

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**sBLA 125057/110**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

A/BLA #: 125057/110 Supplement Type (e.g. SE5): SE1 Supplement Number: \_\_\_\_\_

Stamp Date: 03/23/07 PDUFA Goal Date: 1/21/08

HFD 540 Trade and generic names/dosage form: Humira® (adalimumab) (D2E7)

Applicant: Abbott Laboratories Therapeutic Class: monoclonal antibody

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.  
 No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): Humira® is currently approved for 1) reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active **rheumatoid arthritis**, 2) reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patient with **psoriatic arthritis**, 3) reducing signs and symptoms in patients with active **ankylosing spondylitis**, and 4) reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active **Crohn's disease** who have had an inadequate response to conventional therapy.

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: moderate to severe chronic plaque psoriasis

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.  
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.  
 No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population  
 Disease/condition does not exist in children  
 Too few children with disease to study  
 There are safety concerns  
 Other: \_\_\_\_\_

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 0 Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. up to 4 Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 4 Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 17 Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: pending results of the long-term safety registry

Date studies are due (mm/dd/yy): 3rd Quarter 2015

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

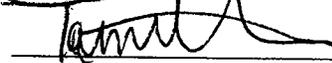
Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

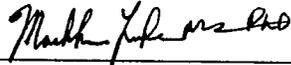


Tamika White  
Regulatory Project Manager

Concurrence:



Denise Cook, M.D.  
Clinical Reviewer



Markham Luke, M.D., Ph.D.  
Clinical Team Leader



Susan J. Walker, M.D.  
Director

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 10/10/2006)

Abbott Laboratories  
Global Pharmaceutical Regulatory Affairs  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

**Certification Requirement  
For Approval of a Drug Product  
Concerning Using Services of Debarred Persons**

**DEBARMENT STATEMENT**

Any application for approval of a new drug product submitted on or after June 1, 1992, per FD&C Act Section 306(k)(1), must include:

A certification that the applicant did not and will not use in any capacity the services of any person debarred under Section 306, subsection (a) or (b), in connection with such application.

Abbott certifies that it did not and will not use in any capacity the services of any person debarred under Section 306, subsection (a) or (b), in connection with this application.

[Generic Drug Enforcement Act of 1992, Section 306(k)(1) of 21 USC 335a(k)(1)]



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Meg Drew, MPH  
Associate Director, Immunology Development  
Global Pharmaceutical Regulatory Affairs  
Abbott Laboratories

**Abbott**

**CERTIFICATION: FINANCIAL INTERESTS AND  
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

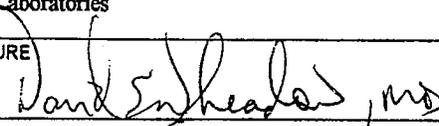
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attached List	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME David E. Wheadon, MD	TITLE Vice President, Global Pharmaceutical Regulatory Affairs
FIRM / ORGANIZATION Abbott Laboratories	
SIGNATURE 	DATE 26 Feb 2007

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857





**DISCLOSURE: FINANCIAL INTERESTS AND  
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

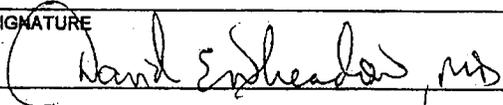
TO BE COMPLETED BY APPLICANT

The following information concerning C J, who participated  
Name of clinical investigator  
as a clinical investigator in the submitted study C J,  
Name of clinical study  
is submitted in accordance with 21 CFR part 54. The  
named individual has participated in financial arrangements or holds financial interests that are  
required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME David E. Wheadon, MD	TITLE Vice President, Global Pharmaceutical Regulatory Affairs
FIRM / ORGANIZATION Abbott Laboratories	
SIGNATURE 	DATE 26 Feb 2007

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857

b(6)



16 January 2008

Ms. Tamika White  
Food and Drug Administration  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Department of Dermatology and Dental Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Reference: Adalimumab (D2E7)  
BLA 125057/110**

### **Postmarketing Commitments**

Dear Ms. White,

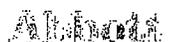
The sponsor, Abbott Laboratories, submits the following information under the provisions of section 351 of the Public Health Service Act and 21 CFR 601.2.

The purpose of this letter is to provide FDA with Abbott's commitments that will serve as conditions of approval for the psoriasis indication. They are as follows:

1. Deferred pediatric study under PREA for the treatment of moderate to severe chronic plaque psoriasis in pediatric patients ages 4 to 17. The pediatric plan is to assess data anticipated from on-going trials as well as further analysis and assessment of data, and to establish a study plan that incorporates this new data.

