIREMENTS**
638
639 Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for
640 new active ingredients (which includes new salts and new fixed combinations), new
641 indications, new dosage forms, new dosing regimens, or new routes of administration are
642 required to contain an assessment of the safety and effectiveness of the product for the
643 claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or
644 inapplicable.
645
646 If you have questions related to requirements under PREA, you may contact the Division
647 of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For
648 further guidance on pediatric product development, please refer to:
649 [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm04](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm)
650 [9867.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm).
651

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](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- 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 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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) Requests

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. Please 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. Please 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. Please 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.

770 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify
771 the location and/or provide a link if provided elsewhere in the submission).

772

773 5. For each pivotal trial provide original protocol and all amendments ((or identify
774 the location and/or provide a link if provided elsewhere in the submission).

775

776 **II. Request for Subject Level Data Listings by Site**

777

778 1. For each pivotal trial: Site-specific individual subject data listings (hereafter
779 referred to as “line listings”). For each site, provide line listings for:

780

781 a. Listing for each subject consented/enrolled; for subjects who were not
782 randomized to treatment and/or treated with study therapy, include reason not
783 randomized and/or treated

784 b. Subject listing for treatment assignment (randomization)

785 c. Listing of subjects that discontinued from study treatment and subjects that
786 discontinued from the study completely (i.e., withdrew consent) with date and
787 reason discontinued

788 d. Listing of per protocol subjects/ non-per protocol subjects and reason not per
789 protocol

790 e. By subject listing of eligibility determination (i.e., inclusion and exclusion
791 criteria)

792 f. By subject listing, of AEs, SAEs, deaths and dates

793 g. By subject listing of protocol violations and/or deviations reported in the
794 NDA, including a description of the deviation/violation

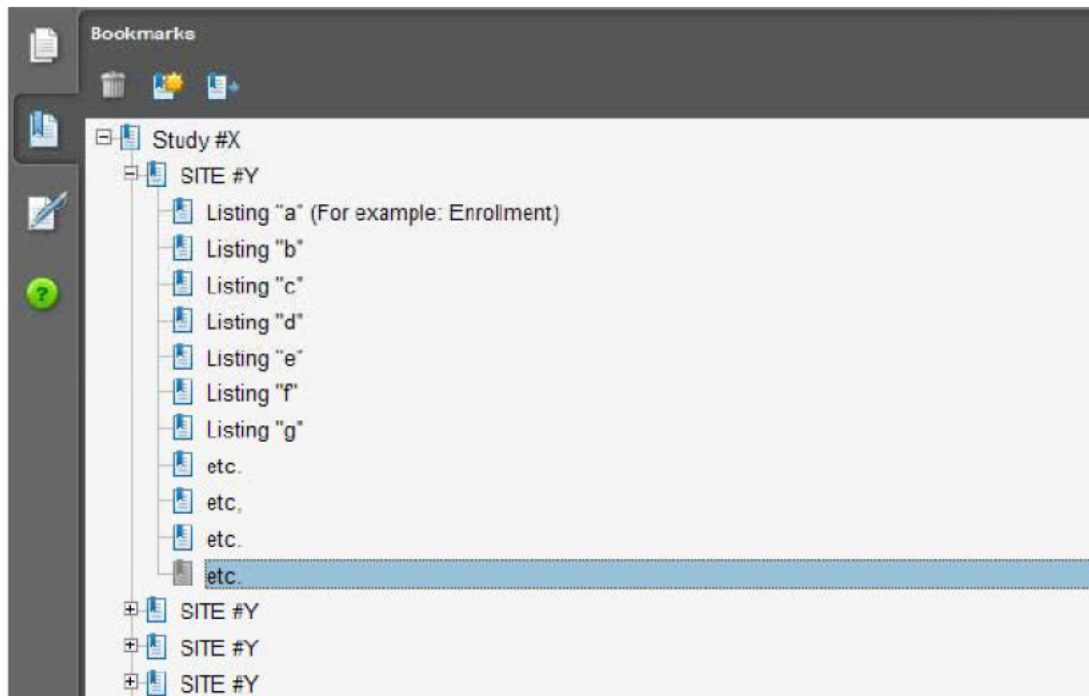
795 h. By subject listing of the primary and secondary endpoint efficacy parameters
796 or events. For derived or calculated endpoints, provide the raw data listings
797 used to generate the derived/calculated endpoint.

798 i. By subject listing of concomitant medications (as appropriate to the pivotal
799 clinical trials)

800 j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety
801 monitoring

802

803 2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3
804 study using the following format:



805

806

807

808 III. Request for Site Level Dataset:

809

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

818

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

847 References:

848

849 eCTD Backbone Specification for Study Tagging Files v. 2.6.1

850 ([http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmission](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)
851 [Requirements/ElectronicSubmissions/UCM163560.pdf](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf))

852

853 FDA eCTD web page

854 ([http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequiremen](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)
855 [ts/ElectronicSubmissions/ucm153574.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm))

856

857 For general help with eCTD submissions: ESUB@fda.hhs.gov

Attachment 2

Pre-NDA

General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

The **Study Data Standards Common Issues Document** can be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>. The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration.

NDA/BLA content and format	
CLINICAL	
1)	Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
2)	Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3)	Investigator instructions that may have been produced in addition to the protocol and investigator brochure
4)	All randomization lists and, if used, IVRS datasets (in SAS transport format)
5)	All datasets used to track adjudications (in SAS transport format), if any
6)	A Reviewers Guide to the data submission that includes, but is not limited to the following: - description of files and documentation - description of selected analysis datasets - key variables of interest, including efficacy and safety variables - SAS codes for sub-setting and combining datasets

e) coding dictionary used f) methods of handling missing data g) list of variable contained in every dataset h) listing of raw data definitions i) analysis data definitions j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item) k) documentation of programs
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf)).
8) <u>Pediatric Studies:</u> All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.
9) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application
10) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.
11) <u>References:</u> There should be active links from lists of references to the referenced article.
Studies, Data And Analyses
12) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).
13) Provide a table with the following columns for each of the completed Phase 3 clinical trials:

a) Site number b) Principle investigator c) Location: City State, Country d) Number of subjects screened e) Number of subjects randomized f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection) g) Number of protocol violations (Major, minor, including definition)
14) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
15) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components: a) subject age and gender b) signs and symptoms related to the adverse event being discussed c) an assessment of the relationship of exposure duration to the development of the adverse event d) pertinent medical history e) concomitant medications with start dates relative to the adverse event f) pertinent physical exam findings g) pertinent test results (for example: lab data, ECG data, biopsy data) h) discussion of the diagnosis as supported by available clinical data i) a list of the differential diagnoses, for events without a definitive diagnosis j) treatment provided k) re-challenge and de-challenge results (if performed) l) outcomes and follow-up information m) an informed discussion of the case, allowing a better understanding of what the subject experienced.
16) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request. 17) Provide reports for any autopsies conducted on study.
18) For patients listed as discontinued due to “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for

discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.
19) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis
20) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including: a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling. b) Exposure-Response Relationships – important exposure-response assessments. c) Less common adverse events (between 0.1% and 1%). d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values. e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers. f) Marked outliers and dropouts for laboratory abnormalities. g) Analysis of vital signs focused on measures of central tendencies. h) Analysis of vital signs focused on outliers or shifts from normal to abnormal. i) Marked outliers for vital signs and dropouts for vital sign abnormalities. j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value. k) Overview of ECG testing in the development program, including a brief review of the nonclinical results. l) Standard analyses and explorations of ECG data. m) Overdose experience. n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction. o) Explorations for: i) Possible factors associated with a higher likelihood of early study termination;

include demographic variables, study site, region, and treatment assignment. ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered. iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment. iv) Drug-demographic interactions v) Drug-disease interactions p) Drug-drug interactions i) Dosing considerations for important drug-drug interactions. ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
Financial Disclosure Information
21) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm341008.pdf).

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

/s/

MATTHEW E WHITE
12/07/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125104

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Viswanathan (Seenu) Srinivasan, Ph.D.
Director, CMC Regulatory Affairs
81 Columbia Turnpike
Rensselaer, NY 12144

Dear Dr. Srinivasan:

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

We also refer to the meeting between representatives of your firm and the FDA on October 2, 2015.

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 please contact the RBPM, Andrew Shiber at 301-796-4798.

Sincerely,

Cristina Ausin, Ph.D.
Acting Team Leader
Division of Biotechnology Review and Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Biotechnology Products (OBP)/Division of Biotechnology Review and Research I

Michele Dougherty, Ph.D.	Review Chief
Cristina Ausin, Ph.D.	Team Leader
Gunther Boekhoudt, Ph.D.	Product Quality

Office of Process and Facilities

Bo Chi	Microbiology
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Office of New Drugs/Division of Dermatology and Dental Products

Jill Lindstrom, M.D.	Clinical Lead
----------------------	---------------

Office of Combination Products

Bindi Nikhar, M.D.	Associate Director
--------------------	--------------------

Center for Devices and Radiological Health

Richard Chapman	Branch Chief
Kathleen Fitzgerald	Device Quality

Office of Program and Regulatory Operations

Andrew Shiber	Regulatory Business Project Manager
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SPONSOR ATTENDEES

Regeneron Pharmaceuticals

Rajesh Ahuja, M.S. ChE	Senior Director, QA Validation, Regeneron
Ned Braunstein, M.D.	Senior Vice President, Regulatory Affairs, Regeneron
Chad Fish, PMP	Senior Manager, CMC Project Management, Regeneron
Krishnendu Ghosh, Ph. D.	Executive Director, CMC Regulatory Affairs, Regeneron
Mykhaylo Hrytsak, BASc, MBA, PMP	Manager, Combination Products Regulatory Affairs, Regeneron
Farida Laadani, Ph. D.	Validation Dept Representative, Sanofi (Le Trait, France)
Michelle LaFond, BS ChE	Director, Bioreactor Scale-up & Development, Regeneron
Lisa Mauch, M.S.	Associate Director, Regulatory CMC Biologics, Sanofi
Jennifer McNay, Ph.D.	Executive Director, Process Sciences, Regeneron
Seenu Srinivasan, Ph. D.	Director, CMC Regulatory Affairs, Regeneron
Deborah Thomas, M.S. Sr.	Director, Devices and Combination Products, Sanofi
Paul Vescio, Ph. D.	Manager, CMC Regulatory Affairs, Regeneron

MEETING MINUTES

Meeting Type:	B
Category:	CMC Only

Date: October 2, 2015
Time: 12:00PM Eastern Daylight Savings Time

Location: FDA White Oak
10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 107969
Product Name: dupilumab

2.0 DISCUSSION

Drug Substance

Question 1:

The Sponsor may utilize (b) (4) in the
dupilumab drug substance manufacturing process post commercialization to (b) (4)
Does the Agency agree with the proposed implementation plan?

Does the Agency agree (b) (4)

FDA Response to Question 1:

No, we do not agree. (b) (4)

Regarding the adequacy of the validation data, a final decision will be a review issue.

In addition, we notice that during the side-by side comparison you intent to use (b) (4)
in your analysis. You should
provide a justification for the historical lot(s) chosen.

We do agree (b) (4)

The adequacy of the supporting data would be a review issue for each product and would be determined in a case by case manner.

Sponsor Response:

The Sponsor acknowledges the Agency's comments. The Sponsor agrees to include drug substance stability studies at accelerated condition as part of the (b) (4) implementation plan. We will also provide a justification for the historical lot(s) manufactured using (b) (4) chosen to perform a side-by-side comparison.

(b) (4)

Meeting Discussion:

FDA acknowledged the Sponsor's plan to include the requested stability studies. While FDA finds the approach generally acceptable, we are not able to comment on issues that might need to be addressed on a product-specific basis.

Regeneron noted that the (b) (4) will be implemented across manufacturing sites. The current strategy was outlined as follows: (b) (4)

For approved products, Regeneron requested information to address the (b) (4) implementation approach in a cross-product fashion, rather than having a separate meeting for each product where the technology will be implemented. FDA recommended that Regeneron submit a single meeting request inclusive of multiple approved products to the BLA for the first product where the technology will be implemented. FDA recommended that both general and, where warranted, product specific questions be included in the meeting request.

Question 2:

The Sponsor has introduced a new processing area (b) (4) at its Rensselaer, NY facility to manufacture dupilumab drug substance. Does the Agency agree that the proposed data package to be supplied in the BLA is sufficient to support licensure of the new process area, (b) (4)?

FDA Response to Question 2:

In general we agree that the proposed data package to be supplied in the BLA could be sufficient to support licensure of the new process area, (b) (4) however a final decision regarding the adequacy of the data to support licensure will be a review issue.

(b) (4)

(b) (4)

Sponsor Response:

The sponsor acknowledges the Agency's comments.

(b) (4)

No Meeting Discussion.

QUESTION 3:

The Sponsor has developed a validated custom

(b) (4)

change to this validated custom
ELISA kit marketed by (b) (4)?

Does the Agency agree with a method
(b) (4) from a commercial

FDA Response to Question 3:

Regarding the development of a validated custom (b) (4), based on the information included in the meeting package, the (b) (4) assay appears superior to the (b) (4). We do not have specific concerns regarding a method change. However, a final decision on the adequacy of the selected assay will be made upon review of your validated method.

No Meeting Discussion.

QUESTION 4:

For commercial production, the Sponsor is considering replacing subvisible particulate counting as described in USP <788> Particulate Matter in Injections with Micro-Flow Imaging™ (MFI). Does the Agency agree with the Sponsor's proposal to remove particulate matter testing using the microscopic method and use only Micro-Flow Imaging™ (MFI) for particulate matter content in future release specifications and stability protocols?

FDA Response to Question 4:

In general we agree that the Micro-Flow Imaging™ (MFI) method could replace the current USP <788> method for subvisible particulate counting. However, a final decision regarding the adequacy of the data to support licensure will be a review issue.

No Meeting Discussion.

QUESTION 5:

Does the Agency agree with the proposed assembly validation for the dupilumab PFS and dupilumab Safety System?

FDA Response to Question 5:

In your meeting package for IND107969 you state that the validation program will demonstrate that the assembly process as unit operation does not adversely affect the integrity of the primary container closure, the quality attributes of the DP and the functionality of the syringe and when assembled with the safety system. As part of the validation, you intend to perform all biochemical testing that is performed on the bulk prefilled syringes, as well as additional functional tests (needle shield removal force, break loose and glide force, CCIT, etc.)

The Agency notes that you have not provided clear requirements related to dose accuracy or durability of the PFS or the ESS. Within your future submission you should establish dose accuracy (at full and partial dose, if applicable) and durability requirements and verify the device meets these requirements in-process and on stability. Note: typical durability assessments for safety syringe systems involve a drop test as prescribed within ISO11608-1.

The Agency also notes that you have not referenced verification of performance of the device constituent parts of the combination product after preconditioning to shipping. Within your future submission you should provide evidence that the device constituent parts are capable of meeting performance requirement after preconditioning to shipping.

Sponsor Response:

The sponsor requests additional clarification on the need for durability assessment including drop test for both PFS and PFS –ESS since both presentations are not clearly listed in the ISO standard.

FDA Response to clarification question from the Sponsor:

The Agency requests that, in addition to the durability assessments you are already performing, you consider executing a drop test on final finished product to simulate the effect of a mis-handling/drop on the ESS to ensure that a drop does not product a potentially unsafe product state (the false appearance of an intact and functional needle safety mechanism). The intention of the test would be to ensure that the device does not fail, or fails in a manner obvious to the user, after drop. ISO11608-1 is a standard developed for needle based injection systems but has been used by sponsors in the past as a standardized drop test method for ESSs. If you choose to execute the test, you should provide rationale for executing it on packaged or un-packaged product and rationale for test acceptance criteria. If you choose not to execute the test, you should describe why your durability test plan is sufficient.

The Sponsor intends to conduct appropriate dose accuracy and functional testing during design verification of the combination product. Shipping validation and stability studies will be conducted as part of the development process.

The Sponsor references FDA Guidance documents for the combination products: the Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features, Guidance for industry: Container Closure Systems for Packaging Human Drugs and Biologics (as noted in prior Agency correspondence, simulated clinical use testing was successfully performed by the device manufacturer for the 510(k) cleared safety system) and

Guidance for Industry and FDA Staff Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4.

The Sponsor confirms that for assembled drug product PFS and ESS, expellable volume is part of the requirements necessary to assess assembly validation impact. Indeed, expellable volume (listed as volume in container in Tables 16 and 18 in the briefing book) is performed according to USP chapter <1> on assembled drug product and requirements are verified during in-process assembly, at release and during stability.

The minimum deliverable dose for the fully assembled combination product is controlled by the product specification for volume in container ($\geq 2.0\text{ml}$; (b) (4)).

Note: PFS and ESS are intended to be administered as a single dose whereby the entire deliverable volume is expelled.

The Sponsor will provide requirements related to durability of the PFS and ESS within the future submission.