Pediatric plan proposal due: January 2013

2. To conduct a prospective, multi-center registry including 5000 adult psoriasis patients treated with commercial Humira in the United States. This registry will characterize and assess the incidence of serious adverse events (including serious infections, tuberculosis, opportunistic infections, malignancies, hypersensitivity reactions, autoimmune reactions and deaths) as well as other adverse events of interest in the study cohort. All enrolled study patients will be evaluated for a period of at least 10 years with comprehensive annual reports provided to the Agency. Collect data on the patient characteristics, demographics and drug exposure (including dose, duration and time to onset of adverse event). The collection of data will be via active surveillance methods and data will be validated by a review of

Abbott

medical records as per the Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

Final study protocol submitted: March 2008  
Patient accrual initiated: September 2008  
Progress Reports: Annually starting February 2009  
Interim Reports: Every other year starting February 2010  
Study Completion: October 2022  
Final Report Submission: January 2023

The final study protocol will incorporate the design methods agreed upon in your submissions up to and including December 26, 2007 and any revisions recommended by the Agency in subsequent communication.

3. Submit the final study report for trial M03-658, "A Multicenter Open-Label Continuation Study in Moderate to Severe Chronic Plaque Psoriasis Subjects who Completed a Preceding Psoriasis Clinical Study with Adalimumab".

Final Report Submission: April 2010

4. Provide information on effects of discontinuation of Humira followed by a second course of Humira in patients treated successfully with the drug.

This information will be obtained from a minimum of 120 evaluable subjects currently participating in Study M03-658 "A Multicenter Open-Label Continuation Study in Moderate to Severe Chronic Plaque Psoriasis Subjects who Completed a Preceding Psoriasis Clinical Study with Adalimumab". Subjects meeting response criteria will be discontinued from treatment and reinitiated Humira therapy upon relapse to evaluate whether additional use of Humira will impact safety and efficacy.

Study Report Submission: April 2010

If the information from ongoing clinical trials is insufficient, Abbott will conduct a new trial to assess effects of discontinuation followed by a second course of Humira in patients treated successfully with the drug.

BLA 125057/110

16 January 2008

Page 3

A copy of this letter will be formally submitted to the sBLA via the electronic gateway on 17 January 2008. Should you have any questions concerning this submission, please contact me at the number provided below. Thank you for your consideration in this matter.

Sincerely,

ABBOTT LABORATORIES



Meg Drew, MPH  
Director, Development  
Global Pharmaceutical Regulatory Affairs  
TEL: 847/938-8472  
FAX: 847/887-8251  
email: [meg.drew@secure.abbott.com](mailto:meg.drew@secure.abbott.com)



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation III**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** January 16, 2008

<b>To:</b> Meg Drew, Director	<b>From:</b> Tamika White, Regulatory Project Manager
<b>Company:</b> Abbott Laboratories	Division of Dermatology & Dental Drug Products
<b>Fax number:</b> (847) 938-8476	<b>Fax number:</b> (301) 796-9894
<b>Phone number:</b> (847) 938-8472	<b>Phone number:</b> (301) 796-0310
<b>Subject:</b> BLA 125057/110	

**Total no. of pages including cover:** 3

**Comments:**

Please review and respond to the postmarketing requests.

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**Document to be mailed:**             YES             NO

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**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS  
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND  
PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2110. Thank you.

**The Agency has the following postmarketing requests for BLA 125057/110 Humira (Adalimumab):**

1. Deferred pediatric study under PREA for the treatment of moderate to severe chronic plaque psoriasis in pediatric patients ages 4 to 17. The pediatric plan is to assess data anticipated from on-going trials as well as further analysis and assessment of data, and to establish a study plan that incorporates this new data.

Pediatric plan proposal due: January 2013

2. To conduct a prospective, multi-center registry including 5000 adult psoriasis patients treated with commercial Humira in the United States. This registry will characterize and assess the incidence of serious adverse events (including serious infections, tuberculosis, opportunistic infections, malignancies, hypersensitivity reactions, autoimmune reactions and deaths) as well as other adverse events of interest in the study cohort. All enrolled study patients will be evaluated for a period of at least 10 years with comprehensive annual reports provided to the Agency. Collect data on the patient characteristics, demographics and drug exposure (including dose, duration and time to onset of adverse event). The collection of data will be via active surveillance methods and data will be validated by a review of medical records as per the Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

Final study protocol submitted:	March 2008
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Final Report Submission:	January 2023

The final study protocol will incorporate the design methods agreed upon in your submissions up to and including December 26, 2007 and any revisions recommended by the Agency in subsequent communication.

3. Submit the final study report for trial M03-658, "A Multicenter Open-Label Continuation Study in Moderate to Severe Chronic Plaque Psoriasis Subjects who Completed a Preceding Psoriasis Clinical Study with Adalimumab".

Final Report Submission: Provide Date

4. Provide information on effects of discontinuation of Humira followed by a second course of Humira in patients treated successfully with the drug.

This information should be obtained with a minimum of 120 evaluable subjects to include those who have relapsed after discontinuation of Humira and whether additional use of Humira will impact safety and efficacy.

You may provide this information from ongoing clinical trials or by initiating a new clinical trial. If the information from ongoing clinical trials is insufficient, you will conduct a trial to assess effects of discontinuation followed by a second course of Humira in patients treated successfully with the drug.