Durability is evaluated according to the following description:

- Stability ICH conditions (corresponding to preconditioning described in ISO11608-1):

	Long term	Accelerated	Stress
Temperature	5°C	25°C	45°C
Humidity	No humidity requirement	No humidity requirement	No humidity requirement
Duration	36 months	6 months	3 months

- Durability is evaluated on 3 different product presentations :
 - Bulk prefilled syringe (considered as the injection system), at long term and accelerated conditions, on three different batches and one batch at stress conditions
 - Assembled Drug Product PFS at long term and accelerated conditions, on three different batches and one batch at stress conditions
 - Assembled Drug Product ESS at long term and accelerated conditions, on three different batches and one batch at stress conditions

Testing requirements are performed to confirm the absence of damage, verified by visual inspection (including, appearance, color), chemistry and functional testing. Selection of functional testing is based on risk assessments, the instruction for use and are defined as essential output during development of the combination products:

- o Needle Shield removal force,**
- o Volume in container (delivered volume),**
- o Break loose/gliding force,**
- o Visual inspection of the glass barrel, finger flange, piston/plunger rod, and needle shield**
- o Activation and safety feature override force (ESS only).**

Note: Regarding durability for stand-alone components, all technical data included aging/shelf-life studies on device constituent parts are checked to ensure the achievement of design conception of components.

We would like further discussion on the requirements for durability denoted in the following documents relative to their applicability for the PFS and safety system:

- o Impact of vibration is assessed during shipping validation studies according to ASTM D4169-14. Visual and functional testing listed above are performed on syringes involved in these tests.**
- o Free fall testing (also named drop resistance test) is performed according to ISO11608-1 during Design Verification.**

FDA acknowledged the response.

Additionally, there are a number of lower-level device requirements which do not appear within your briefing package. These include but may not be limited to: dimensional specifications for system components, syringe-needle pull-out force, and device material biocompatibility. Within your future submission you should establish requirements for these lower level device attributes and provide evidence that these requirements have been verified. Note: it is acceptable to provide references to master files or 510(k) submissions, where appropriate, to satisfy these concerns.

All verification and validation data should be performed on the final finished sterilized combination product. Within future investigational or marketing applications, the Agency expects that you will provide all necessary information to support the safety and functionality of the constituent parts. You are advised to consult the following guidance documents and prior to future investigational or marketing applications:

Sponsor Response:

The Sponsor confirms that design requirements including lower level, are part of development activities which are performed in order to evaluate and demonstrate conformance to the following requirements: protection, performance, manufacturability, stability, compatibility and safety as required in:

Guidance for industry: Container Closure Systems for Packaging Human Drugs and Biologics

Guidance for Industry and FDA Staff Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4

Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features.

Sponsor will describe lower level device data in 3.2.P.2.4 in the frame of design development program in the final application.

Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda/gen/documents/document/ucm147095.pdf>

Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard

11040-4 <http://www.fda.gov/RegulatoryInformation/Guidances/ucm346727.htm>

Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071663.htm>

Additional FDA Response to Question 5:

Please conduct container closure integrity (CCI) test for the proposed study of plunger rod insertion at the extreme positions and speed limit. In addition, validate the assembly process (within the target parameters) with CCI test using three lots. Use CCI test to validate the transportation processes to demonstrate that the transportation processes do not negatively impact the CCI of the PFS.

Sponsor Response:

The Sponsor would like to clarify that the following testing strategy will be applied to verify CCI:

The Sponsor intends to submit a cross-validation study to confirm that the CCIT using the dye ingress method provides equivalent sensitivity to detect a breach as the microbial ingress test method.

The Sponsor proposes to include dye ingress CCI testing on the three lots used for assembly process validation and during shipping validation.

Meeting Discussion:

Regarding the FDA's request to ensure adequate parameters for plunger insertion by testing the container closure integrity of syringes manufactured using extreme plunger rod positions and insertion speeds, the sponsor indicated that data are available to demonstrate that plunger rod

insertion does not impact the position of the plunger stopper. FDA indicated that the data should be provided in the BLA to justify not conducting the requested container closure integrity study.

Additional FDA Response to Question 5:

In addition, provide data evaluating the potential impact of air freight on stopper movement in PFS from sterility assurance perspective.

Sponsor Response:

**The Sponsor confirms that potential impact of air freight on piston movement in PFS from a sterility stand point will be assessed during transportation validation studies.
The Sponsor will perform a validation study according to ASTM D4169-14.**

Meeting Discussion:

FDA clarified that the study evaluating the potential impact of air freight on plunger stopper movement should evaluate the position of the stopper during simulated transportation studies from a sterility assurance perspective. The study should demonstrate that the plunger stopper stays within the sterile boundary during the simulated worst-case air pressure changes. Sponsor indicated that they understood and further clarified if the study could be conducted using the bulk PFS (without the plunger rod) only. FDA stated that is acceptable as the bulk PFS is the worst-case from plunger stopper movement perspective.

QUESTION 6:

The Sponsor intends to include three different visual inspection methods (manual, semi-automatic, and automatic) for the bulk PFS in the BLA submission. Provided method qualification data show that each of the inspection methods performs comparably with regard to detection of visual defects and drug product quality is not impacted as demonstrated by side by side stability studies, does the Agency agree that each of the visual inspection methods may be used interchangeably during commercial production?

FDA Response to Question 6:

The interchangeably visual inspection methods appear to be acceptable if as stated in the meeting package the provided data demonstrates that each of the inspection methods performs comparably with regard to detection of visual defects is not impacted as demonstrated by side by side stability studies.

The approach appears to be acceptable provided that each visual inspection method is qualified and the methods are comparable, which will be evaluated during an inspection.

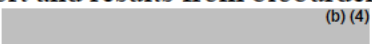
Additional FDA comments:

Product Quality Microbiology

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

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). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
-  (b) (4)
- 
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4). Please note that DS specification for bioburden is  (b) (4)
- Summary report and results from bioburden and endotoxin test methods qualification performed for  (b) (4) the drug substance (3.2.S.4).

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support 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” at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>

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

-  (b) (4)
- 

-  (b) (4)
-
-
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.
- A description of the routine environmental monitoring program.
- Shipping validation study results.

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 and during stability. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. 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).
- Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for  (b) (4) (if applicable) and the drug product, as appropriate.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21CFR610.13(b).
- Formulations with certain excipient and polysorbate combinations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted in-process samples (if applicable), the drug substance, and the drug product and then testing for recoverable endotoxin over time. These studies should be conducted in the containers in which the product and samples are held prior to endotoxin testing.

No Meeting Discussion.

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/s/

CRISTINA AUSIN-MORENO
11/19/2015

PREMEETING COMMUNICATION**IND: 107969****Product:** Dupilumab**Regulatory** §351 of the Public Health Service Act**Sponsor:** Regeneron Pharmaceuticals, Inc.**Proposed Indication:** For the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapy,

(b) (4), or (b) (4)
(b) (4). Dupilumab can be used alone or in combination with topical prescription therapy.

Type of Meeting: Type B**Meeting Date:** June 22, 2015**Introductory Comment:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 22, 2015, at 8:30 a.m. in White Oak Building 22 between Regeneron Pharmaceuticals, Inc. and the Division of Dermatology and Dental Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Matthew White, Matthew.White@fda.hhs.gov). 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 telecom). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions.

Purpose of the Meeting:

The purpose of this meeting is to discuss the development program for dupilumab.

Regulatory Correspondence History

We have had the following meeting(s)/teleconference(s) with you:

- 8/4/2014: Type A (guidance) meeting
- 5/21/2014: Type B (End-of-Phase 2) meeting
- 5/8/2014: Type B (CMC End-of-Phase 2) meeting

- 3/31/2014: Teleconference to discuss the pediatric study plan
- 1/23/2013: Type C (guidance) meeting
- 11/ 22/2011: Teleconference to discuss Grade 4 adverse events (elevated CPK) which occurred during Study R668-AD-0914
- 5/26/2010: Type B (pre-IND) meeting

We have sent the following correspondences:

- 6/12/2015: Advice letter
- 4/30/2015: Advice letter
- 4/13/2015: Advice letter
- 4/2/2015: Advice letter
- 4/2/2015: Advice/information request letter
- 2/19/2015: Advice letter
- 2/4/2015: Advice letter
- 1/30/2015: Advice letter
- 11/18/2014: Grant breakthrough therapy designation request letter
- 11/10/2014: Advice letter
- 10/27/2014: Advice letter
- 10/23/2014: Advice/information request letter
- 10/21/2014: Information request letter
- 10/7/2014: Information request letter
- 10/6/2014: Acknowledge breakthrough therapy designation request letter
- 8/27/2014: Advice letter
- 12/20/2013: iPSP advice letter
- 11/14/2013: Advice letter
- 10/4/2013: IRB waiver granted letter
- 8/21/2010: Study may proceed letter
- 7/12/2010: Acknowledge IND letter
- 7/12/2010: Advice letter

Chemistry, Manufacturing and Controls (CMC)

Question 2:

For commercialization, the Sponsor may introduce dupilumab in a pre-filled syringe (PFS) assembled with an Ergonomic Safety System (ESS). A comparative analysis of the component material and performance between the ESS and the PFS used in Phase 3 clinical trials will be provided in the BLA. This assessment, along with the planned formative human factors evaluations, and the (summative) human factors validation study for the ESS, is expected to provide sufficient data to demonstrate that no significant differences in device performance and handling by the intended users exist between the clinical and proposed commercial drug product (DP) presentations. In the event the two presentations are determined to be comparable (no significant differences exist between the clinical PFS and the proposed commercial ESS presentations), does the Agency agree that this approach is sufficient to support registration and approval of the ESS?

Response:

Your approach appears reasonable provided the following comments are addressed. The adequacy of the data is a review issue.

1. Within your briefing package, you provided three comparative performance tests for the clinical syringe presentation and planned ergonomic syringe presentation: glide force, break loose force, and extractable volume.
 - a. You do not appear to have compared any elements of ingress or leakage at the needle/needle shield interface. To support this, you state, "The design of the (b) (4) and RNS differ slightly but does not impact the sealing performance." The Agency is unable to agree with this position without a detailed description of the changes made to the design characteristics of the needle shield.
 - b. The extractable volume study did not include an assessment of partial dosing. Clearly state if partial dosing is anticipated for this combination product, and if it is anticipated, provide rationale for why partial dosing assessments between the clinical and proposed versions is not required.
2. Please note that the Agency expects that you will provide information supporting the tissue, fluid, or skin contacting materials used within the syringe system are biocompatible and free from unacceptable toxicological risk. Regardless of any determination that the changes made to the syringe system do not require clinical experience, future marketing applications should have appropriate non-clinical information supporting the safety of all materials used.
3. Submit a detailed summative Human Factors protocol for review and feedback prior to starting the study. In addition, include the following:
 - a. A summary and analysis of your formative studies results.
 - b. Discussion of changes made to your product after the formative studies, including how the results from the formative studies were used to update the user interface and use-risk analysis.
 - c. An updated use-risk analysis.
 - d. Instructions for Use and Quick Reference Guide in MS Word format.

Send three samples of the proposed PFS with your submission.

Clinical**Question 1:**

Given the recent designation of dupilumab as a Breakthrough Therapy for the treatment of adult patients with moderate to severe atopic dermatitis and the implied need to expedite development to fulfill patients' unmet needs, does the Agency agree that a Phase 3 clinical program comprising two 16-week monotherapy studies, a 52-week combination therapy study, and an open-label extension/retreatment study could be sufficient to support the initial licensure of dupilumab? The completion and submission of the ongoing maintenance study would be post-marketing commitment that the Sponsor will fulfill in a sBLA immediately following licensure. The data package supporting the initial BLA is proposed to support the following indication:

“Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapy, (b) (4) y, or (b) (4) not advisable. (b) (4) ,”

Response:

You propose to include the following trials in your initial BLA submission

R668-AD-1334, R688-AD-1416

- Identical monotherapy 16 week treatment trials
- Each in 600 subjects with moderate to severe AD not adequately controlled with topical treatments or for whom topical treatments are inadvisable
- Randomized 1:1:1 to Dupilumab 300 mg qw; 300 mg q2w; and placebo after an initial loading dose of 600 mg to the active arms
- Efficacy assessed at week 16

R668-AD-1224

- 52 week combination trial with topical corticosteroids (TCS)
- 700 subjects with moderate to severe AD with inadequate control on conventional therapy with topical medications
- Randomized 3:1:3 to Dupilumab 300 mg qw; 300 q2w; and placebo after an initial loading dose of 600 mg to the active arms
- All subjects will receive a standardized regimen of TCS from day 1 to week 52
- Efficacy assessed at weeks 16 and 52

R668-AD-1225

- An open label extension/re-treatment study to assess the long term safety and immunogenicity of dupilumab for patients who participated in a prior dupilumab clinical study.
- 800 subjects on dupilumab 300 mg q wk for approximately 2 years

You propose to submit

(b) (4)

(b) (4)

You propose to submit the results of R668-AD-1433, the drug-drug interaction trial, in a subsequent submission following approval of the BLA.

You estimate that this will provide data from ~2100 AD patients in total, of whom ~730 patients with AD (250 of these will be placebo-controlled) will have been exposed for ≥ 1 year at the highest dose. These data will be supplemented in the Day 120 Safety Update Report with an additional approximately 300 patients exposed for ≥ 1 year at 300 mg qw dose regimen (from the OLE study), resulting in a database of ~1030 patients exposed to dupilumab 300 mg qw for >1 year.

This proposal is acceptable.

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 the information submitted to the IND might identify additional comments or information requests.
2. For the review timeline for all submissions to a breakthrough therapy-designated drug, refer to MAPP 6025.6 *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics* available at:
<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407009.pdf>.

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 (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. 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. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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 Division of Pediatric and Maternal Health 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>

PROPRIETARY NAME

We encourage you to submit your requests for FDA review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>). Please note that such a request can be made as early as at the End-of- Phase 2 of the IND review process.

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/s/

MATTHEW E WHITE
06/15/2015



IND 107969

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Senior Manager, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Babilonia:

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

We also refer to your September 26, 2014, request for Breakthrough Therapy designation. We have reviewed your request and have determined that dupilumab for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are not adequately controlled with or are intolerant to topical prescription therapy or when those treatments are not advisable meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of dupilumab for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are not adequately controlled with or are intolerant to topical prescription therapy or when those treatments are not advisable to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

breakthrough therapy meeting². Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*³ for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for dupilumab for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are not adequately controlled with or are intolerant to topical prescription therapy or when those treatments are not advisable is rescinded, submission of portions of the BLA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

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

²

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

³ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

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/s/

KENDALL A MARCUS
11/18/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND107969

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Senior Manager, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Babilonia:

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

We also refer to the teleconference between representatives of your firm and the FDA on August 4, 2014. The purpose of the meeting was to discuss the development program for (dupilumab) for the (b) (4) treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are not adequately controlled with (b) (4) topical prescription therapy or (b) (4) not advisable.

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 Matthew White, Senior Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
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 A
Meeting Category: Guidance

Meeting Date and Time: August 4, 2014 at 9am
Meeting Location: White Oak Building 22, Room 5266

Application Number: IND 107969
Product Name: (dupilumab)

Proposed Indication: For the (b) (4) treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are not adequately controlled with (b) (4) or (b) (4)

Sponsor Name: Reneneron Pharmaceuticals, Inc.

Meeting Chair: Stanka Kukich, M.D.
Meeting Recorder: Cristina Attinello, MPH

FDA ATTENDEES

Kendall A. Marcus, MD, Acting Director, DDDP
Stanka Kukich, MD, Deputy Director, DDDP
Jane Liedtka, MD, Clinical Reviewer, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Carin Kim, PhD, Biostatistics Reviewer, DB III
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, DCP3
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Dhananjay Marathe, PhD, Pharmacometrics Reviewer, DPM
Laurie Graham, MS, Team Leader, DMA
James Andrews, PhD, Product Quality Reviewer, DMA
Cristina Attinello, MPH, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Gianluca Pirozzi, MD, PhD, VP, Global Project Head, Sanofi
Nia Tatsis, PhD, Associate VP, Regulatory Affairs, Sanofi
Rand Sutherland, MD, MPH, Global Clinical Head, Dupilumab and Immunology, Sanofi
Christian Antoni, MD, PhD, VP, Immunology & Inflammation Development Franchise, Sanofi
Shelley Amendola, PhD, Associate Director, Regulatory Affairs, Sanofi
Lin Wang, PhD, Biostatistics, Sanofi

Frank Seebach, MD, Executive Director of Regulatory Affairs, Regeneron
Kristen Dougherty, Dupilumab Program Manager, Regeneron
Judith Cusick, Therapeutic Area Project Management, Immunology and Inflammation, Regeneron
Vera Mastey, Head of Health Economics and Outcomes Research, Medical Affairs, Regeneron
Richard Swanson, PhD, Senior Director, Regulatory Affairs, Regeneron
Robert Evans, PharmD, Senior Director, Clinical Sciences, Inflammation, Regeneron
Neil Graham, MD, VP, Program Direction, Regeneron
Marius Ardeleanu, MD, Senior Director, Clinical Sciences, Inflammation, Regeneron
Yuhwen Soo, PhD, VP, Biostatistics and Data Management, Regeneron
Thomas DiCioccio, PhD, Executive Director, Pharmacometrics, Regeneron
Elisa Babilonia, PhD, Senior Manager, Regulatory Affairs, Regeneron

Purpose of the Teleconference:

To discuss the development program for (dupilumab)

Regulatory Correspondence History

We have had the following meeting(s)/teleconference(s) with you:

- 5/21/2014: End-of-Phase 2 meeting
- 5/8/2014: Type B (CMC End-of-Phase 2) meeting
- 3/31/2014: Teleconference to discuss the pediatric study plan
- 1/23/2013: Type C (guidance) meeting
- 11/ 22/2011: Teleconference to discuss Grade 4 adverse events (elevated CPK) which occurred during Study R668-AD-0914
- 5/26/2010: Type B (pre-IND) meeting

We have sent the following correspondences:

- 12/20/2013: iPSP advice letter
- 11/14/2013: Advice letter
- 10/4/2013: IRB waiver granted letter
- 8/21/2010: Study may proceed letter
- 7/12/2010: Acknowledge IND letter
- 7/12/2010: Advice letter

Clinical/Clinical Pharmacology/Biostatistics

Phase 3 Studies Design

Question 1:

Does the Agency agree that the proposed Phase 3 clinical development program could be sufficient to support an indication for “(b) (4) treatment of moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with (b) (4) (b) (4) or (b) (4) not advisable. (b) (4) ”?