Study Report Submission

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**Please send a letter stating the commitments as outlined above, and your agreement to those commitments and timelines. Propose dates when applicable. Fax your letter to my attention as soon as possible but no later than 3:00 p.m. today.**

**If you have any questions, please let me know.**

### Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
<input type="checkbox"/> If foreign applicant, US Agent signature.	N/A	
Comprehensive Table of Contents	Y	
Debarment Certification with correct wording (see * below)	Y	
User Fee Cover Sheet	Y	
User Fee payment received	Y	
Financial certification &/or disclosure information	Y	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Pediatric rule: study, waiver, or deferral	Y	The sponsor has requested a waiver for ages 0-4 years. The sponsor has also requested a deferral from ages 4-17 years with studies to be completed by <input type="checkbox"/> <input type="checkbox"/>
Labeling:	Y	
<input type="checkbox"/> PI –non-annotated	Y	
<input type="checkbox"/> PI –annotated	Y	
<input type="checkbox"/> PI (electronic)	Y	
<input type="checkbox"/> Medication Guide	N	
<input type="checkbox"/> Patient Insert	Y	
<input type="checkbox"/> package and container	N	
<input type="checkbox"/> diluent	N	
<input type="checkbox"/> other components	N	
<input type="checkbox"/> established name (e.g. USAN)	N	
<input type="checkbox"/> proprietary name (for review)	N	

b(4)

\* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge..."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review? Examples include:	Y	
<input type="checkbox"/> legible	Y	
<input type="checkbox"/> English (or translated into English)	Y	
<input type="checkbox"/> compatible file formats	Y	
<input type="checkbox"/> navigable hyper-links	Y	
<input type="checkbox"/> interpretable data tabulations (line	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
listings) & graphical displays <input type="checkbox"/> summary reports reference the location of individual data and records <input type="checkbox"/> protocols for clinical trials present <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y  Y  Y	
companion application received if a shared or divided manufacturing arrangement	Y    N	Not applicable
if CMC supplement: <input type="checkbox"/> description and results of studies performed to evaluate the change <input type="checkbox"/> relevant validation protocols <input type="checkbox"/> list of relevant SOPs	Y    N  Y    N  Y    N	Not applicable
if clinical supplement: <input type="checkbox"/> changes in labeling clearly highlighted <input type="checkbox"/> data to support all label changes <input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)	Y  Y  Y	
if electronic submission: <input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted	N	Sent a request to the sponsor to submit paper copies.

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

None identified.

Has orphan drug exclusivity been granted to another drug for the same indication?  
 If yes, review committee informed? \_\_\_\_\_ No \_\_\_\_\_

Does this submission relate to an outstanding PMC? \_\_\_\_\_ No \_\_\_\_\_

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: N/A
- Dates: N/A

Recommendation (circle one): File RTF

RPM Signature: Mary Owens

Branch Chief concurrence: Maria Walsh 1/11/08

# MEMORANDUM OF TELECON

DATE: December 10, 2007

APPLICATION NUMBER: sBLA 125057/110

BETWEEN:

Name: Meg Drew, MPH, Director of Global Pharmaceutical Regulatory Affairs  
Phone: (866) 836-1533  
Representing: Abbott Laboratories

AND

Name: Tamika White, Regulatory Project Manger  
Division of Dermatology and Dental Products (DDDP), HFD-540

SUBJECT: Clarification to Phase 4 Registry Comments

FDA Participants

Markham Luke, Medical Team Leader, DDDP  
Denise Cook, Medical Officer, DDDP  
Carolyn McCloskey, Epidemiologist, OSE  
Rita Ouellett-Hellstrom, Acting Team Leader, OSE

Abbott Participants

Thomas Harris, Global Project Head  
Martin Okun, Medical Director, Dermatologist  
Susan Glad, Clinical Operations  
Renee Perdok, Biostatistics  
Yihua Gu, Biostatistics  
Ray Votzmeyer, US Regulatory

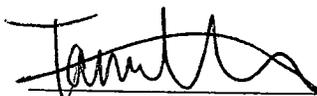
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On November 29, 2007, the FDA sent a letter to Abbott Laboratories providing recommendations on and information requests for the Clinical Study Protocol P10-023, "A 5-year, Post-marketing, Observational Study of HUMIRA® (Adalimumab) in Patients with Chronic Plaque Psoriasis (Ps)". In the letter, the FDA offered to provide a teleconference to provide Abbott with clarification on any of the recommendations and information requests.

During the teleconference, the FDA provided clarification on the points as Abbott requested in the attached document. Abbott agreed to submit a revised protocol based on the original letter and the clarification provided during the teleconference by December 28, 2007.