Response:

For your development program for Dupilumab, you are proposing to conduct two Phase 3 “monotherapy trials” (Trials 1334 and 1416) followed by a “maintenance trial” (Trial 1415), a single Phase 3 “combination trial” (Trial 1224), and an open-label trial (Trial 1225).

(b) (4)

The duration of treatment studied in clinical trials would be described in Section 14, Clinical Studies, and dosage regimens in Section 2, Dosage and Administration. Whether your trials will provide data that merit inclusion in labeling will be a review issue. We may have further comments upon review of the full protocols.

Regarding a claim for use as an adjunctive to (b) (4) the Agency reiterates its previous comments (5/21/2014) that following the establishment of an efficacy claim for one paradigm (e.g., monotherapy), it is possible that a single adequate and well-controlled Phase 3 trial would be sufficient to support an additional claim for the other paradigm (e.g., adjunctive therapy). Concurrent pursuit of efficacy claims for both paradigms (monotherapy and adjunctive therapy) using that approach (two trials in one paradigm and a single trial in the other paradigm) entails some risk, and the success of this approach will be a review issue. Non-sequential concurrent pursuit of efficacy claims for both paradigms using a standard approach to replication (i.e., provision of data from two Phase 3 trials in each paradigm), or sequential pursuit (obtainment of an efficacy claim for the first paradigm, followed by pursuit of a claim for the second paradigm), would reduce your risk.

Meeting Discussion:

The Agency clarified that for the indication of adjunctive therapy, based on a single study, the results need to meet certain criteria, including but not limited to robust statistical finding and consistency of the treatment effect across centers and subgroups. For a single study submission, the sponsor should refer to guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

Question 2:

Does the Agency agree with the proposed design of each trial, including the primary and secondary endpoints, sample size and duration?

Response:

You submitted protocol synopses for your planned Phase 3 trials. Submit full protocols along with the Statistical Analysis Plan for detailed comments. The following are general comments based on your synopses.

For your 16-week “Monotherapy Trials” 1334 and 1416, and “Combination Trial” 1224:

- In Trials 1334 and 1416, you plan to randomize 600 subjects from 160 centers to each of the three treatment arms, which implies that on average, 1 subject per treatment arm per center would be enrolled. As the investigation of center-to-center variability in efficacy is important for interpretation of study findings, we recommend that you reduce the

number of study centers so that a reasonable number of subjects per treatment arm per center is planned to enable estimation of treatment effect on the center level and consequently, the center-to-center variability.

- You proposed several secondary endpoints. We recommend, as per our previous comments at the End of Phase 2 meeting, that secondary endpoints intended for labeling claim(s) should be clinically relevant, limited in number, and adjusted for multiplicity (5/21/2014).

Your proposed analyses of the binary endpoints, including the primary endpoint using the CMH test and the continuous secondary endpoints using the MMRM, are not consistent as one is based on the assessment at one time-point while the other uses data from previous measurements as well. This lack of consistency in the analyses of the two types of endpoints would lead to difficulty in interpretation of study findings. For a meaningful interpretation of study findings, consider the same time-point for both the primary as well as the secondary endpoints.

Meeting Discussion:

The Agency clarified that analyses of the primary (success/failure) and secondary endpoints (some might be continuous) should be consistent, that both should be analyzed at the same time-point (week 16) and using similar methodology for handling missing data. The MMRM uses data during the course of the trial in contrast to the CMH, which uses data at week 16 only. Furthermore, the MMRM is reasonable for ignorable missing data, an assumption which is difficult to test in practice. The Agency referred the sponsor to the report by NAS, "The prevention and the treatment of missing data in clinical trials" 2010 as well as the recent publication "The role of statistics in regulatory decision making" in Therapeutic Innovation and Regulatory Science, 2014, which discussed issues related to using the MMRM.

- Do you anticipate that any subjects enrolled in the clinical trial may have a relatively low pruritus score at baseline? If so, those subjects with low scores based on the pruritus categorical score (PCS) might not be able to contribute to a meaningful evaluation of efficacy for the pruritus secondary endpoint. In addition, the percent change in the pruritus score might not be able to convey a clinically meaningful difference when the pruritus score at baseline is low. Your analysis should be limited to subjects who have a clinically recognizable severity for pruritus at baseline. In addition, whether a change of ≥ 3 improvement (reduction) from baseline on an 11-point NRS scale is meaningful would require justification. For a claim in pruritus, the trials would need a good proportion of subjects with a certain minimum level of pruritus severity at baseline along with a clinically meaningful, fixed threshold for defining responders.
- Your synopsis specified that a hierarchical testing procedure will be used for the multiple endpoints, and at $\alpha=0.025$ for each dose regimen independently. While you are proposing to test two dose regimens (300 mg QW and 300 mg Q2W), please note that establishing efficacy for the two dose regimens might not guarantee approval of both dose regimens.

The regulatory action might be limited to one dose regimen based on the risk-benefit ratio.

- You are reminded of our previous comments (5/21/2014) that for handling missing data, you should propose a scientifically sound method, and propose sensitivity analyses to ensure that efficacy results are not driven by the method of handling missing data.

For your “Maintenance Trial” 1415:

-  (b) (4)

Meeting Discussion:

-  (b) (4)
- 

For your “Combination Trial” 1224:

- You may compare Dupilumab + topical corticosteroids (TCS) arm against placebo + TCS under the assumption that the concomitant medication has efficacy and that the TCS use can be considered similar across the treatment arms. Therefore, for establishment of an efficacy claim for this population, provide scientific evidence that the concomitant medication has some efficacy (i.e., higher than placebo alone); FDA approval for marketing for the treatment of atopic dermatitis (or corticosteroid-responsive dermatoses) would constitute such evidence. Replication of study findings would be needed if you intend to pursue this indication before you establish the efficacy of Dupilumab as monotherapy.

Additional Comments:

-  (b) (4)

(b) (4)
the recently published American Academy of Dermatology “Guidelines of care for the management of atopic dermatitis Section 3: Management and treatment with phototherapy and systemic agents” specifically recommends against the use of systemic corticosteroids because of “short- and long-term adverse effects and an overall unfavorable risk-benefit profile.” We recommend that Dupilumab be discontinued in any subject who receives rescue treatment with oral corticosteroids.

- Clarify whether subjects who require “rescue therapy” in trial #1224 will be considered failures with regard to efficacy evaluation.

Meeting Discussion:

The sponsor clarified that subjects who require “rescue therapy” in trial #1224 will be considered failures.

- Clarify the TCS standard regimen you propose as concomitant therapy in trial #1224. In your protocol, provide details regarding adjunctive and rescue medications.

Phase 3 Dose Regimen

Question 3:

Assuming that primary analysis results at week 16 are consistent with the interim analysis results of R668-AD-1021, does the Agency agree with the dose regimens proposed for the initial treatment monotherapy and combination studies (300 mg qw and 300 mg q2w) and the maintenance study (b) (4)?

Response:

For evaluation of dupilumab as monotherapy, you proposed Dupilumab dosing regimens of 300 mg qw and 300 mg q2w, each with an initial loading dose of 600 mg, in the initial treatment period (16 weeks) of the Phase 3 trials R668-AD-1334 and R688-AD-1416, and you proposed Dupilumab dosing regimens of (b) (4) for evaluation of the maintenance treatment effect in Phase 3 trial R668-AD-1415. The proposed dosing regimens appear to be reasonable for evaluation of Dupilumab as monotherapy in Phase 3 trials.

Your efficacy endpoint analyses by body weight category (≤ 90 kg vs. >90 kg) suggest that exposure differences due to body weight should not impact response for the two proposed Phase 3 Dupilumab dosing regimens. As such, it is reasonable that weight-based dosing does not need to be evaluated in the proposed trials. However, we request that similar body weight category analyses be conducted using data from the Phase 3 trials and be provided at the time of the BLA submission.

(b) (4)

For evaluation of Dupilumab as adjunctive therapy, you proposed Dupilumab dosing regimens of 300 mg qw and 300 mg q2w administered concomitantly with topical treatment over the entire 52 weeks of the study period of the Phase 3 trial R668-AD-1224. You proposed not to conduct a separate maintenance study; however, we recommend that you evaluate the maintenance treatment effect of Dupilumab in less frequent dosing regimens (e.g., 300 mg q4w and 300 mg q8w) in the adjunctive therapy trial(s). As these subjects will be on both Dupilumab and TCS, a different and possibly less frequent maintenance regimen may be sufficient to maintain response in these patients. One potential maintenance study design could mirror that described above for the monotherapy setting.

Additional Comment:

If you have information about human biologic variants which could provide context for your product, such as information about patients with genetic absence of the alpha subunit of the IL-4 receptor (or related conditions), we would find provision of this information, along with your discussion of it, to be helpful.

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. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)**. Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.
3. 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).
4. You are encouraged to request a Pre-BLA Meeting at the appropriate time.

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>.

Attachments and Handouts

Attachment provided by Regeneron Pharmaceuticals, Inc. on August 1, 2014.

7 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately
following this page

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

/s/

STANKA KUKICH
08/28/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107969

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Viswanathan Srinivasan, Ph.D.
Director, CMC Regulatory Affairs
81 Columbia Pike
Rensselaer, NY 12144

Dear Dr. Srinivasan:

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

We also refer to the meeting between representatives of your firm and the FDA on May 8, 2014. The purpose of the meeting is to obtain concurrence from the Division on the proposed CMC development program to support the registration of dupilumab, including: (1) (b) (4); (2) data package to establish comparability following changes to the drug product formulation and container closure system; (3) filling process validation strategy; and (4) device stability and assembly validation.

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}

Laurie Graham, M.S.
Team Leader
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
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: CMC Only

Meeting Date and Time: May 8, 2014 at 11:30AM
Meeting Format: Teleconference

Application Number: 107969
Product Name: dupilumab
Sponsor/Applicant Name: Regeneron Pharmaceuticals, Inc.

Meeting Chair: Laurie Graham
Meeting Recorders: Andrew Shiber

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Biotechnology Products (OBP)

Laurie Graham, M.S.	Team Leader, Division of Monoclonal Antibodies (DMA)
James Andrews, Ph.D.	Quality Reviewer, DMA
Andrew Shiber, Pharm.D.	Regulatory Project Manager

Office of New Drugs (OND)/Division of Dermatology and Dental Products

Jill Lindstrom, M.D.	Clinical Team Leader
Jane Liedtka, M.D.	Medical Officer
Matthew White	Regulatory Project Manager

Office of Combination Products

Patricia Love, M.D., MBA	Deputy Director
Bindi Nikhar, M.D.	Associate Director Clinical

SPONSOR ATTENDEES

Regeneron Pharmaceuticals, Inc.

Frank Seebach, M.D.	Executive Director, Regulatory Affairs
Elisa Babilonia, Ph.D.	Senior Manager, Regulatory Affairs
Alexei Goraltchouk, BASc, MASc , MBA, MSF	Associate Director, Drug Product Sciences
James Fandl, Ph.D.	Vice President, Protein Expression Sciences

Jennifer McNay, Ph.D.
Marius Ardeleanu, M.D.

Senior Director, Process Sciences
Senior Director, Clinical Sciences Immunology and
Inflammation
Associate Director, CMC Regulatory Sciences
Director, CMC Regulatory Affairs
Vice President, Preclinical Development and
Protein Chemistry

Michele Lastro, Ph.D.
Seenu Srinivasan, Ph.D.
Thomas Daly, Ph.D.

1.0 BACKGROUND

Objectives: The purpose of the requested meeting is to discuss some key elements of the planned CMC development program for Phase 3 and commercial manufacturing. The Sponsor plans to employ the drug product solution for sub-cutaneous injection administered with pre-filled syringes (b) (4) in Phase 3 studies and for commercial distribution, respectively.

The objectives of the meeting are to obtain concurrence from the Agency on the proposed CMC development program to support Phase 3 studies and registration of dupilumab, including:

1. (b) (4)
2. Data package to establish comparability following changes to the drug product, including formulation, container closure system and DP manufacturer.
3. Filling process validation strategy
4. Device stability and assembly validation

2.0 DISCUSSION

Question 1: The Sponsor proposes that provided cell line clonality is established and genetic characterization of the MCB and WCB demonstrate genetic stability, it is sufficient to characterize the genetic stability of cells (b) (4) (b) (4)

Does the Agency concur? Does the Agency agree that these general concepts would apply to similar products produced using the Sponsor's manufacturing platform?

FDA Response to Question 1:

The general testing plan for genetic characterization of the cell banks might be adequate, but a review of the data, and additional information submitted to the BLA, will be required to support the testing plan. For example, the BLA will need to contain summary information on the referenced experiments conducted to determine the probability of clonality as well as information that addresses the Agency comments (b) (4)

(b) (4) However, we cannot agree (b) (4)

Based on the information provided in the briefing document, it appears that the (b) (4) provide documentation to the IND on the country of origin, commercial source, raw material testing requirements, and certificates of analysis for these materials. In addition, submit (b) (4) and virus risk assessments to the IND. The virus risk assessment should include information to support that the MCB is free from adventitious viruses, classified as pathogenic to humans, associated with the use of the (b) (4). This may include additional testing of the MCB for these viruses, information demonstrating that the tests already performed on the MCB would have detected these agents if present, or data demonstrating that the (b) (4) used for cell bank generation were free from these agents. Of note, your assessment of testing that has already been performed should include consideration for whether a (b) (4) day or amplified in vitro adventitious virus test was performed.

Sponsor Response: We will submit to the IND the recommended (b) (4) and virus risk assessments for (b) (4) related antibodies as well as a more detailed description of our adventitious agent testing. We would like to clarify that the (b) (4)

Meeting Discussion: The Agency disagreed (b) (4). The Agency indicated that certain manufacturing changes, such as a new cell line, would require EOPC testing. The sponsor inquired about a specific situation (b) (4). The Agency responded that for a production method transfer with minimal changes, EOPC testing most likely would not be necessary.

Question 2: For Phase 3 clinical trials, the Sponsor plans to introduce (b) (4) with a different (b) (4) excipient, (b) (4) and a new container closure system. Does the Agency agree with the proposed analytical assessment to support the comparability of the post change drug products for use in Phase 3 clinical studies and agree that no clinical bridging study is needed?

FDA Response to Question 2:

No we do not agree. With regard to the analytical comparability plan, we have the following comments:

- a. Based on the information provided, the pre-change material includes only the current 150

mg/mL strength in the (b) (4) formulation filled in vials. (b) (4)

Separate comparability assessments should be provided for each of the post-change materials.

- b. It is unclear from the information provided if you only intend to provide pooled results for “pre-change” material that includes the referenced research PFS lots. We recommend that you provide the historical release and stability data for vial lots separately from the referenced research material (i.e. (b) (4)), as the vial lots represent the pre-change material.
- c. The release results of the post-change material should be compared to the historical pre-change material in vials and the referenced release trending control charts should be provided.
- d. The chromatograms for the applicable release and stability assays should be provided.

A conclusion regarding the need for additional studies to support the proposed CMC changes will require a review of the analytical data. However, even if the analytical data support comparability, it is unclear that this will be sufficient to justify the lack of clinical bridging data to support some of the proposed changes. For example, there are concerns that the described changes may result in PK changes for a subcutaneous administered product that will not be detected in the biochemical biophysical analytical analysis. Additional information will be provided on this topic for the clinical meeting EOP2 to be held on May 21, 2014

Of note, for licensure, information on the polysorbate raw material’s control strategy, including acceptance criteria, storage conditions, and shelf-life for the polysorbate stock material will need to be submitted. We strongly recommend that polysorbate 80 testing be included in DP specifications.

Sponsor’s Response: Based on the R668-AD-1021 (dose ranging study) interim analysis results, the Sponsor is proposing 300 mg qw and 300 mg q2w as the dose regimens for phase 3 (to be confirmed with the Division on May 21, 2014). Assuming this is acceptable, only the 150 mg/mL concentration in prefilled syringe (PFS) (b) (4) will be used in Phase 3. As described in the briefing book, the changes to the drug product include: 1) container closure (prefilled syringes instead of vials), 2) (b) (4) and 3) (b) (4). As such, analytical comparability will be demonstrated between the 150 mg/mL concentration (b) (4) vial and the 150 mg/mL concentration PFS (b) (4) only. We intend to include the Agency’s recommendations a, b, c, and d in the analytical testing plan to compare “pre-change” and “post-change” materials. We would like to confirm with the Agency that release and stability testing as described in the briefing book (pages 29 to 35), will be adequate to demonstrate analytical comparability of the proposed Phase 3 DP (150 mg/mL PFS (b) (4)) to the DP used in Phase 2 (150 mg/mL vials (b) (4)).