Tamika White  
Regulatory Project Manager

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NOV 29 2007

Our STN: BL 125057/110

Abbott Laboratories  
Attention: Meg Drew, MPH  
Associate Director, Immunology Development  
Global Pharmaceutical Regulatory Affairs  
Dept. PA72, Bldg. AP34-3  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

Dear Ms. Drew:

This letter is in regard to the supplement to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed Clinical Study Protocol P10-023, "A 5-Year, Post-marketing, Observational Study of HUMIRA<sup>®</sup> (Adalimumab) in Patients with Chronic Plaque Psoriasis (Ps)" included in your supplement dated March 23, 2007 for Humira<sup>®</sup> (adalimumab) and have the following recommendations and information requests.

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b(4)

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3 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

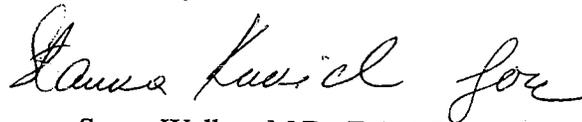
Deliberative Process (b5)

Please submit a complete response to the items above, including a revised protocol, as soon as possible but no later than December 28, 2007. A teleconference has been scheduled for December 10, 2007 at 1:00 p.m. to provide you with clarification on any of the recommendations and information requests. Agreements on the phase 4 protocol must be reached prior to taking an action. Failure to respond in a timely manner or submission of a partial response may result in a determination that your supplement is not approvable. Review of the other sections of your supplement is continuing.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Tamika White, at (301) 796-0310.

Sincerely,

A handwritten signature in cursive script that reads "Susan Walker for".

Susan 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

b(4)

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** October 19, 2007

**TO:** Tamika White, Regulatory Project Manager  
Denise Cook, M.D., Medical Officer  
Division of Dermatologic and Dental Drug Products

**THROUGH:** Constance Lewin, M.D., M.P.H.  
Chief, Good Clinical Practice Branch I (GCPB1, HFD-46)  
Division of Scientific Investigations (DSI)

**FROM:** Roy Blay, Ph.D.  
Reviewer, GCPB1, DSI, HFD-46

**SUBJECT:** Evaluation of Clinical Inspections

**BLA:** 125057/110

**APPLICANT:** Abbott Laboratories

**DRUG:** Humira® (adalimumab)

**THERAPEUTIC CLASSIFICATION:** Standard

**INDICATION:** Treatment of psoriasis

**CONSULTATION REQUEST DATE:** June 14, 2007

**DIVISION ACTION GOAL DATE:** November 2, 2007

**PDUFA DATE:** January 21, 2008.

## I. BACKGROUND

The indication for the investigational drug Humira® is the treatment of psoriasis. This drug is not a New Molecular Entity.

In support of this NDA, FDA inspected protocol# M03-656, entitled, "A Phase 3, Multicenter Study of the Efficacy and Safety of Long-Term Adalimumab Treatment in Subjects with Moderate to Severe Chronic Plaque Psoriasis". The objective of this study was to confirm the long and short term clinical efficacy and safety of subcutaneously administered adalimumab, as well as determine the proportion of subjects losing an adequate response (i.e., achieving an event) after Week 33 and on or before Week 52 after withdrawal of long-term adalimumab therapy in the treatment of adult subjects with moderate to severe chronic plaque psoriasis. The PASI score (Psoriatic Area and Severity Index) is the measure of the extent and severity of psoriasis and the primary efficacy variable in Period A is the proportion of subjects with clinical response, defined at least as a 75% reduction in PASI score ( $\geq$  PASI 75 response) at Week 16 relative to the Baseline (Week 0) PASI score. The subsequent primary efficacy variable in Period C is the proportion of subjects losing an adequate response (i.e., achieving an event) after Week 33 and on or before Week 52.

The following sites were selected for inspection for the protocol identified above based on enrollment numbers, adverse events, and reported protocol violations.

## II. RESULTS (by site):

Name	City, State, Country	Protocol	Inspection Date	EIR Received Date	Final Classification
[			]	Pending	NAI
				Pending	NAI

b(7)

### Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

b(7)

- a. What was inspected: Details unknown at this time, as EIR receipt is pending.
- b. Limitations of inspection: Unknown at this time.
- c. General observations/commentary: The inspection did not reveal any regulatory violations in the conduct of this study. This observation is based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.
- d. Data acceptability/reliability: The data appear acceptable in support of the relevant indication.

b(7)

- a. What was inspected: Consent forms for all - subjects were reviewed. For  subjects, records reviewed included inclusion and exclusion criteria, PASI scores, laboratory tests, ECGs, and chest x-rays. As appropriate, information on CRFs was correlated with office notes, subject histories, and other relevant source documentation.
- b. Limitations of inspection: There were no limitations to the inspection.
- c. General observations/commentary: The inspection did not reveal any regulatory violations in the conduct of this study. This observation is based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.
- d. Data acceptability/reliability: The data appear acceptable in support of the relevant indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections of   did not identify any regulatory violations. Overall, the data appear acceptable in support of the respective indication. Observations noted above are based on preliminary communications from the field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR

b(7)

Roy Blay Ph.D.

Roy Blay, Ph.D.  
Reviewer, Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations

CONCURRENCE:

Constance Lewin, MD, MPH

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations

# DSI CONSULT: Request for Clinical Inspections

**Date:** June 14, 2007

**To:** Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46  
 Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

**cc:** Gary Della'Zanna, D.O., Director, Division of Scientific Investigations, HFD-45

**Through:** Susan Walker, M.D., Division Director *SW 6/15/07*  
 Markham Luke, M.D., Ph.D., Clinical Team Leader *ML 6/14/07*

**From:** Margo Owens, Regulatory Health Project Manager, HFD-540  
 Division of Dermatology and Dental Products

**Subject:** Request for Clinical Site Inspections

**Drug:** BLA 125057/110  
 Humira (adalimumab) Solution  
 Abbott Laboratories

**Protocol/Site Identification:**

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
J	[ ]	[ ]	Psoriasis

*b(7)*

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Psoriasis

b(7)

**Domestic Inspections:**

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other: SPECIFY

b(7)

**International Inspections:**

We have requested inspections because (please check all that apply):

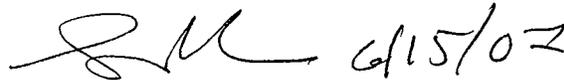
- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: SPECIFY

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) November 2, 2007. We intend to issue an action letter on this application by (division action goal date) December 1, 2007. The PDUFA due date for this application is January 21, 2007.

Should you require any additional information, please contact Margo Owens.

Concurrence:



Susan Walker, M.D., Division Director  
Division of Dermatology and Dental Products



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125057/110

Abbott Laboratories  
Attention: Meg Drew, MPH  
Associate Director, Immunology Development  
Global Pharmaceutical Regulatory Affairs  
Dept. PA72, Bldg. AP34-3  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

Dear Ms. Drew:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the response to the information request dated July 7, 2007, for Humira (adalimumab) and have determined that the response was not sufficient. The following information is necessary to take a complete action on your application:

Provide incidence tables for all treatment-emergent AEs that occurred at a rate of  $\geq 1\%$  for the following three study sets: the "placebo controlled study set", the "all adalimumab treatment study set", and the "EOW study set". When generating these tables from the data, refer to Table 19 on page 67 and Table 22 on page 77 of the integrated summary of safety (ISS) for the format. The incidence tables should also include the corresponding exposure adjusted rates.

It is requested that you submit a complete response by October 12, 2007. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other sections of your application is continuing.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Tamika White, at (301) 796-2110.

Sincerely,

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research



Our STN: 125057/110

INFORMATION REQUEST LETTER

Abbott Laboratories  
Attention: Meg Drew, MPH  
Associate Director, Immunology Development  
Global Pharmaceutical Regulatory Affairs  
Dept. PA72, Bldg. AP34-3  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

Dear Ms. Drew:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

We have reviewed the statistical section of your application dated March 23, 2007, for Humira (adalimumab) and have determined that the following information is necessary to take a complete action on your application:

1. The data sets for Study M03-656 only contain data pertaining to Periods A and C. Because some endpoints are to be evaluated based on data from the open-label Period B, please provide data sets for Period B in SAS transport files, preferably in the format of your 'analysis ready' data sets (for example, \analysis ready\m03-656\pasi656a.xpt), with variable descriptions. The data sets should account for all subjects who completed Period A and received at least a PASI 75 response at Week 16, and indicate observed/missing status.
2. The values of the PASI scores in Study M03-658 (variable 'PISCORE' in \m03-658\pi.xpt) are all missing. However, one of the co-primary endpoint of this open-label study was PASI 50/75/90. For the observed PASI scores, provide such values.
3. Provide data sets for Study M03-658 in your 'analysis ready' format (for example, in the format as \analysis ready\m03-656\pasi656a.xpt).

Promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the other section(s) of your application is continuing.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Vickey Lutwak, at (301) 796-2110.

Sincerely,

Handwritten signature of Cristi Stark and the date 10/10/07.

Cristi Stark, M.S.  
Acting Chief, Project Management Staff  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research



Our STN: 125057/110

INFORMATION REQUEST LETTER

AUG 28 2007

Abbott Laboratories  
Attention: Meg Drew, MPH  
Associate Director, Immunology Development  
Dept. PA72, Bldg. AP34-3  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

Dear Ms. Drew:

Please refer to your March 23, 2007, supplemental biologic application submitted under section 351 of the Public Health Service Act for Humira (adalimumab).

We are reviewing your submission and have determined that a Medication Guide is necessary for patients' safe and effective use of this drug product based on the following circumstances:

1. [21 CFR 208(c)(1)]: The drug product is one for which patient labeling could help prevent serious adverse effects.
2. [21 CFR 208(c)(2)]: The drug product is one that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decision to use, or to continue to use, the product.

Please submit a Medication Guide following the content and format specified under 21 CFR 208.20. The Medication Guide will replace the Patient Package Insert. We request a prompt written response in order to continue our evaluation of your Biologic License Application (BLA).