As the FDA suggested, we will further discuss the clinical bridging requirements on the EOP2 clinical meeting scheduled for May 21, 2014. We acknowledge the Agency's suggestion to include polysorbate 80 testing in the DP specifications.

Meeting Discussion:

The Agency indicated that the planned analytical testing appears reasonable. However the analytical comparability will be evaluated in the context of the clinical bridging plan to be discussed on May 21, 2014 at the End of Phase II clinical meeting.

The Agency indicated that it would be helpful if there was a risk assessment provided on the proposed manufacturing changes to support the analytical comparability plan. This would include the identification of quality attributes that would most likely be impacted by the proposed CMC changes. An example would be that (b) (4)

Regeneron inquired about testing (b) (4)
(b) (4) The Agency noted that this strategy may be acceptable but the overall strategy will need to be evaluated.

Question 3: The Sponsor plans to fill three validation lots per concentration (150 mg/mL (b) (4) These batches will be manufactured with a (b) (4) The Sponsor is also considering a dosage form that may contain a rigid needle shield (RNS). Does the Agency agree with the validation plan outlined in the briefing package in regards to the introduction of the RNS?

FDA Response to Question 3:

The process validation approach for the RNS appears reasonable. Sterilization validation information supporting the (b) (4) and RNS product groups should be provided in the application. Shipping validation studies should be performed with the final commercial container closure system. Data and supporting information should be provided in the BLA.

Sponsor's Response: We acknowledge your comments and no further discussion is necessary on May 8, 2014.

Question 4: Does the Agency agree (i) that the data associated with verifying the device stability of all design and functional specifications as defined for the combination drug product can be provided through the device design verification studies; and, (ii) that device testing does not need to be repeated as part of the DP quality attributes stability testing on the assembly process validation batches for registration?

FDA Response to Question 4:

Based on the briefing document, there is insufficient information to support an Agency response. The document indicates that you intend to use two different prefilled syringes in phase 3. In

addition, it appears that you intend to market [REDACTED] (b) (4)

In order to provide a more comprehensive response, we refer you to the following FDA guidance documents:

- Final - Guidance for Industry and FDA Staff; Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products is accessible at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>
- Draft - Guidance for Industry and FDA Staff - Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4 accessible at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM346181.pdf>

In particular, tests for the combination product should be conducted to assure that not only is the volume of dupilumab injected the required amount but that the dose accuracy, or the biologic product activity, is not compromised by the action of injection.

In addition, the proposed approach to not include [REDACTED] (b) (4) device functionality in DP stability testing may be acceptable, but will depend upon a review of the proposed device stability data. Provide clarification on what is meant by “production equivalent active drug product”.

For further discussion on these issues, we recommend that you request an additional meeting to discuss the CMC-device related issues in conjunction with other topics that might result from the CMC meeting of May 8, 2014 and the clinical meeting of May 21, 2014. For this future meeting request, we recommend that you submit details on the device designs (including drawings) for the products you intend to validate. Also, provide a table of when each PFS and PFS+ [REDACTED] (b) (4) will be used in Phase 3. The table should identify the study number, the number of patients, and number of doses for each combination product.

Sponsor’s Response: As the FDA suggested, we will request a separate meeting to discuss the CMC-device related issues

Question 5: Does the agency agree with the proposed risk-based assembly validation approach?

FDA Response to Question 5:

Based on the briefing document, it appears that this question refers to the assembly of the final finished combination product (not the device alone). The following comments should be addressed:

- a. The validation approach for the final combination product should consider maintenance of container closure integrity during [REDACTED] (b) (4) assembly and shipping. Data and supporting information should be provided in the BLA.
- b. Clarification should be provided on when DP release testing is performed relative to

- the release testing of the assembled (b) (4) listed in Table 15 of the meeting package.
- c. The BLA should include a description of the functional and attribute tests that are relevant to the assembly process.
 - d. The validation protocol should clearly describe the tests to be performed during QC pass/fail testing and the criteria by which batches of finished combination products would be failed.
 - e. The validation protocol and report should demonstrate how ANSI/ASQ Z1.4 and Z1.9 were followed during quality control testing
 - f. An attachment to the validation protocol should be provided with data to support the maximum TOR.
 - g. You should be prepared to verify, and support with evidence, that the equipment used during the validation was validated, as well.

ADDITIONAL COMMENTS:

Combination Products are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at

<https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>

The following recommendations apply to the location of device manufacturing information in the marketing application.

1. All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with applicable 21 CFR part 820 regulations should be located in Section 3.2.P.3.
2. The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part.
3. Suggestions on the types of documents to submit for review related to 21 CFR Part 820 can be found in the guidance document titled "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," issued on February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

eCTD Format Related to the Device Constituent Parts

The following provides recommendations apply to combination drug and device product such as PFS, pens and other injectors in an eCTD application. Please do not use module 3.2.R for this information.

1. For eCTD format and use of the system, please adhere to eCTD headings as defined

per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say "Container Closure System."

2. Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.
3. We recommend the following when including and referencing device information:
 - a. You may reference files under 3.2.P.7 which are not currently listed as numerical items in ICH and FDA specifications and guidance.
 - b. In 3.2.P.7 you could include a leaf titled something similar to the following, "Table of Contents for Drug-Device (b) (4)". This leaf/document could provide reference links to the other files in module 3.2.P.7. Obtaining concurrence from the Review Division on the proposed outline is recommended.
 - c. The leaf titles should be clear, concise and indicative of the document's content.
4. Module 1.4.4 cross reference to other applications is a location where you can provide references to other applications and you can include copies of an application's table of contents, reference tables, or other similar documents. If you are cross referencing another company's application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 Letter of Authorization, 1.4.2 Statement of Right of Reference, 1.4.3 List of Authorized Persons to Incorporate by Reference). If there are standards you will reference in the Performance Specifications which also meet these criteria, then please put them in module 1.4.4. The Performance Specifications section should link to this information.

Although it's not required, providing a "Information to Reviewers" or "Reviewers Guide" document in Module 1.2 Cover letters can be helpful. This document would be separate from the cover letter and referenced after the cover letter. It would provide a high level overview (with reference links) of the submission's content and list where the information is located in the eCTD. For example, it would identify where drug, device and combination product information including manufacturing and human factors information is located.

In reference to 21 CFR Part 4, the submission should provide the procedures necessary to demonstrate that it has satisfied the requirements of 21 CFR 820.30 (Design Control), 820.50 (Purchasing Controls) and 820.100 (Corrective and Preventive Action). These procedures should be provided to demonstrate compliance for these specific areas of the Quality System Regulation for the combination product as a whole, not just the device constituent parts. The procedural information to provide and level of detail necessary to be provided should be consistent with what is recommended in the Agency guidance referenced above under Additional Comments item 3. If then firm has specific questions please submit them to the IND.

The device constituents are part of the combination product as a whole. The facilities on the 356h form or attachment to the form should include manufactures of the device constituent part(s) and the location from which the finished combination product is distributed.

Reference ID:

Sponsor's Response: We acknowledge your comments and no further discussion is necessary on May 8, 2014.

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

/s/

LAURIE J GRAHAM
06/13/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107969

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Senior Manager, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Babilonia:

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

We also refer to the meeting between representatives of your firm and the FDA on May 21, 2014. The purpose of the meeting was to discuss the development program for (dupilumab), a monoclonal antibody (mAb), for the (b) (4) treatment of moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with (b) (4) topical prescription therapy or when those treatments are not advisable.

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 Matthew White, Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Acting Director
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 B
Meeting Category: End-of-Phase 2

Meeting Date and Time: May 21, 2014 at 10:00 am
Meeting Location: White Oak Building 22, Room 1313

Application Number: IND 107969
Product Name: (dupilumab)

Proposed Indication: For the (b) (4) treatment of moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with (b) (4) topical prescription therapy or when those treatments are not advisable

Sponsor: Regeneron Pharmaceuticals, Inc.

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Matthew White

FDA ATTENDEES

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Kendall A. Marcus, MD, Acting Director, DDDP
Stanka Kukich, MD, Deputy Director, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
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Emma Guttman, MD, PhD, Associate Professor, Dermatologist Mount Sinai School of Medicine

Purpose of the Meeting:

To discuss the development program for (dupilumab), a monoclonal antibody (mAb), for the (b) (4) treatment of moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with (b) (4) topical prescription therapy or when those treatments are not advisable

Regulatory Correspondence History

We have had the following meeting(s)/teleconference(s) with you:

- 5/8/14: Type B (CMC End-of-Phase 2) meeting
- 3/31/14: Teleconference to discuss the pediatric study plan
- 1/23/13: Type C (guidance) meeting
- 11/ 22/2011: Teleconference to discuss Grade 4 adverse events (elevated CPK) which occurred during Study R668-AD-0914
- 5/26/2010: Type B (pre-IND) meeting

We have sent the following correspondences:

- 12/20/13: iPSP advice letter
- 11/14/2013: Advice letter
- 10/4/2013: IRB waiver granted letter
- 8/21/2010: Study may proceed letter
- 7/12/2010: Acknowledge IND letter
- 7/12/2010: Advice letter

Pharmacology/Toxicology

Question 13:

The Agency has previously agreed that the toxicology program seems reasonable to support the clinical development plan and registration of dupilumab administered SC in adult patients with atopic dermatitis [Type C meeting (23-Jan-2013; Reference ID: 3249587)]. In response to a

request from the Agency at the January 23, 2013 Advice meeting (Reference ID: 3249587), the Sponsor provided historical control information that addressed the various histopathological findings noted in the 6-month monkey toxicology study and confirmed the study NOAEL was 100 mg/kg/week SC, the highest dose administered [IND 107969 SN0028]. Does the Agency agree that the general toxicology and reproductive studies of the toxicology program support the phase 3 clinical development program and registration of dupilumab administered via the subcutaneous (SC) route for adult patients with atopic dermatitis?

Response:

Yes, we agree that your toxicology program supports the proposed Phase 3 clinical development program and registration of dupilumab administered via the subcutaneous (SC) route for adult patients with atopic dermatitis.

Question 14:

The Sponsor conducted a weight-of-evidence based carcinogenicity risk assessment based on results from toxicology studies with REGN646 and REGN1103 (monkey and mouse surrogate antibodies, respectively) and review of published literature on the role of IL-4 and IL-13 pathways in tumor development and anti-tumor immunity, and the impact of IL-4R α inhibition on these processes. Does the Agency agree that, given the available data with the anti-IL-4R surrogate antibodies REGN646 and REGN1103, and data in the literature on IL-4R α inhibition, together with clinical monitoring and post-marketing surveillance approaches, that no additional nonclinical studies are necessary to assess the carcinogenic potential of dupilumab for registration?

Response:

Yes, we agree that no additional nonclinical studies are needed to evaluate the carcinogenic potential of dupilumab for registration. The Executive Carcinogenicity Assessment Committee provided concurrence with this assessment on May 5, 2014. The carcinogenic potential of dupilumab will be further reviewed under the BLA.

Question 15:

The Agency had previously agreed that no additional nonclinical or juvenile toxicology studies were required to support pediatric clinical trials in ≥ 1 year old subjects [Type C meeting (Reference ID: 3249587)]. The Sponsor has recently modified the proposed pediatric program such that younger patients (6 months vs. 1 year) than those previously discussed will be included. Does the Agency agree that, given the available nonclinical data with REGN646 and REGN1103 (including general toxicology and reproductive studies in animals) and the rationale submitted for not conducting juvenile toxicology studies in the Type C meeting background package [IND 107969 SN0026], juvenile toxicology studies are not necessary to support administration of dupilumab to pediatric patients 6 months to 18 years of age?

Response:

Yes, we agree that no additional nonclinical studies are required to support conduct of clinical trials in pediatric subjects ≥ 6 months old.

Clinical Pharmacology

Question 9:

The Sponsor proposes to conduct in vitro experiments to assess the potential effect of dupilumab on cytochrome P450 isoforms reported to be modulated by IL-4 and IL-13. Does the Agency agree that, if no meaningful modulation of the functional activity of these CYP isoforms is observed, no further studies will be necessary?

Response:

No, we do not agree. You should conduct in vivo studies in the target patient population to evaluate the drug-drug interaction (DDI) potential between your drug product and CYP450 substrates, because recent studies have indicated that in vitro or animal studies have limited value in the qualitative and quantitative projection of clinical interactions and translation of in vitro to in vivo and animal to human results to date has been inconsistent. The in vivo evaluation of your drug product in targeted populations can be conducted with individual substrates for specific CYP enzymes, or studies can be conducted using a “cocktail approach”. We are open to further discussion regarding the clinical study design to evaluate the DDI for your product.

Refer to the following guidance for more information:

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

Sponsor's Comment:

“We acknowledge the Agency's comment. The sponsor will design the study and submit it to the Agency for review and comment.”

Additional Clinical Pharmacology comments:

- Based on the briefing packages for two EoP2 meetings (current meeting and the CMC meeting), we understand that you have used dupilumab supplied in vials thus far and you plan to use dupilumab in prefilled syringe (PFS) with 150 mg/mL strength (b) (4) in the Phase 3 trials. (b) (4)

(b) (4) e have the following comments about the planned changes in formulation/presentation of dupilumab.

- We recommend that you compare the PK between the Phase 2 formulation and Phase 3 formulation(s)/presentation(s) to facilitate extrapolation of dose from the Phase 2 trial to Phase 3 pivotal trials because the formulation differences between PFS and vial presentation could potentially impact PK of dupilumab.
- We recommend you conduct a frequently-sampled PK trial to characterize and compare the full dupilumab PK profiles of the PFS formulation(s)/presentation(s) that will be used in Phase 3 trials (b) (4)

- (b) (4)
3. We remind you that characterization of the PK profiles of the to-be-marketed formulation(s)/presentation(s) in the target patient population will be required to support the approval and labeling of your product.
4. (b) (4)
- Your study synopses indicated that you have planned to collect sparse PK samples in the proposed Phase 3 clinical trials to assess PK of your product in subjects with atopic dermatitis. We recommend you additionally conduct a frequently-sampled PK sub-study in an adequate number of subjects in the Phase 3 trials (R668-AD-1334 (b) (4)) to characterize the full PK profile of dupilumab at steady state, e.g., following the last dose administration. For the proposed Phase 3 trial R668-AD-1224, we recommend you collect sparse PK samples during long-term treatment. The recommended additional PK sampling will also be beneficial for evaluating exposure-response relationship and the effect of immunogenicity on PK, efficacy and safety. We may have additional comments on your PK trial design such as blood sampling scheme after we review your final Phase 3 protocols submitted under the IND.

Meeting Discussion:

The sponsor stated they will only use the prefilled syringe with 150 mg/mL strength in the proposed Phase 3 trials. (b) (4)

Based on the additional information, the Agency recommended one 2-arm PK trial to characterize the PK of the to-be-marketed formulation and to evaluate the potential differences between the Phase 2 and Phase 3 formulations. The Agency recommended that the sponsor conduct this trial prior to Phase 3; however, the sponsor stated that they propose to conduct this trial in parallel with Phase 3 and understood the risk.

The Agency acknowledged that the sponsor plans to collect trough PK samples in the proposed Phase 3 trials. The Agency stated that this will be sufficient in combination with the planned 2-arm PK trial. As such, the PK substudy with frequent sampling is optional.

Clinical

Introductory Comment:

Your submission includes synopses for two Phase 3 trials, each with the treatment duration of 16 weeks: Trial 1334 will investigate dupilumab as monotherapy and Trial (b) (4) will investigate dupilumab as adjunctive therapy to topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI). In addition, your submission included synopses for Trial 1224, a 52-week treatment trial to assess the long-term safety and efficacy of dupilumab versus placebo in what you called “a

real-world scenario” and Trial 1225, an open label extension/re-treatment trial for subjects who participated in prior dupilumab clinical trials with the goal to collect long-term safety data on re-exposure of previously treated patients. With this clinical development program, you seek an indication for “(b) (4) treatment of moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with (b) (4) topical prescription therapy or when those treatments are not advisable. (b) (4) ”.

We have the following general comments about your clinical development program for dupilumab:

1. (b) (4)

Meeting Discussion:

The sponsor provided a new proposal in response to the Agency’s preliminary comments. There was extensive discussion about various components of their proposed development program including:

- Replication of monotherapy, adjunctive therapy, (b) (4)
- Primary endpoint (IGA) and key secondary endpoint (EASI75)
- Dose and dose regimen
- Timing of submission of applications for treatment (b) (4)
- The number of subjects to be enrolled for efficacy and safety
- Use of standard of care versus standardized topical therapy (b) (4)

Based on today’s discussion, the Agency requested that the sponsor submit a detailed proposal and questions for Agency consideration, which could be discussed in a subsequent teleconference.

2. To establish an efficacy claim, replication of study findings is needed. (b) (4)

In general, replication of study findings from two adequate and well-controlled Phase 3 trials would be needed for *each* treatment paradigms (monotherapy, adjunctive therapy) for which you seek a claim. Alternatively, you could consider a sequential clinical development program in which you conduct two adequate and well-controlled Phase 3 trials for one of the treatment paradigms (either monotherapy or

adjunctive therapy); following establishment of an efficacy claim in one paradigm, it is possible that a single adequate and well-controlled Phase 3 trial would be sufficient to support an additional claim for the other paradigm. See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

Question 1:

Dupilumab is being developed for the (b) (4) treatment of moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with (b) (4) topical prescription therapy or when those treatments are not advisable. Does the Agency concur with this proposed target patient population?