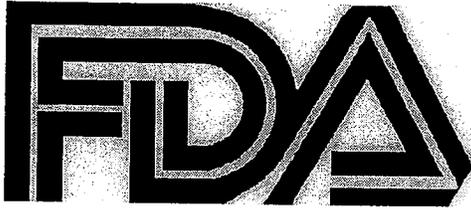
Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Vickey Lutwak, at (301) 396-2110.

Sincerely,

A handwritten signature in black ink, appearing to be 'SJW', written in a cursive style.

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



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation III  
Division of Dermatology and Dental Products

FACSIMILE TRANSMITTAL SHEET

DATE: 8/15/2007

To: Meg Drew, MPH	From: Vickey Lutwak
Company: Abbott Laboratories	Division of Dermatology and Dental Products
Fax number: 847 887-8251	Fax number: 301 796- 9894/ 9895
Phone number: 847 938-8472	Phone number: 301 796-2445

Subject: Request for information BLA 125057 Adalimumab (D2E7)

Total no. of pages including cover: 2

Document to be mailed:  YES  NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-2110. Thank you.

*e-mail from Clara in e-mail file  
e request*

BLA 125057/ Adalimumab (D2E7)

Aug. 15, 2007

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Humira.

Please refer to your efficacy supplement for a new indication for the treatment of moderate to severe chronic plaque psoriasis for BL 125057 (Humira). Please refer to your letter date March 23, 2007.

We have the following information request from the statistician

1. The data sets for Study M03-656 only contain data pertained to Periods A and C. As some endpoints are to be evaluated based on data from the open-label Period B, please provide data sets for Period B in SAS transport files, preferably in the format of your 'analysis ready' data sets (for example, \analysis ready\m03-656\pasi656a.xpt), with variable descriptions. The data sets should account for all subjects who completed Period A and received at least a PASI 75 response at Week 16, and indicate observed/missing status.
2. The values of the PASI scores in Study M03-658 (variable 'PISCORE' in \m03-658\pi.xpt) are all missing. However, one of the co-primary endpoint of this open-label study was PASI 50/75/90. For the observed PASI scores, please provide such values.
3. It would be preferable if data sets for Study M03-658 were provided in your 'analysis ready' format (for example, in the format as \analysis ready\m03-656\pasi656a.xpt).

If you haven any questions, please call Vickey Lutwak at 301- 796-2445.

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0430  
Expiration Date: April 30, 2009  
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,  
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**  
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT <b>Abbott Laboratories</b>	DATE OF SUBMISSION <b>07/20/2007</b>
TELEPHONE NO. (Include Area Code) <b>847-938-8472</b>	FACSIMILE (FAX) Number (Include Area Code) <b>847-887-8251</b>
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): <b>Dept. PA72, Bldg. AP34-3 200 Abbott Park Rd. Abbott Park, IL 60064-6188</b>	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) <b>BLA 125057</b>	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) <b>adalimumab</b>	PROPRIETARY NAME (trade name) IF ANY <b>Humira</b>
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) <b>adalimumab</b>	CODE NAME (If any) <b>D2E7, LU 200134</b>
DOSAGE FORM: <b>solution</b>	STRENGTHS: <b>40 mg/ 0.8 mL</b>
(PROPOSED) INDICATION(S) FOR USE: <b>Approved: Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease. Proposed: Psoriasis</b>	ROUTE OF ADMINISTRATION: <b>subcutaneous injection</b>

**APPLICATION DESCRIPTION**

APPLICATION TYPE (check one)  
 NEW DRUG APPLICATION (CDA, 21 CFR 314.50)  ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)  
 BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE  505 (b)(1)  505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug \_\_\_\_\_ Holder of Approved Application \_\_\_\_\_

TYPE OF SUBMISSION (check one)  
 ORIGINAL APPLICATION  AMENDMENT TO PENDING APPLICATION  RESUBMISSION  
 PRESUBMISSION  ANNUAL REPORT  ESTABLISHMENT DESCRIPTION SUPPLEMENT  EFFICACY SUPPLEMENT  
 LABELING SUPPLEMENT  CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT  OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: \_\_\_\_\_

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY  CBE  CBE-30  Prior Approval (PA)

REASON FOR SUBMISSION  
**Safety Update Report**

PROPOSED MARKETING STATUS (check one)  PRESCRIPTION PRODUCT (Rx)  OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED \_\_\_\_\_ THIS APPLICATION IS  PAPER  PAPER AND ELECTRONIC  ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)  
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please refer to attached established information  
**Fax 847-887 8251**

Cross References (list related License Applications, INDs, NDAs, PMAs, 610(k)s, IDEs, BMFs, and DMFs referenced in the current application)

**IND 10811 and US License No. 0043**

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c)).
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input checked="" type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify)

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 680, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 		TYPED NAME AND TITLE Meg Drew, MPH, Associate Director	DATE: 07/20/2007
ADDRESS (Street, City, State, and ZIP Code) Dept. PA72, Bldg. AP34-3, 200 Abbott Park Rd., Abbott Park, IL 60064-8188		Telephone Number ( 847 ) 938-8472	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (HFM-99)  
1401 Rockville Pike  
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

## FDA Facsimile Memorandum

**Date:** July 7, 2007  
**To:** Meg Drew, M.P.H.  
Associate Director, Immunology Development  
Global Pharmaceutical Regulatory Affairs  
**From:** Margo Owens, Project Manager  
**Subject:** sBLA 125057/110 Humira® (adalimumab)

Ms. Drew,

The Clinical Reviewer has the following information request for your sBLA 125057/110 Humira (adalimumab).

**Clinical Reviewer's Information Request:**

1. Please explain the discrepancy between the BLA 12057 for Humira which describes only 3 deaths in the psoriasis development program and the six deaths that were described in the BBIND 10811/SN152 for the development program. Please submit as an amendment to the BLA and include all six deaths, the studies in which they occurred, a narrative for each death and the complete CRF for each. If the CRFs for the 3 deaths mentioned in the BLA are included in the BLA, please provide the location.
2. Please provide adverse event tables for the following placebo controlled portion of the trials which occurred at a 1% or greater incidence: MO3-656 and MO4-716

This should include all adverse events in the adalimumab arm as compared to placebo whether felt to be treatment related or not.

Please submit your response to these questions by COB Monday, July 9, 2007. Please submit 4 desk copies of this submission to the attention of Margo Owens.

Margo Owens  
Project Manager



DEPARTMENT OF HEALTH & HUMAN SERVICES

Margo  
Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125057/110

JUN 13 2007

Abbott Laboratories  
Attention: Meg Drew, M.P.H.  
Associate Director, Immunology Development  
Global Pharmaceutical Regulatory Affairs  
Dept. PA72, Bldg. AP34-3  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

Dear Ms. Drew:

We have received your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

**STN 125057            adalimumab**

BL [125057/110]      Humira Solution, 40 mg/0.8mL

**Reason for the submission:** This supplement provides for labeling changes to the Humira (adalimumab) package insert, including the addition of a new indication for the treatment of moderate to severe chronic plaque psoriasis.

**Date of Supplement:** March 23, 2007

**Date of Receipt:** March 23, 2007

**Action Due Date:** January 23, 2008

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 waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver and deferral of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Margo Owens, at (301) 796-2110.

Sincerely,

A handwritten signature in black ink that reads "Margo Owens". The signature is written in a cursive style with a long horizontal stroke extending to the right.

Margo Owens  
Regulatory Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

**Part B – Product/CMC/Facility Reviewer(s)**

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y <input checked="" type="radio"/> N	
Introduction to the summary documents (1 page) [2.2]	Y <input checked="" type="radio"/> N	
Quality overall summary [2.3]	Y <input checked="" type="radio"/> N	Use of approved DS [ ] [ ] [ ] b(4)
<input type="checkbox"/> Drug Substance	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Drug Product	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Facilities and Equipment	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Novel Excipients	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Executed Batch Records	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Method Validation Package	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Comparability Protocols	Y <input checked="" type="radio"/> N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y <input checked="" type="radio"/> N	
Drug Substance [3.2.S]		Use of approved DS.
<input type="checkbox"/> general info	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> description of manufacturing process	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	Y <input checked="" type="radio"/> N	
<input type="checkbox"/> justification of specifications		
<input type="checkbox"/> analytical method validation		
<input type="checkbox"/> reference standards		
<input type="checkbox"/> stability		
<input type="checkbox"/> process validation (prospective	Y <input checked="" type="radio"/> N	

CTD Module 3 Contents	Present?	If not, justification, action & status
<p>plan, results, analysis, and conclusions)</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)</li> <li><input type="checkbox"/> characterization of drug substance</li> <li><input type="checkbox"/> control of drug substance               <ul style="list-style-type: none"> <li><input type="checkbox"/> specification                   <ul style="list-style-type: none"> <li><input type="checkbox"/> justification of specs.</li> </ul> </li> <li><input type="checkbox"/> analytical procedures</li> <li><input type="checkbox"/> analytical method validation</li> <li><input type="checkbox"/> batch analyses                   <ul style="list-style-type: none"> <li><input type="checkbox"/> consistency (3 <u>consecutive</u> lots)</li> <li><input type="checkbox"/> justification of specs.</li> </ul> </li> </ul> </li> <li><input type="checkbox"/> reference standards</li> <li><input type="checkbox"/> container closure system</li> <li><input type="checkbox"/> stability               <ul style="list-style-type: none"> <li><input type="checkbox"/> summary</li> <li><input type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval                   <ul style="list-style-type: none"> <li><input type="checkbox"/> protocol</li> <li><input type="checkbox"/> results</li> <li><input type="checkbox"/> method validation</li> </ul> </li> </ul> </li> </ul>	<p>Y (N)</p>	<p>Approved DS</p>
<p>Drug Product [3.2.P]</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> description and composition</li> <li><input type="checkbox"/> pharmaceutical development</li> <li><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)</li> <li><input type="checkbox"/> batch formula</li> <li><input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)</li> <li><input type="checkbox"/> controls of critical steps and intermediates</li> <li><input type="checkbox"/> process validation including aseptic processing &amp; sterility assurance:               <ul style="list-style-type: none"> <li><input type="checkbox"/> 3 <u>consecutive</u> lots</li> <li><input type="checkbox"/> other needed validation data</li> </ul> </li> <li><input type="checkbox"/> control of excipients (justification of specifications; analytical method</li> </ul>	<p>(Y) N</p> <p>Y (N)</p>	<p>Same excipients as approved DP</p>