Response:

We agree with the population you plan to enroll, as defined by your inclusion/exclusion criteria. Consider an additional inclusion criterion, “candidate for systemic treatment.” We think that the population identified by your inclusion/exclusion criteria would be considered to have severe disease.

Question 2:

Does the Agency agree that the definition of inadequate responder outlined below can be used to identify, in our Phase 3 study inclusion criteria, the patient population referred to in our proposed indication?

Response:

You propose to define an inadequate responder as

...failure to achieve and maintain remission or a low disease activity state (eg, IGA 0=clear to 2=mild) despite treatment with topical corticosteroids of medium to high potency ($\pm$ topical calcineurin inhibitors as appropriate), applied daily for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent topical corticosteroids), whichever is shorter. The definition of intolerance is based on the presence of important side effects or safety risks that outweigh the potential treatment benefits (e.g., hypersensitivity reactions, significant skin atrophy, systemic effects, etc., or imminence thereof), as assessed by the investigator or by patient’s treating physician. Acceptable documentation includes contemporaneous chart notes that record topical corticosteroids prescription and treatment outcome, or investigator documentation based on communication with patient’s treating physician.

In addition, you propose that “patients with a history of inadequate response to topical treatments, with documented treatment for AD with systemic non-steroidal immunosuppressive drugs (e.g., cyclosporine, mycophenolate, azathioprine, methotrexate) within the last 6 months, also be considered inadequate responders to topical treatments and potentially eligible for treatment with dupilumab after appropriate washout.

See the response to Question 1. Clarify "...imminence thereof." Your proposal otherwise appears reasonable.

Question 3:

The Sponsor defines patients with moderate-to-severe atopic dermatitis as those who meet all of the following criteria: IGA score ≥ 3 (0-4 scale, where 3=moderate and 4=severe disease), BSA $\geq 10\%$ and EASI score ≥ 16 at baseline. Does the Agency agree with this definition?

Response:

In general, the above proposed inclusion criteria seem reasonable; however we think that patients/subjects who meet these criteria and the other inclusion criteria represent a population with severe disease. See the response to Question 1.

You propose the following Investigatory Global Assessment Scale:

Modified Investigator Global Assessment Scale and Morphological Descriptors

Score	Standard Definitions	Proposed Morphological Descriptors
0 = Clear	No inflammatory signs of atopic dermatitis	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration)
2 = Mild disease	Mild erythema and mild papulation/infiltration	Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration)
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration	Dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive
4 = Severe disease	Severe erythema and severe papulation/infiltration	Deep/dark red erythema; marked and extensive elevation (papulation/infiltration)

The currently proposed scale does not include the presence of excoriations and/or oozing and crusting. Provide your rationale for this decision.

Meeting Discussion:

The sponsor provided their rationale.

Question 4a:

Does the Agency agree with the proposed design of each trial, including the primary and secondary endpoints, sample size, and duration?

Response:

For co-primary efficacy endpoints you propose:

- Proportion of patients with IGA 0-1 and with a reduction from baseline of ≥ 2 points at week 16
- Proportion of patients with EASI50 ($\geq 50\%$ improvement from baseline) at week 16

For our purposes, a primary endpoint defined as the proportion of subjects with IGA 0-1 and with a reduction from baseline of ≥ 2 points at week 16 would be sufficient for demonstration of efficacy. Change in EASI score could be included as a key secondary endpoint. If you wish to include EASI in a co-primary endpoint, subjects should win on both IGA and EASI to be considered a success, e.g., proportion of subjects with an IGA 0-1 and with a reduction from baseline of ≥ 2 points at week 16 AND with an EASI90 ($\geq 90\%$ improvement from baseline) at week 16.

As previously conveyed during the meetings held on May 26, 2010 and Jan 23, 2013, the change in EASI score uses a measure (EASI) that is not used in routine clinical practice in the U.S. and which is difficult to translate into meaningful labeling. In addition, EASI 50 may not represent a sufficient degree of improvement to be considered a success in subjects with significant disease at baseline. If you wish to incorporate a change in EASI score as part of your primary endpoint, we request that you propose a threshold which would translate to clinically meaningful improvement consistent with success on the IGA, based on analysis of data with your product.

For key secondary endpoints you propose:

1. Change from baseline to week 16 in pruritus NRS
2. Percent change in EASI score from baseline to week 16
3. Change from baseline to week 16 in %BSA
4. Change from baseline to week 16 in individual AD signs
5. Proportions of patients achieving EASI75 and EASI90 (≥ 75 , and $\geq 90\%$ reduction from baseline in EASI score)
6. Incidence of skin infection TEAEs requiring systemic treatment from baseline through week 20
7. Change from baseline to week 2 in pruritus NRS
8. (b) (4)

You proposed a NRS for measurement of pruritus to be used as an important secondary endpoint. We agree that assessment of pruritus is important. Provide evidence of the instrument's reliability, validity and ability to assess change; see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

To successfully demonstrate improvement on a symptom measure, it is important to select subjects with sufficient level of symptom severity on that scale at baseline; therefore, the inclusion criteria for your Phase 3 trials should include a threshold baseline severity for pruritus. Propose a definition of a responder, taking into consideration your threshold for enrollment.

For the NRS for measurement of pruritus, not only is the definition (i.e., success criteria) of a responder on the NRS a critical element, but also the proportion of subjects who are responders. In addition, such an endpoint should be prespecified and controlled for multiplicity along with the other secondary endpoints.

In order to be considered for labeling, secondary endpoints need to be clinically relevant, limited in number, and analyzed with appropriate multiplicity control.

For safety endpoints you propose:

- Incidence of TESAEs from baseline through week 20
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 20
- Overall incidence of TEAEs through week 20

You proposed a treatment duration of 16 weeks followed by a 12 week follow-up period for Phase 3 trials 1334 (b) (4). This seems acceptable at this time.

You provided a brief synopsis for your planned Phase 3 trials 1334 (b) (4). Additional comments and revisions to the above comments will be provided following receipt of the full protocols for your Phase 3 trials.

Meeting Discussion:

The sponsor's proposal for one primary endpoint (IGA 0-1) and EASI75 as a key secondary endpoint appears reasonable.

Question 4b:

Does the Agency agree that the proposed Phase 3 clinical development program could be sufficient to support an indication for “(b) (4) treatment of moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with (b) (4) topical prescription therapy or when those treatments are not advisable. (b) (4)”?
(b) (4)

Response:

It does not appear that your proposed Phase 3 development program would be sufficient to support the above indication (b) (4)
(b) (4)

You propose to conduct the following Phase 3 trials:

Trial 1334 - a 16 week monotherapy trial of dupilumab in 600 adults subjects with moderate to severe AD who are not adequately controlled by or are intolerant to topical prescription therapy or for whom those treatments are not advisable

(b) (4)

Trial 1224 – a 52 week treatment trial to assess the long-term safety and efficacy of dupilumab versus placebo in a real-world scenario (allowing combination with TCS, TCI and/or oral steroids) in 1050 adult subjects

Trial 1225 - an open label extension/re-treatment trial for 800 subjects who participated in prior dupilumab clinical trials to collect long-term safety data on re-exposure of previously treated patients to dupilumab and to assess the safety profile of long-term exposure of dupilumab. This trial is ongoing (b) (4)

(planned duration is 2 years)

See the introductory comments.

(b) (4)

You propose to establish efficacy of dupilumab using 16 weeks of either monotherapy or combination therapy. To determine the optimal management strategy for patients who achieve an adequate treatment response with 16 weeks treatment with dupilumab, we recommend that you explore different doses and dosing regimens, as well as duration of effect (such as with randomized withdrawal), to inform future trial design.

Trials 1224 and 1225 may provide supportive safety data.

Question 4c:

Does the Agency agree that the proposed Phase 3 clinical development program, which includes a 52-week placebo controlled efficacy and safety study, would be sufficient to support a chronic sustained treatment regimen?

Response:

Clarify the context of your question, specifically what is meant by, "...sufficient to support a chronic sustained treatment regimen."

The safety database needed to support approval will depend upon the anticipated benefit relative to the risk of your product and the safety signals that emerge in your development program. We refer you to "Drugs Intended for Long Term Treatment of Non-Life-Threatening Conditions" which can be found in International Conference on Harmonization (ICH) E1A.

See the introductory comments.

Question 4d:

Does the Agency agree with the proposed rescue medication strategy?

Response:

You propose the following rescue medication strategy for trials 1334 and (b) (4)

If medically necessary (e.g., to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator. For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered study treatment failures, but they may continue study treatment if rescue consisted of topical medications (b) (4) or systemic corticosteroids administered for 2 weeks or less. Patients who receive systemic corticosteroids for longer than 2 weeks or systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) will be discontinued from study drug.

Individual subjects and investigators might have different thresholds for what constitutes the need for rescue therapy. We recommend that you document the results of efficacy assessments, such as the IGA, NRS for pruritus and EASI at any visit where rescue therapy is initiated.

Additionally, we recommend that you document the drugs, doses, and duration of use of any rescue therapy.

Question 4e:

Does the Agency agree with the proposed analysis plans for each phase 3 study, including analysis methods, multiplicity adjustments, handling of missing values, and accounting for the impact of rescue medication on efficacy endpoints?

Response:

You submitted protocol synopses for two short-term Phase 3 trials, a 52-week long-term Phase 3 trial, and an open-label trial. (b) (4)

(b) (4) Submit full protocols for detailed comments. Based on your protocol synopses, the following are general comments:

- For your Trials 1334 (b) (4), you did not specify the number of sites in each trial. For investigating the center-to-center variability, you trials should plan to enroll a reasonable number of subjects per treatment arm per center (i.e., 8 subjects), and the analysis should account for such stratification.
- You specified an endpoint based on EASI score to be a co-primary endpoint. The Agency reiterates its previous comments at the Guidance Meeting (1/23/2014) that the sponsor's proposed approach to use IGA and EASI score as co-primary endpoints appears

reasonable. In such case, efficacy should be established on each co-primary endpoint, starting with the IGA endpoint. Note that the proposed EASI 50 might not translate to sufficient clinical improvement to be considered success (see the response to Question 4a).

- You proposed to use a repeated measures analysis method (MMRM) for analyzing continuous endpoints. Note that such analyses consider measurements at each timepoint, which might not be meaningful. For establishing a claim, we prefer that you conduct an analysis at a prespecified timepoint.
- For handling missing data, you should propose a scientifically sound method, and propose sensitivity analyses to ensure that efficacy results are not driven by the method of handling missing data.
- For calculating the sample size for your Trials 1334 (b) (4), you assumed the same response rates for the two trials although Trial 1334 is a monotherapy trial, and Trial (b) (4) is “in combination with topical prescription therapy” trial. As you powered your trial based on assumed rates based on the success rates of IGA and EASI 50 from your Phase 2a Proof of Concept (POC) Study R668-AD-1117, you run the risk of underpowering your Phase 3 trials. See the introductory comments.
- You plan to investigate 2 doses (300 mg QW, 300 mg Q2W) and included a plan to adjust for multiplicity for the 2 doses. While the trials are controlled for the Type I error rate for the two doses, note that a Phase 3 study design based on a single dose would require a smaller number of subjects for each trial, and would allow hypothesis testing to be done at $\alpha=0.05$. Therefore, for Phase 3 trials, it might be beneficial to consider investigating a single dose of dupilumab, selected based on the findings from your Phase 2 development program. Note that in a Phase 2 trial, you might investigate response rates of dupilumab as a monotherapy or as a combination therapy, and results from such trial would enable you to obtain useful treatment effect estimates for planning your future Phase 3 trials.

Question 5:

The Sponsor proposes to define a flare of AD as any episode of worsening of disease (as reported by the patient or noted by the investigator) requiring an escalation/intensification of AD treatment. Does the Agency agree with this definition?

Response:

Clarify the relationship of flare with the initiation of rescue therapy. We recommend that you document the results of efficacy assessments, such as the IGA, NRS for pruritus and EASI at any point when a flare is diagnosed.

Question 6:

(b) (4)

(b) (4)

Response:

(b) (4)

Ultimately, the content of labeling will be determined during review of your BLA.

Question 7:

Assuming that primary analysis results at week 16 are consistent with the interim analysis results of R668-AD-1021, does the Agency agree with the dose regimens (300 mg qw and 300 mg q2w) proposed for the phase 3 pivotal trials?

Response:

You proposed dosing regimens of 300 mg qw and 300 mg q2w, each with an initial loading dose of 600 mg, for evaluation in the Phase 3 trials. The dosing regimens were selected primarily based on interim analysis of the Phase 2b dose ranging study (R668-AD-1021) with available safety and efficacy data at Week 12. We acknowledge that you have planned to revisit the dose selection when the primary analysis of the Phase 2b data at Week 16 is completed and we anticipate that you will provide a complete dosing regimen justification with your Phase 3 protocol submission. We have the following comments and recommendations based on the current interim analysis results of R668-AD-1021.

In general we are in agreement that for regimens with the same dosing frequency 300 mg offers a greater response at Week 12 compared to lower dupilumab doses of 200 or 100 mg, though the available data is not sufficient to determine whether there are any relationships between dose and/or exposure and safety with dupilumab. In addition, the current data from study R668-AD-1021 supports 300 mg administered every week (qw) or every two weeks (q2w) maintained EASI response and less frequent dosing (every 4 weeks, q4w) could not maintain the concentration achieved by the initial loading dose (Figure 2, page 32 of the briefing document). However, the available data and simulations do not address whether 200 mg qw (or 150 mg qw) could achieve a similar or higher response to 300 mg q2w, particularly in subjects with higher body weight.

The available data is also not sufficient to inform whether the proposed doses are appropriate for maintaining response or whether a lower dose or less frequent dosing would be sufficient to maintain clinical response once a clinical response has been achieved. A maintenance regimen should be informed by relapse data from R668-AD-1021 and other clinical studies from your development program. In general, dose ranging should be conducted in a manner which investigates the treatment phase separately from the maintenance phase, as dosing for maintenance or re-treatment upon relapse maybe different than that required for the initial treatment phase. Therefore, it may be beneficial to evaluate additional dosing regimens in your long-term maintenance study.

The provided modeling and simulation results suggest a body weight effect on dupilumab pharmacokinetics which translates into an impact on response based on the simulations provided in Figure 4 of the briefing package. As such, it is uncertain if a fixed-dose regimen for all patients would be appropriate for the Phase 3 study as opposed to evaluating different doses based on body weight. Consideration of body weight in the dosing regimen may be of particular importance for the proposed 300 mg q2w regimen. Patients weighing 100 kg or more are predicted to have mean steady state trough concentrations approaching 50 mcg/mL, an identified target concentration to saturate the targets and to maintain the response. We request that you further evaluate the impact of body weight on treatment response with fixed dose regimens by (1) summarizing EASI50, EASI75, EASI90, and IGA 0/1 responses in study R668-AD-1021 based on a body weight cut-off of 90 kg and (2) summarizing the predicted EASI50, EASI75, EASI90, and IGA 0/1 response rates at Week 12 and at Week 16 for multiple dosing regimens (such as 300 mg qw, 300 mg q2w, 200 mg qw, 200 mg q2w, 150 mg qw, 150 mg q2w, and 100 mg qw) in patients with body weight ≤ 90 kg and >90 kg. Differences in the response rates between the two body weight groups from either of these analyses would suggest that the currently proposed Phase 3 fixed-dose regimens may not be appropriate and alternative dosing regimens that aim to account for the body weight effect should be considered. We also request that you further evaluate the impact of body weight on safety of your product when the primary analysis of the Phase 2b data at Week 16 is available. Results of these analyses can be included in the Phase 3 protocol submission as justifications for your selected dose regimens.

Meeting Discussion:

(b) (4)

The sponsor will provide the results of the Phase 2b study and modeling simulations for Agency consideration.

Question 8:

Does the Agency agree that the proposed exposure database would be sufficient to evaluate the safety of dupilumab in the BLA?

Response:

See the response to Question 4c.

Question 10:

Does the Agency agree with the Sponsor's proposed strategy to assess the immunogenicity of dupilumab?

Response:

We agree with your plan to use a screening, confirmatory and titer assays followed by an assessment of neutralizing antibodies in ADA positive subjects. The review of assay validations will be a BLA review issue.

We recommend that you consider assessing drug tolerance using low, medium, and high positive control concentrations. We remind you that the immunogenicity assays should be validated and should be capable of sensitively detecting ADA responses in the presence of drug levels that are expected to be present at the time of patient sampling. (b) (4)

Therefore, optimization for your current ADA assay may be needed to address the potential drug interference issue.

With regard to the neutralizing antibody assay, the Agency generally recommends the use of a cell based assay rather than ligand binding assays as cell based assays more likely to reflect the in vivo situation. It is recommended that data be provided to support that the results of the competitive ligand binding assay reflect the results of a cell-based assay. We recommend that you consider the drug tolerance in developing and validating the assay for neutralizing antibody.

During your product development, you should evaluate the impact of immunogenicity on PK, efficacy and safety.

Please refer to the following guidances for more information.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf>

Meeting Discussion:

The sponsor is developing a new assay with a higher drug tolerance level. The report will be submitted for Agency consideration.

Question 12:

Does the Agency agree that a thorough QT is not required to support the registration of dupilumab?

Response:

Monoclonal antibodies do not need to be evaluated in a thorough QT study. Routine ECG monitoring in Phase 3 trials should be performed to capture important cardiac effects.

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. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)**. Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.
3. 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).
4. You are encouraged to request a Pre-BLA Meeting at the appropriate time.

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.

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](#).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for

IND 107969
Meeting Minutes
Type B (End-of-Phase 2)

Office of Drug Evaluation III
Division of Dermatology and Dental Products

Industry Assessment of Abuse Potential of Drugs”, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

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

/s/

KENDALL A MARCUS
05/30/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107969

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Manager, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Dr. Babilonia:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for REGN668.

We also refer to the teleconference between representatives of your firm and the FDA on January 23, 2013. The purpose of the meeting was to discuss the development program for REGN668.

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 Matthew White, Regulatory Project Manager at (301) 796-4997.

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:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: January 23, 2013 at 9:00 am
Meeting Location: Teleconference

Application Number: IND 107969
Product Name: REGN668
Proposed Indication: For the treatment of patients with moderate-to-severe atopic dermatitis who are inadequately controlled with topical medications.

Sponsor Name: Regeneron Pharmaceuticals, Inc.

Meeting Chair: Susan J. Walker, MD
Meeting Recorder: Matthew White

FDA ATTENDEES

Susan J. Walker, MD, FAAD, Director, DDDP
Jill Lindstrom, MD, Clinical Team Leader, DDDP
Jane Liedtka, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Renqin Duan, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Yuqing Tang, PhD, Biostatistician, DB III
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, DCP3
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Laurie Graham, MS, Product Quality Reviewer, DMA
Carla Lankford, PhD, Product Quality Reviewer, DMA
Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst, PMHS
Jessica Voqui, PharmD, MS, Endpoints Reviewer, SEALD
Laurie Burke, RPh, MPH, Director, SEALD
Matthew E. White, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Gianluca Pirozzi, MD, PhD, Head, anti-IL4, DPU, Sanofi
Jennifer Cairns, PhD, Associate Director, Regulatory Affairs, Sanofi
William Roberts, MD, VP, Clinical Development and Regulatory Affairs, Regeneron
Steve Weinstein, MD, PhD, VP, Clinical Sciences, Immunology, Regeneron
Neil Graham, MD, VP, Program Direction, Regeneron
Marius Ardeleanu, MD, Director, Clinical Sciences, Inflammation, Regeneron
Yuhwen Soo, PhD, VP, Biostatistics and Data Management, Regeneron
Elisa Babilonia, PhD, Manager, Regulatory Affairs, Regeneron

Purpose of the Meeting:

The purpose of the meeting is to discuss the development program for REGN668.

Regulatory Correspondence History

We have had the following meetings/teleconferences with you:

- November 22, 2011: Teleconference to discuss Grade 4 adverse events (elevated CPK) which occurred during Study R668-AD-0914
- May 26, 2010: Pre-IND meeting

We have sent the following correspondences:

- August 20, 2010 Study may proceed letter
- July 12, 2010: Acknowledge IND letter
- July 12, 2010: Advice letter

Pharmacology/Toxicology

Question 12:

Does the Agency agree that the toxicology program as outlined above will support Phase 3 clinical development program and registration of REGN668/ SAR231893 administered via the subcutaneous route for adult patients with atopic dermatitis?

Response:

Your proposed toxicology program appears reasonable. However, the additional historical histopathology data for the 6 month monkey toxicology study requested during the Advice meeting [REDACTED] (b) (4) should be submitted to IND 107969. This information is needed to determine NOAELs for the various toxicities noted in the 6 month monkey toxicity study. These NOAELs will be used to determine if the 6 month monkey toxicity study supports the safety of the Phase 3 clinical development program.

[REDACTED] (b) (4). However, you should submit the completed nonclinical study reports to IND 107969 to allow for assessment of safety to support the proposed Phase 3 clinical study.

It is acceptable for you to submit your plan to assess the carcinogenic risk associated with REGN668/SAR231893. This information should be submitted to IND 107969 for review.

Question 13:

Given the absence of untoward findings in the repeat-dose, ePPND, and fertility studies and the current safety profile in humans, the Sponsor believes that the existing data adequately evaluate the safety of IL-4R α inhibition and that no additional studies in juvenile animals (e.g. mice and monkey) with a surrogate antibodies are warranted.

- A) Does the Agency agree that the completed nonclinical studies provide sufficient support to initiate clinical trials in adolescents once the safety and efficacy in adults (phase 2b study) have been demonstrated?
- B) Provided sufficient safety and efficacy are established in adolescent patients 12-17 years of age and in adults, does the agency agree that the existing nonclinical studies provide sufficient support to initiate pediatric clinical trials in patients 6-11 and 1-5 years of age in a stepwise approach?

Response:

Yes, provided that acceptable NOAELs can be determined in the 6 month monkey toxicology study based on review of the additional requested historical histopathology data (refer to response for Question 12).

Clinical/Biostatistics

Question 1:

Does the Agency agree with the proposed target population as defined by the key eligibility criteria?

Response:

The key eligibility criteria proposed for your phase 2b trial include:

1. Male or female, 18 years or older
2. Chronic AD, (according to the AAD Consensus Criteria, [Eichenfeld 2004]), that has been present for at least 3 years before the screening visit
3. EASI score ≥ 16 at the screening and baseline visits
4. IGA score ≥ 3 at the screening and baseline visits
5. $\geq 10\%$ body surface area (BSA) of AD involvement at the screening and baseline visits
6. Patients with documented recent history (within 3 months before the screening visit) of inadequate response to outpatient treatment with topical medications, or for whom topical treatments are otherwise inadvisable (eg, because of important side effects or safety risks)*

*NOTE: For the purpose of this protocol, inadequate response represents failure to achieve and maintain remission or a low disease activity state (eg, IGA 0=clear to 2=mild) despite adequate treatment with topical corticosteroids of medium to high potency ($\pm$ topical calcineurin inhibitors as appropriate), applied daily for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent topical corticosteroids), whichever is shorter. Important side effects or safety risks are those that outweigh the potential treatment benefits (e.g., hypersensitivity reactions, significant skin atrophy, systemic effects, etc., or imminence thereof), as assessed by the investigator or by patient's treating physician. Acceptable documentation includes contemporaneous chart notes that record topical corticosteroids prescription and treatment outcome, or investigator documentation based on communication with patient's treating physician.

These eligibility criteria seem reasonable at this time for the proposed Phase 2b study.

Question 2:

Does the Agency agree with the study design, as described, including the primary endpoint defined as percent change from baseline in Eczema Area and Severity Index (EASI)?

Response:

For your Phase 2 trial, you proposed the primary endpoint of percent change in EASI score. You might investigate different endpoints for evaluating the treatment effect in Phase 2. As the goal of a Phase 2 trial is to select the dose that is most likely to succeed in future confirmatory trials based on the trend in efficacy, no formal statistical testing is required and consequently the study does not need to be powered.

However, for establishment of efficacy in future Phase 3 trials, the primary endpoint recommended by the Division is the proportion of subjects with a score of 0 or 1 along with at least 2 grade improvement on a 5-point Investigator's Global Assessment (IGA) scale. Your proposed primary endpoint, change in EASI score, is difficult to translate into clinically-meaningful labeling and is therefore not recommended as a primary efficacy endpoint.

This was previously conveyed at the Pre-IND meeting held with the Agency on May 26, 2010:

“In confirmatory Phase 3 trials the primary efficacy endpoint should be based on the IGA. The IGA categories should contain morphological descriptors of each level of disease severity to promote consistency and clarity... Customarily, success using an IGA has been defined as clear or almost clear (with a two grade improvement).

We recommend using 5-point scales; it may be difficult to distinguish ‘severe’ subjects from ‘very severe’ subjects and these categories could be collapsed....”

The signs and symptoms of atopic dermatitis (particularly erythema, induration/ papulation, and oozing/crusting) should be evaluated as secondary endpoints. These signs should be evaluated globally as opposed to by body region (as in the EASI score).

You have proposed the following scale for your IGA assessment:

Investigator's Global Assessment (IGA)

Score	Description
0 = Clear	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration
2 = Mild disease	Mild erythema and mild papulation/infiltration
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration
4 = Severe disease	Severe erythema and severe papulation/infiltration
5 = Very severe disease	Severe erythema and severe papulation/infiltration with oozing/crusting

Your scale currently utilizes descriptors that mimic the category grade i.e., mild erythema and mild papulation in the “mild” category. You should improve your assessment scale. The IGA categories should contain morphological descriptors of each level of disease severity to promote consistency and clarity. Simple descriptors such as mild, moderate and severe are not sufficient. Qualities desirable for a good scale include that it be static, noncomparative with a limited number of categories. Each category should be distinct and non-overlapping and should represent a clinically meaningful gradation of disease. As was noted at the Pre-IND meeting in 2010, it may be difficult to distinguish severe from very severe patients and these categories should be collapsed.

You planned to randomize 240 to 288 subjects from 120 sites to 6 treatment arms. With such a large number of study sites, the number of subject per site would be very small, i.e., 2 subjects per site on average. Note that it would be difficult to evaluate the treatment effect as the dose effects may be confounded with the site effects. You should reduce the number of study sites to obtain reasonable estimates of the treatment effect for planning future Phase 3 trials.

In your proposed Phase 2b dose ranging study, all subjects will receive a fixed dose of 100, 200, or 300 mg at different dosing frequencies. We recommend that you investigate the impact of body weight on REGN668 exposure and clinical responses in this study. Such understanding will help you to assess whether body weight needs to be considered in the design of dosing regimens for your future trials.

Meeting Discussion:

The Sponsor provided details on additional descriptors to modify the IGA scale.

The Agency responded that the Sponsor's modifications appear reasonable. The revised IGA scale should be submitted for review. The Agency reiterated that the IGA scale should be limited to 5 categories.

The Sponsor proposes co-primary endpoints, using the IGA and EASI score. The Agency responded that this approach appears reasonable. Commitments for Phase 3 study design will be discussed following review of the data from Phase 2 studies. Defining the threshold for treatment success utilizing the EASI score should be investigated based on the data from the Phase 2 trials.

Question 4:

Does the Agency agree with the proposed primary and key secondary endpoints for the phase 3 studies?

Response:

No, see response to question #2.

Question 5:

Does the Agency agree that, contingent upon a positive outcome, these two pivotal studies, in conjunction with the placebo controlled long term treatment (PC-LTT; will provide 1 year safety data) and open label extension re-treatment (OLE-RT) study discussed below ([Section 9.2.2.1](#); [Appendix C](#)), will support a BLA application for the treatment of adult patients with moderate-to-severe atopic dermatitis who are inadequately controlled with (b) (4) topical therapies?

Response:

Information from your Phase 2 trials will be needed to address this question. The Agency recommends that, after completing these studies, you request an End-of-Phase 2 Meeting at which time these issues can be discussed.

Question 6:

Does the Agency agree with the proposed designs of the (b) (4) long-term safety studies?

Response:

See response to question #5.

Question 7:

The dose-regimen planned for these long-term studies will not exceed the dose regimen shown to have a favorable safety profile and evidence of efficacy in the phase 2a POC study (R668-AD-1117), (b) (4). After selecting the phase 3 dosing regimen(s), based on results from the phase 2b dose ranging study, the dose-regimen administered to patients in the long term safety studies will be adjusted accordingly (i.e., to the selected dose-regimen investigated in phase 3). Does the Agency agree with the dose selection and dose adjustment strategy in the long term safety studies?

Response:

See response to question #5.

Meeting Discussion:

The Sponsor provided clarification.

The Agency stated that the Sponsor's proposed approach appears reasonable.

Question 8:

Does the Agency agree that a safety database of approximately 2000 AD patients treated with REGN668/SAR231893 of whom approximately 1200 AD patients will be exposed for one year is sufficient to support an indication for the treatment of adult patients with moderate-to-severe atopic dermatitis who are poorly controlled by, or intolerant to topical therapies?

Response:

As noted at the Pre-IND meeting held in 2010:

“The number of subjects needed to demonstrate safety may be substantially higher than the number of subjects needed to demonstrate efficacy, and as such will greatly depend on the safety data collected from the pending trials. Additionally, the number of subjects needed to demonstrate safety will be dependent on the indication/s pursued, the ages of subjects exposed, and the signals detected.”

Question 9:

Assuming a favorable benefit/risk ratio in adults and supporting pre-clinical data (see question 13a), does the Agency agree a study in adolescents can be initiated after demonstration of safety and efficacy in the phase 2 dose-ranging study in adults?

Response:

The Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 changes the timeline for submission of a Pediatric Study Plan, and includes a timeline for the implementation of these changes. You should review this law and assess how your application is affected by these changes. If you have any questions regarding timelines, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

It is premature for the Agency to respond to your questions regarding pediatric studies without considering your Pediatric Study Plan (PSP) in its entirety. Submit your Pediatric Study Plan (PSP) for review. Your PSP must include the following:

- 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, along with supporting information. (Note: Although requests must be submitted with PSP, decisions on whether or not waivers and deferrals will be granted do not become final until approval)

A template will be available in the first quarter of 2013 to aid sponsors in formulating a Pediatric Study Plan. Should you elect to move forward without the template, the PSP should include (but is not limited to) the following:

- An overview of the disease in the pediatric population and the product under development
- Potential plans and justification for use of extrapolation
- Plans and justification for full or partial waiver
- Plans for pediatric specific formulation development
- Nonclinical data, complete or planned, to support studies in children
- Synopsis/summary of all clinical studies planned
- Timeline for the Pediatric Study Plan
- Any agreements with other Health authorities (e.g., Pediatric Investigation Plan for EMA)

Question 10:

Does the FDA concur that the pruritus NRS has the potential to support a label claim related to a reduction in itch severity among patients with atopic dermatitis?

Response:

No, we do not concur.

It is unclear how the patient is expected to respond to this question (e.g., whether to focus on itchiness on average, worst itchiness, etc.). We recommend clarifying the question for patients to answer appropriately. The appropriate wording of the question should be based on empiric data in the target population that provides evidence of whether the intensity of this symptom waxes and wanes over the course of a day or whether it remains relatively constant.

The recall period described in the study protocol (12 hours) is different than the instrument that was submitted for review (24 hours). While either recall period would be acceptable, it should be consistent throughout the study.

It is unclear how subjects will be assigned to use either IVRS or IWRS. Additionally, we will need to review the comparability of data obtained when using multiple administration modes within a single clinical trial to determine whether the treatment effect varies by method or mode. Future submissions should also include the instructions to the patients and case report forms or screenshots of the IWRS (if applicable), and data to show the comparability of the two modes of administration. Refer to the 2009 *Guidance for Industry - Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

Meeting Discussion:

The Sponsor proposed two questions using the pruritis NRS to measure worst itch and overall average itch.

The Agency stated that the Sponsor's proposal appears reasonable.

Question 11:

Does the FDA concur that the POEM has the potential to support a label claim related to a reduction in atopic dermatitis symptom severity?

Response:

No, we do not concur due to several concerns regarding the content validity of the instrument as follows:

- The POEM is listed as an exploratory endpoint in the clinical study protocol. You should note that exploratory endpoints cannot be used to support labeling claims. If you wish to use the POEM score for that purpose, then it should be prespecified as a secondary endpoint in the clinical trial protocol. Preferably, a full endpoint model showing all primary and secondary endpoints, as well as the full analysis plan that addresses the issue of multiplicity should be provided.
- The items measure the frequency of each symptom. The relationship between symptom severity and frequency is not obvious and should be supported by qualitative evidence. Additionally, a summed score of the frequency of different symptoms is not easily interpreted.
- An overall summed score would not be appropriate since different concepts are being measured (i.e., sleep disturbance versus topical symptoms such as itching and bleeding). We recommend that the instrument focus on the core symptoms of the disease. Sleep disturbance is an impact of the disease and should be scored separately.
- The instructions allow patients to leave questions blank. If the patient does not experience the symptom for an item, an appropriate response would be "no days." Therefore, there is no reason to leave a question blank, and it should be discouraged.
- The POEM will only be administered in a subset of patients who fluently speak a language in which it has already been translated. You may consider translating and adapting the instrument to increase the subset in which it can be used. If any PRO instruments are translated or adapted, the methods used should be described in future submissions as described in the 2009 *Guidance for Industry - Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.
- It is unclear how you will handle missing PRO data. In future submissions, the SAP should address plans for how the statistical analysis will handle missing data, including all rules for handling missing data. Please refer to the 2009 *Guidance for Industry -*

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

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 NDA might identify additional comments or information requests.
2. You are encouraged to request and attend an End-of-Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for Phase 3 trials. Comments on Phase 1 and 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

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>

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
01/24/2013



PIND 107969

MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, Ph.D.
Regulatory Associate, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Babilonia:

Please refer to your Pre-Investigational New Drug Application (PIND) file for REGN668.

We also refer to the teleconference between representatives of your firm and the FDA on May 26, 2010. The purpose of the meeting was to discuss the clinical development program for REGN668.

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

If you have any questions, call Cristina Attinello, Regulatory Project Manager at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND Meeting

Meeting Date and Time: May 26, 2010, 3PM
Meeting Location: Teleconference

Application Number: PIND 107969
Product Name: REGN668
Indication: Treatment of atopic dermatitis
Sponsor/Applicant Name: Regeneron Pharmaceuticals, Inc.

Meeting Chair: Susan Walker
Meeting Recorder: Cristina Attinello

FDA ATTENDEES

Susan J. Walker, M.D., Division Director, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Jane Liedtka, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Carmen Booker, Ph.D., Pharmacology Reviewer, DDDP
Margo Owens, Team Leader, Project Management Staff, DDDP
Cristina Attinello, MPH, Regulatory Project Manager, DDDP
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DB III
Haeyoung Ahn, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Julia Cho, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Ruth Cordoba, Ph.D., Product Quality Team Leader, OBP/DMA
Carla Lankford, Ph.D., Product Quality Reviewer, OBP/DMA
Lisa Mathis, M.D., Associate Director, PMHS
Hari Sachs, M.D., Medical Officer Team Leader, PMHS
Beth Durmowicz, M.D., Medical Officer, PMHS
Denise Pica-Branco, Regulatory Project Manager, PMHS
Jared Lantzy, Regulatory Information Specialist, OPI/OBI/DRRS
Valerie Gooding, Regulatory Information Specialist, OPI/OBI/DRRS

SPONSOR ATTENDEES

Thomas Daly, Ph.D., Vice President, Preclinical Development & Protein Chemistry, Regeneron
Edward Zimmer, Ph.D., Senior Director, Toxicology, Regeneron
Allen Radin, M.D., Senior Director, Translational Medicine, Regeneron
Elisa Babilonia, Ph.D., Regulatory Associate, Regulatory Affairs, Regeneron
Ned Braunstein, M.D., Executive Director, Regulatory Affairs, Regeneron
William G. Roberts, M.D., Vice President Regulatory and Clinical Development, Regeneron
Ross Rocklin, M.D., Senior Director, Clinical Investigations, sanofi-aventis
Linda Gambone, Ph.D., Associate Director, Regulatory Affairs, sanofi-aventis

Purpose of the Meeting:

The purpose of the meeting is to discuss the clinical development program for REGN668.

Regulatory

Question 14:

Regeneron is planning to cross-application link Modules 2, 3, and 4 of this IND (b) (4).
Regeneron will use (b) (4) to perform submission publishing activities. (b) (4) recently submitted a successful cross-application pilot that passed FDA review on (b) (4).

Does the Agency agree with the sponsor's plan to a cross-application approach to Module 2, 3, and 4 (b) (4)

Response:

The Agency agrees with the sponsor's plan to use cross-application linking and offers the following guidance:

The leaf titles of each cross application link should include "Cross Ref to <insert application prefix and number>" (i.e. Cross Ref to ind123456, then the rest of the leaf title...) in the beginning of each leaf title which is a cross reference. This helps the reviewer know that when they click on the document, it is a cross application link taking them to a document in another application. We also strongly recommend that a document be placed in Module 1.4.4 that lists the cross referenced documents and the locations of those documents in case any cross reference links don't work.

(b) (4)

Chemistry, Manufacturing and Controls (CMC)

There are no CMC questions submitted in this briefing package, however, the Agency has the following comment:

Earlier information submitted indicated that you intend to modify the current formulation for REGN668 drug product. If changes are introduced, the IND will need to contain detailed information on the changes and information and data to support drug product manufacture and testing of the new formulation. This should include, but not be limited to, stability data to support storage of drug product in the new formulation at its recommended storage temperature and a stability protocol for the new formulation.

Pharmacology/Toxicology

Question 1:

The proposed 6-month SC and IV toxicology study in cynomolgus monkeys will support long-term human SC and IV clinical studies, (b) (4)

(b) (4) The toxicology study will include two SC (25 and 100 mg/kg) treatment arms and a single IV (25 mg/kg) treatment arm to assess any systemic toxicities and local injection site reactions following chronic administration of REGN646. In this study, REGN646 will be administered once weekly for 6 months with a recovery period of 3 months. Provided any toxicities observed in the study are readily monitorable in humans and there is a NOAEL demonstrated in the study that provides an adequate exposure margin, an interim audited report from the dosing phase with complete histopathology and toxicokinetics (b) (4)

(b) (4). The final report including histopathology and toxicokinetics data would be submitted within an additional 3 months of submission of the interim audited report. Please refer to Appendix E for the study synopsis.

Does the Agency agree that (b) (4) IV and SC doses, duration of dosing and recovery and the proposed reporting plan for the 6-month chronic toxicology study are adequate (b) (4)?

Response:

The adequacy of the completed study will be a review issue under the IND. It is recommended that the study include a second IV dosing group for a more thorough analysis (b) (4)

(b) (4) In addition, you should consider adding a hematology and immunotoxicity assessment in between the baseline and Week 14 evaluations. This additional timepoint will aid in identifying earlier and possibly transient changes in the immune system induced by your product.

Question 2:

(b) (4), Regeneron is conducting a combined embryo-fetal and pre-/postnatal reproductive and developmental toxicology study (ePPND) in non-human primates and will provide all the data up to 1 week postpartum prior to the initiation of Phase 3 clinical studies or large Phase 2 studies with treatment duration ≥ 3 months. The remaining data will be provided with the BLA.

The sponsor plans to conduct a fertility study in mice using mouse surrogate antibody for REGN668 and plans to submit the data from this study prior to initiation of Phase 3 clinical trials (Appendix G).

Does the Division agree that the reproductive toxicology program as agreed to with the Pulmonary and Allergy Division is appropriate to support clinical development in patients with atopic dermatitis?

Response:

The proposed reproductive toxicology program appears to be appropriate; however, the adequacy of the completed studies will be a review issue under the IND. It is recommended that a complete study protocol be submitted to the IND for review by the nonclinical reviewer and the CDER PTCC Immunotoxicology Subcommittee before the study is initiated to ensure that the immunotoxicity assessment of the infants is adequate.

Additional Nonclinical Comments:

1. Atopic dermatitis is a chronic indication; therefore, development would need to be supported by a carcinogenicity assessment. You should provide a plan to assess the carcinogenic potential of your drug product.
2. Before conducting pediatric clinical studies, we recommend that the sponsor conduct juvenile animal studies using the murine and monkey surrogate antibodies and submit the complete study report for the proposed combined embryofetal and pre-/postnatal reproductive and developmental toxicology study in cynomolgus monkeys. The sponsor may consult the guidance entitled “Nonclinical Safety Evaluation of Pediatric Drug Products”, if further guidance is desired.

Meeting Discussion:

The sponsor indicated that their five-week and six-month monkey toxicity studies were conducted in 2 – 4 year old juvenile animals. The sponsor proposed extending their pre-/post-natal reproductive toxicology study in monkeys for one month to assess the effects on younger animals. The sponsor also proposed a ten to fourteen day study in neonatal mice. The Agency responded that the sponsor should submit a scientific rationale to the original IND which supports the adequacy of this program.

3. A full characterization, including purity and binding affinity, should be submitted for both the monkey and murine surrogate antibodies to aid in the review of the adequacy of the proposed chronic and reproductive toxicology studies.

Clinical Pharmacology/Biopharmaceutics

There are no Clinical Pharmacology/Biopharmaceutics questions submitted in this briefing package, however; the Agency has the following comments:

1. Pharmacokinetics of a protein drug could be different between healthy volunteers and patients. Therefore, it is recommended that you assess the pharmacokinetics of the drug in subjects with atopic dermatitis. It is ideal that the study be conducted before the Phase 2 proof-of-concept (POC) study to guide the dosing regimen.
2. Following the proposed POC study in atopic dermatitis, you are strongly encouraged to conduct a Phase 2 dose finding study to select doses to be tested in pivotal Phase 3 studies. In your development program, you should establish the exposure-response relationship.

Meeting Discussion:

The sponsor agreed to obtain PK data in the atopic dermatitis population.

Clinical/Biostatistics

General Clinical Comments:

You will need to establish safety and activity of REGN668 in adults (18 and older) before beginning investigations in a pediatric population.

We reiterate the comments

(b) (4)

:

From a clinical perspective, there are ethical concerns with pediatric studies and the study must show the potential for benefit. Benefit must be shown in the adult population prior to initiation to pediatric studies.

Determination of the timetable for pediatric trials will depend on efficacy and safety information gained from the adult trial experience. You are referred to ICH E11 *Guidance for Industry Clinical Investigation of medicinal Products in the Pediatric Population*.

In addition, we remind you of comments regarding women of child bearing potential (WOCBP) from the (b) (4) meeting:

We agree that women of childbearing potential may be enrolled in Phase 1b and Phase II studies, provided that studies are carefully monitored and include the use of double barrier pregnancy prophylaxis and pregnancy testing. Informed consents should note the potential for risk. Segment I and II studies should be completed before the enrollment of women of childbearing potential using birth control in Phase III studies. Segment III studies should be submitted at the time of the BLA submission or earlier if there is cause for concern.

Data from both the nonclinical studies and from clinical trials in adults will need to be submitted prior to enrollment of pre-pubescent or adolescent girls.

Meeting Discussion:

The sponsor agreed to initiate their development program in the adult population. The sponsor proposed a novel adaptive trial design for Phase 2 to enhance efficiency. The Agency advised the sponsor to consider whether this design would provide the overall safety and dose ranging information necessary for proceeding to Phase 3.

Question 3:

Please refer to Appendix A for the proposed POC study synopsis in atopic dermatitis.

The initial study proposed for the IND in atopic dermatitis is designed to assess the safety, tolerability, efficacy and pharmacodynamics of multiple doses of subcutaneously administered

REGN668 in adults with moderate-to-severe atopic dermatitis. Approximately 345 patients will be randomized in a 1:1:1 ratio to receive SC REGN668 150 mg, 300 mg, or placebo weekly for 3 months (12 weeks). The primary endpoint is the proportion of patients who achieve $\geq 90\%$ improvement in Investigator Global Assessment (IGA) score from baseline to Week 12 (Refer to Appendix A for the IGA description table). Secondary endpoints will include the mean percent change from baseline in eczema area and severity index (EASI) score at 12 weeks. Please refer to Section 6.2 for additional details about the patient population, including inclusion/exclusion criteria, and study endpoints. In this Phase 2 POC study, we will define moderate to severe atopic dermatitis according to the Eichenfield revised criteria of Hannifin and Rajka (Eichenfield 2004).

The dosing for this multiple dose study will be based on an escalation from the highest dose that was well-tolerated in the FIH study. For example, if the highest well-tolerated dose in the FIH study is 12 mg/kg IV (equivalent to 840 mg in a 70 kg subject), the sponsor would select a SC dose of 300 mg per week as the highest dose for the multiple dose study [equivalent to 2700 mg IV over 12 weeks assuming 75% bioavailability (Investigator Brochure, Section 1.3.2)]. Thus, patients in the high dose active arm of the multiple dose study will receive a cumulative dose over 12 weeks which is approximately 3-fold the highest dose, administered as a single dose, evaluated in the FIH study. Because REGN668 will be administered by SC route and the weekly dose will be significantly lower than those administered IV to the latter cohorts in the single-dose study, peak drug blood levels in this SC POC study are anticipated to be lower than those encountered in the IV FIH study. The Regeneron Safety Monitoring Team (SMT) will assess the data from the FIH and approve the final dosing regimen for the multi-dose study. Justification for the dosing will be provided in the protocol included in the IND.

Because this is the first time REGN668 is being administered in this population, a safety analysis will be conducted after the first 60 patients have received 4 weekly SC doses of study medication or placebo. Study sites will be instructed to suspend enrollment until after these first 60 patients have been enrolled and evaluated. The Regeneron SMT will review and advise whether enrollment may proceed.

The sponsor is planning to provide in the IND application a blinded safety summary of all cohorts (through at least day 15) from the FIH healthy volunteer study. In addition, the sponsor commits to wait until the 300 mg SC cohort (or highest tolerated dose) in the FIH study is completed through Study Day 85 with acceptable safety and tolerability before starting the Phase 2 atopic dermatitis study.

Does the Agency agree that the submission to the IND of reports demonstrating satisfactory safety in the 5-week IV and 13-week SC toxicology studies in cynomolgus monkeys along with the above approach to submitting/assessing clinical data from the FIH study are adequate to support the proposed 12-week proof-of-concept (POC) study assuming acceptable safety and tolerability?

Response:

Regarding the nonclinical studies, the 5 week IV and 13 week SC toxicology studies in cynomolgus monkeys may be acceptable to support the proposed 12 week proof-of-concept

study. The adequacy of these studies to support the proposed 12 week proof-of-concept study will be a review issue.

However, to date, you have conducted a single-dose study in forty-eight adults, only 12 of whom received either 150mg or 300mg (the doses proposed in study R668 (b) (4) 0914). We therefore strongly recommend that you conduct a small proof-of-concept study of short duration in adults before progressing to longer, larger studies in adults.

Question 4:

Providing acceptable safety in the FIH study at the 12 mg/kg IV level, does the Agency agree with the highest SC dose (300 mg weekly for 12 weeks) proposed for this POC study?

Response:

Assuming safety and tolerability is demonstrated in the FIH study, the dose of 300 mg seems reasonable. Ideally, drug development is an iterative process; we recommend your initial multiple-dose study be of limited size and duration. Such a study could provide safety and efficacy data that would be useful for the design of longer, larger Phase 2 studies. Please see the response to Question 3.

Question 5:

The sponsor intends to develop REGN668 for (b) (4) treatment of moderate to severe atopic dermatitis (b) (4) in patients (b) (4) who are not adequately responsive to (b) (4) topical therapies. The sponsor would like to initiate planning activities for a dose-ranging study, which optimally would utilize the same endpoints as the Phase 3 program. Thus, the sponsor would appreciate some guidance concerning the Agency's views about acceptable endpoints for pivotal studies.

(b) (4)

(b) (4)

Response:

No, we do not agree. Because atopic dermatitis is a chronic condition which may recur upon discontinuation of treatment, a run-in period (of sufficient duration to affect a response) with implementation of standard measures (e.g., relevant allergen and irritant avoidance, moisturization and skin protection) combined with topical corticosteroid treatment would be needed to identify the population with truly refractory atopic dermatitis. Those who fail to respond to these measures and manifest moderate or severe atopic dermatitis at the end of the run-in period could then be randomized. We refer you to the following article for an example of an appropriate approach to conventional therapy, “Soak and smear: a standard technique revisited by Gutman AB, Kligman AM, Sciacca J, James WD published in the *Archives of Dermatology* 2005 141(12): 1556-1559.

Question 6:

Does the Agency agree with the study design approach of monotherapy as described wherein topical steroid treatment is only used as rescue therapy as opposed to development of REGN668 as an add-on treatment to topical steroids?

Response:

A monotherapy approach seems reasonable. The Agency does not agree that allowing rescue therapy with topical corticosteroids is an appropriate approach at this stage of product development. The current safety database in humans is insufficient to allow the use of additional immunosuppressant therapy.

In addition, the sponsor should provide their rationale for proposing rescue therapy with topical corticosteroids in a population that has been specifically chosen for being poorly responsive to or intolerant of topical corticosteroid therapy.

Question 7:

Does the Agency agree with the proposed approach of assessing IGA score as primary endpoint for the induction phase in the pivotal studies?

Response:

The Agency is making no commitments regarding Phase 3 trials. In confirmatory Phase 3 trials the primary efficacy endpoint should be based on the IGA. The IGA categories should contain morphological descriptors of each level of disease severity to promote consistency and clarity. We recommend using 5-point scales, it may be difficult to distinguish ‘severe’ subjects from ‘very severe’ subjects and these categories could be collapsed. It is not clear how you would measure your proposed endpoint, “the proportion of patients that achieve $\geq 90\%$ improvement in Investigator Global Assessment (IGA) score from baseline to Week 12” using your proposed 6-point scale. Customarily, success using an IGA has been defined as clear or almost clear (with a two grade improvement). The Agency suggests you look at labeling for other products approved for the indication of atopic dermatitis for examples of IGA scales.

Question 8:

Does the Agency agree with the proposed approach of assessing time to flare after re-randomization of single-blind responders as primary endpoint for the chronic maintenance phase in the pivotal studies?

Response:

Information from preliminary trials will be needed to address this question. The Agency recommends that after completing adequate Phase 2a and Phase 2b studies that you request an End-of-Phase 2 Meeting at which time these issues can be discussed.

Question 9:

Does the Agency agree with the proposed definition of moderate to severe atopic dermatitis as both an IGA score ≥ 3 and EASI score ≥ 12 at screening and baseline visits?

Response:

The Agency is making no commitments. At this point, your definition of moderate to severe atopic dermatitis as an IGA score ≥ 3 and EASI score ≥ 12 at screening and baseline visits appears reasonable. However, ultimately the population that would be appropriate for treatment with this product will depend on the risk-benefit profile identified.

Question 10:

At the time of the initial BLA submission the sponsor expects to provide data on approximately 3500 randomized patients, of which 1900 will be on 1-3 active dose regimens. The data will include approximately 2000 patients with ≥ 6 months exposure, and 800 patients with ≥ 1 year of exposure. The sponsor plans to provide more precise estimates at the time of the End-of-Phase 2 Meeting (after conclusion of the Phase 2a study). However, the sponsor is seeking early feedback from the Agency on the proposed general size of the safety database for planning purposes.

Does the Agency agree with the proposed size of the safety database for REGN668 in (b) (4) adult atopic dermatitis patients?

Response:

The number of subjects needed to demonstrate safety may be substantially higher than the number of subjects needed to demonstrate efficacy, and as such will greatly depend on the safety data collected from the pending trials. Additionally, the number of subjects needed to demonstrate safety will be dependent on the indication/s pursued, the ages of subjects exposed, and the signals detected.

Question 11:

(b) (4)

Response:

(b) (4)

Clinical studies in pediatric subjects should not be initiated until safety and effectiveness have been demonstrated in adult subjects (18 and older). Although proceeding with nonclinical studies is acceptable, pediatric clinical trials should not proceed until substantial data from adequate adult (18 and older) exposure (e.g. from Phase 3) is obtained.

For more information, see General Clinical Comments above.

Question 12:

Based on additional data from the 6-month repeat dose and the ePPND reproductive toxicology studies in monkeys, along with the results from the Phase 2 POC study

(b) (4)

(b) (4)

?

Response:

No, see response to Question 2, Question 11 and General Clinical Comments above.

Question 13:

(b) (4), the sponsor intends to submit a Fast Track development application in the near future to seek the Agency's guidance on the development plan for this

(b) (4) Will the Agency consider such an application based on the current pre-clinical development program (completed 5-week IV and 13-week SC toxicology studies, ongoing ePPND reproductive and 6 month chronic toxicology studies and literature evaluation of the role of the IL-4R α pathway during post-natal development) and safety from the FIH study?

Response:

Based on the April 11, 2010 briefing package, REGN668 does not appear to meet the criteria for fast track designation. Fast track development programs are designed to facilitate the development and expedite the review of new drugs that intend to treat serious or life-threatening conditions AND demonstrate the potential to address an unmet medical need for the condition (See 21 CFR 312 regarding Procedures for Drugs Intended to Treat Life-threatening and Severely Debilitating Illnesses:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.5>).

For more information, see General Clinical Comments above.

Additional 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 the information submitted to the IND might identify additional comments or information requests.
2. Your pre-IND has been assigned 107969. Please reference this number on all submissions and correspondence. **Please note, studies in humans may not be conducted under this PIND.** Before you may conduct studies in humans, you must submit an Investigational New Drug Application (IND, see 21 CFR Part 312). When you submit your IND, please submit 4 desk copies in addition to the 3 archival copies.
3. You are encouraged to request and attend an End-of-Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for Phase 3 trials. Comments on Phase 1 and 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-107969	GI-1	REGENERON PHARMACEUTICA LS INC	(REGN668)

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
05/28/2010

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761055

LATE-CYCLE MEETING MINUTES

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Associate Director Regulatory Affairs
777 Old Saw Mill River Rd
Tarrytown, NY 10579

Dear Dr. Babilonia:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Dupixent (dupilumab) injection, 150 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 21, 2017.

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 Matthew White, Senior Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

Enclosures:

Late Cycle Meeting Minutes
Applicant's topics for discussion
Summary of Key Efficacy Results for R668-AD-1224



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: February 21, 2017 at 2:00 p.m. EST
Meeting Location: Teleconference

Application Number: BLA 761055
Product Name: Dupixent (dupilumab) injection, 150 mg/mL
Applicant Name: Regeneron Pharmaceuticals, Inc.

Meeting Chair: Snezana Trajkovic, MD
Meeting Recorder: Matthew White

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Drug Evaluation III (ODE III)
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Jill Lindstrom, MD, FAAD, Deputy Director, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Nancy Xu, MD, Acting Associate Director for Labeling, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Brenda Carr, MD, Clinical Reviewer, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, Division of Biometrics III (DB III)
Rebecca Hager, PhD, Statistical Reviewer, DB III
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3 (DCP 3)
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Cristina Ausin-Moreno, PhD, Product Quality Team Leader, Division of Biotechnology Review and Research IV (DBRR IV)
Gunther Boekhoudt, PhD, Product Quality Reviewer, DBRR IV
Lakshmi Narasimhan, PhD, Microbiology Reviewer, Division of Monoclonal Antibodies, Branch IV (DMA/BIV)
Wayne Seifert, Consumer Safety Officer, Division of Inspectional Assessment (DIA)
Robert Pratt, PharmD, Risk Management Analyst, Division of Risk Evaluation (DRISK)
Kira Leishear White, PhD, MS, Acting Team Leader, Division of Epidemiology I (DEPI I)
Joel L. Weissfeld, MD, MPH, Epidemiologist, DEPI I
Tri Bui-Nguyen, PhD, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)
Matthew E. White, Senior Regulatory Health Project Manager, DDDP

APPLICANT ATTENDEES

Gianluca Pirozzi, MD, PhD, VP, Global Project Head, Sanofi
Barry Sickels, PhD, Associate VP, Regulatory Affairs, Sanofi
Armi-Desiree Luthman, VP, Regulatory Affairs, Sanofi

Heribert Staudinger, MD, Associate VP, Clinical, Sanofi
Frank Seebach, MD, Executive Director, Regulatory Affairs, Regeneron
Neil Graham, MD, VP, Program Direction, Regeneron
Elisa Babilonia, PhD, Associate Director, Regulatory Affairs, Regeneron
Ned Braunstein, MD, Senior VP, Regulatory Affairs, Regeneron
Bolanle Akinlade, MD, Executive Director, Clinical Sciences, Regeneron
Daniel Van Plew, PhD, Executive Senior VP, IOPS, Regeneron
Alexandria Richart, PhD, CMC Regulatory Sciences Specialist, Regeneron
Kris Ghosh, PhD, Executive Director, CMC Regulatory Affairs, Regeneron

1.0 BACKGROUND

BLA 761055 was submitted on July 29, 2016, for Dupixent (dupilumab) injection, 150 mg/mL.

Proposed indication(s): Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids

PDUFA goal date: March 29, 2017

FDA issued a Background Package in preparation for this meeting on February 7, 2017.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

The following substantive review issues have been identified to date:

Product Quality

Pre-approval inspection of Sanofi Winthrop Industrie FEI: 3003259844 is currently pending.

Meeting Discussion:

The pre-approval inspection of Sanofi Winthrop Industrie FEI: 3003259844 was conducted February 6 – 10, 13 – 14, 2017 and is currently under review. The Agency acknowledged receipt of Sanofi's response to the LeTrait pre-approval inspection 483. The Field Management Directive (FMD)-145 and Establishment Inspection Report (EIR) will be forthcoming.

3. Information Requests

Information request sent February 7, 2017.

Meeting Discussion:

The Agency acknowledged receipt of the Applicant's response to the February 7, 2017, information request.

4. REMS or Other Risk Management Actions

No issues related to risk management have been identified to date.

5. Postmarketing Requirements/Postmarketing Commitments

Product Quality PMCs:

- Revise the (b) (4) CFU/ (b) (4) mL bioburden limit for product sampled (b) (4) after data from 10 additional drug product batches has been analyzed.
- Qualification of the bioburden and sterility test methods was performed with only two batches of drug product. Provide bioburden and sterility test qualification data from one additional batch of 150 mg/mL dupilumab drug product. Provide the data in the first annual report.

Clinical Pharmacology PMC:

- Complete the ongoing drug-drug interaction clinical study R668-AD-1433 to determine the potential for dupilumab to alter the pharmacokinetics of CYP substrates in subjects with moderate-to-severe atopic dermatitis (AD).

Clinical PMRs:

- A randomized, double-blind, placebo-controlled phase 3 study to investigate the efficacy and safety of dupilumab in patients, 12 years to less than 18 years of age, with moderate-to-severe Atopic Dermatitis
- A randomized, double-blind, placebo-controlled phase 3 study to investigate the efficacy and safety of dupilumab in patients, 6 years to less than 12 years of age, with severe Atopic Dermatitis
- A two-part phase II/III study to evaluate the safety, pharmacokinetics (PK) and efficacy of dupilumab in patients, 6 months to less than 6 years of age, with severe Atopic Dermatitis
 - (b) (4)
 - (b) (4)
- An open-label extension study to assess the long-term safety and efficacy of dupilumab in patients ≥ 6 months to <18 years of age with Atopic Dermatitis
- A prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to dupilumab during pregnancy to an unexposed control population.
- A retrospective cohort study using administrative databases to identify pregnancy outcomes.
- We may have additional PMRs/PMCs.

Meeting Discussion:

The Product Quality and Clinical Pharmacology PMCs were sent to the Applicant on February 15, 2017. The Clinical PMRs will be forthcoming.

6. Labeling Issues

- [REDACTED] (b) (4)

Discussion

[REDACTED] (b) (4) we considered the conditional probability for subjects, with severe disease at baseline, who were non-responders on the Q2W dose, who might be responders on the higher (QW) dose. To answer this question, the clinical trial design should have involved dose escalation, that is, advance subjects who did not respond on the lower dose (Q2W) at the first treatment cycle to the higher dose (QW) for the next treatment cycle. However, your trials were of parallel group design. For parallel design, one can only estimate the difference in the response rates for the two dosing regimen (QW vs Q2W).

Although the difference in the response rates for the two dosing regimen (QW and Q2W) is relatively small (3%-6%), the pattern differs by the IGA severity. Specifically, for the IGA=3 group the response for the Q2W group is higher than for the QW group, and this is consistent across the 3 trials, 1334, 1416, and 1224. However, this pattern is reversed for the IGA=4 group.

As the IGA is a categorical scale with limited number of categories, we considered analysis of a related continuous scale, the EASI score. The results of this exercise show that, for responders who were in the IGA=3 category at baseline, the baseline EASI scores for the Q2W group are generally slightly lower than those for the QW group. This may suggest that Q2W dosing is reasonable for small EASI scores within the IGA=3 category. However, for the IGA=4 responders, a similar trend is not observed. In 1334, the baseline EASI score is higher for the Q2W group compared to QW group, but the opposite is observed for the trial 1416.

In summary, the difference between the response rates for the two dosing regimens is small, and the results of further exploration of the data by subgroup analyses do not support a specific dose for a specific subgroup. Additional analyses increase the chance of false findings.

Additionally, from Week 0 to Week 16, the two dosing regimens showed a similar time-course to IGA response of 0/1. Therefore, there was no increase in the time to response for subjects in QW group compared to the Q2W group.

Meeting Discussion:

The Applicant agreed [REDACTED] (b) (4)

- **Clinical Studies - R668-AD-1224 (Trial 3) Study Results**

Applicant's proposal (see enclosed Applicant's topics for discussion):

(b) (4)

Meeting Discussion:

In response to the Applicant's proposal to report the placebo-controlled data at Week 52 in the labeling as it is highly relevant for prescribers to understand that a positive benefit/risk was demonstrated after 52-week treatment with DUPIXENT, the Agency noted the relevance of information from beyond the initial treatment period (Week 16). However, the Agency raised concerns about the interpretation of findings in comparing the response rates for DUPIXENT vs. placebo at Week 52. The Agency clarified that responders at Week 52 consist of a mixture of two subpopulations: (i) those who achieved success at Week 16 and remained success at Week 52 and (ii) those who were not responders at Week 16 and became responders at Week 52. Consequently, it would be difficult to interpret the efficacy results at Week 52 in their totality. The Agency requested the Applicant to submit their analysis results for these two subpopulations for review. Specifically, the Agency requested the Applicant to estimate the proportion of subjects who were success at Week 16 and remained success at Week 52; and estimate the proportion of subjects who were not success at Week 16 and became success at Week 52.

Furthermore, the Agency noted that a formal comparison of the response rates for an active vs. placebo is meaningful for the initial treatment period where the objective is to establish efficacy for the enrolled subjects with a certain minimum disease severity at the time of enrollment. Once efficacy is established at Week 16, a formal statistical testing to establish efficacy at later time point is not meaningful considering the characteristics of the subject population as discussed above. Further, achieving statistical significance at Week 52 would be easier due to some non-responders at Week 16 achieving success at Week 52 which may compensate for the relapse of Week 16 responders. For responders at Week 16, the relevant question is estimation of the proportion of subjects who remained success at later time point (e.g., Week 52) as they are followed up during the "maintenance" period. That is, the concept of interest would be estimating the maintenance of response in a longitudinal manner and not testing for efficacy against the placebo.

In addition, the Agency reminded the Applicant of a previous advice letter dated October 27, 2014, which pointed out that the endpoints at Week 52 (i.e., IGA at Week 52, EASI 75 at Week 52) "do not appear to add significant additional information to what has been shown by the primary endpoint and the first secondary endpoint and will therefore be unlikely to be incorporated into labeling".

7. Review Plans

- Labeling discussions
- PMC/PMR discussions
- Manufacturing and clinical site inspection recommendations
- Take action on BLA application

8. Wrap-up and Action Items

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

10 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

SNEZANA TRAJKOVIC
03/01/2017



BLA 761055

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Associate Director Regulatory Affairs
777 Old Saw Mill River Rd
Tarrytown, NY 10579

Dear Dr. Babilonia:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Dupixent (dupilumab) injection, 150 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for February 21, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at Matthew.White@fda.hhs.gov, at least one week prior to the meeting.

Sincerely,

{See appended electronic signature page}

Jill 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 Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: February 21, 2017
Meeting Location: FDA WO-22/Room 1415

Application Number: BLA 761055
Product Name: Dupixent (dupilumab) injection, 150 mg/mL
Proposed Indication: Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable

Applicant Name: Regeneron Pharmaceuticals, Inc.

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

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Product Quality

Pre-approval inspection of Sanofi Winthrop Industrie FEI: 3003259844 is currently pending.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – RPM/CDTL

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – (Product Quality)

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

Product Quality

Pre-approval inspection of Sanofi Winthrop Industrie FEI: 3003259844 is currently pending.

3. Information Requests – Product Quality

Information request sent February 7, 2017.

4. REMS or Other Risk Management Actions – (RPM)

No issues related to risk management have been identified to date.

5. Postmarketing Requirements/Postmarketing Commitments –(Product Quality/Clinical Pharmacology/Clinical)

Product Quality PMCs:

- Revise the (b) (4) CFU/(b) (4) mL bioburden limit for product sampled (b) (4) after data from 10 additional drug product batches has been analyzed.
- Qualification of the bioburden and sterility test methods was performed with only two batches of drug product. Provide bioburden and sterility test qualification data from one additional batch of 150 mg/mL dupilumab drug product. Provide the data in the first annual report.

Clinical Pharmacology PMC:

- Complete the ongoing drug-drug interaction clinical study R668-AD-1433 to determine the potential for dupilumab to alter the pharmacokinetics of CYP substrates in subjects with moderate-to-severe atopic dermatitis (AD).

Clinical PMRs:

- A randomized, double-blind, placebo-controlled phase 3 study to investigate the efficacy and safety of dupilumab in patients, 12 years to less than 18 years of age, with moderate-to-severe Atopic Dermatitis
- A randomized, double-blind, placebo-controlled phase 3 study to investigate the efficacy and safety of dupilumab in patients, 6 years to less than 12 years of age, with severe Atopic Dermatitis
- A two-part phase II/III study to evaluate the safety, pharmacokinetics (PK) and efficacy of dupilumab in patients, 6 months to less than 6 years of age, with severe Atopic Dermatitis
 - a.  (b) (4)
 - b. 
- An open-label extension study to assess the long-term safety and efficacy of dupilumab in patients ≥ 6 months to <18 years of age with Atopic Dermatitis
- A prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to dupilumab during pregnancy to an unexposed control population.
- A retrospective cohort study using administrative databases to identify pregnancy outcomes.
- We may have additional PMRs/PMCs.

6. Labeling issues – Clinical/Biostatistics

Clinical Studies

 (b) (4)

- **Discussion**

To investigate whether a statement about dose escalation is appropriate for labeling, we considered the conditional probability for subjects, with severe disease at baseline, who were non-responders on the Q2W dose, who might be responders on the higher (QW) dose. To answer this question, the clinical trial design should have involved dose escalation, that is, advance subjects who did not respond on the lower dose (Q2W) at the first treatment cycle to the higher dose (QW) for the next treatment cycle. However, your trials were of parallel group design. For parallel design, one can only estimate the difference in the response rates for the two dosing regimen (QW vs Q2W).

Although the difference in the response rates for the two dosing regimen (QW and Q2W) is relatively small (3%-6%), the pattern differs by the IGA severity.

Specifically, for the IGA=3 group the response for the Q2W group is higher than for the QW group, and this is consistent across the 3 trials, 1334, 1416, and 1224. However, this pattern is reversed for the IGA=4 group.

As the IGA is a categorical scale with limited number of categories, we considered analysis of a related continuous scale, the EASI score. The results of this exercise show that, for responders who were in the IGA=3 category at baseline, the baseline EASI scores for the Q2W group are generally slightly lower than those for the QW group. This may suggest that Q2W dosing is reasonable for small EASI scores within the IGA=3 category. However, for the IGA=4 responders, a similar trend is not observed. In 1334, the baseline EASI score is higher for the Q2W group compared to QW group, but the opposite is observed for the trial 1416.

In summary, the difference between the response rates for the two dosing regimens is small, and the results of further exploration of the data by subgroup analyses do not support a specific dose for a specific subgroup. Additional analyses increase the chance of false findings.

Additionally, from Week 0 to Week 16, the two dosing regimens showed a similar time-course to IGA response of 0/1. Therefore, there was no increase in the time to response for subjects in QW group compared to the Q2W group.

7. Review Plans – RPM

- Labeling discussions
- PMC/PMR discussions
- Manufacturing and clinical site inspection recommendations
- Take action on BLA application

8. Wrap-up and Action Items – RPM

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

FDA Foreign Visitor Request

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITIZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER: COUNTRY THAT ISSUED PASSPORT: ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
POINT OF ENTRY (This is the building that the foreign visitor will enter)	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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
02/07/2017