CTD Module 3 Contents	Present	If not, justification, action & status
<ul style="list-style-type: none"> <li>validation; excipients of human/animal origin)</li> <li><input type="checkbox"/> control of drug product (justification of specifications; analytical method validation)</li> <li><input type="checkbox"/> container closure system [3.2.P.7]               <ul style="list-style-type: none"> <li><input type="checkbox"/> specifications (vial, elastomer, drawings)</li> <li><input type="checkbox"/> availability of DMF</li> <li><input type="checkbox"/> closure integrity</li> <li><input type="checkbox"/> administration device(s)</li> </ul> </li> <li><input type="checkbox"/> stability               <ul style="list-style-type: none"> <li><input type="checkbox"/> summary</li> <li><input type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval                   <ul style="list-style-type: none"> <li><input type="checkbox"/> protocol</li> <li><input type="checkbox"/> results</li> <li><input type="checkbox"/> method validation</li> </ul> </li> </ul> </li> </ul>	<p style="text-align: center;">(Y) N</p> <p style="text-align: center;">Y (N)</p> <p style="text-align: center;">(Y) N</p>	<p style="font-size: 1.2em; text-align: center;">Same as in approved DP</p>
<p>Diluent (vials or filled syringes) [3.2P']</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> description and composition of diluent</li> <li><input type="checkbox"/> pharmaceutical development</li> <li><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)</li> <li><input type="checkbox"/> batch formula</li> <li><input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)</li> <li><input type="checkbox"/> controls of critical steps and intermediates</li> <li><input type="checkbox"/> process validation including aseptic processing &amp; sterility assurance:               <ul style="list-style-type: none"> <li><input type="checkbox"/> 3 consecutive lots</li> <li><input type="checkbox"/> other needed validation data</li> </ul> </li> <li><input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)</li> <li><input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)</li> </ul>	<p style="text-align: center;">Y (N)</p>	

CTD Module 3 Contents	Present	If not, justification, action & status
<input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <ul style="list-style-type: none"> <li>○ specifications (vial, elastomer, drawings)</li> <li>○ availability of DMF</li> <li>○ closure integrity</li> </ul> <input type="checkbox"/> stability <ul style="list-style-type: none"> <li>□ summary</li> <li>□ post-approval protocol and commitment</li> <li>□ pre-approval               <ul style="list-style-type: none"> <li>○ protocol</li> <li>○ results</li> </ul> </li> </ul>	Y <input checked="" type="radio"/> N Y <input checked="" type="radio"/> N  Y <input checked="" type="radio"/> N	
Other components to be marketed (full description and supporting data, as listed above): <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit)	Y <input checked="" type="radio"/> N Y <input checked="" type="radio"/> N	NOT applicable
Appendices for Biotech Products [3.2.A] <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <li>○ manufacturing flow; adjacent areas</li> <li>○ other products in facility</li> <li>○ equipment dedication, preparation and storage</li> <li>○ sterilization of equipment and materials</li> <li>○ procedures and design features to prevent contamination and cross-contamination</li> </ul> <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <li>○ avoidance and control procedures</li> <li>○ cell line qualification</li> <li>○ other materials of biological origin</li> <li>○ viral testing of unprocessed bulk</li> <li>○ viral clearance studies</li> <li>○ testing at appropriate stages of production</li> </ul> <input type="checkbox"/> novel excipients	<input checked="" type="radio"/> Y N  Y <input checked="" type="radio"/> N  Y <input checked="" type="radio"/> N	 NO changes in manufacturing process [ ] [ ]  Same as approved product
USA Regional Information [3.2.R] <input type="checkbox"/> executed batch records <input type="checkbox"/> method validation package	Y <input checked="" type="radio"/> N Y <input checked="" type="radio"/> N	NA

b(4)

CITD Module 3 Content	Present?	If not, justification, action & status
<input type="checkbox"/> comparability protocols	Y <input checked="" type="radio"/> N	NA
Literature references and copies [3.3]	Y <input checked="" type="radio"/> N	NA

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> all electronic submission components usable	<input checked="" type="radio"/> Y N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	<input checked="" type="radio"/> Y N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	<input checked="" type="radio"/> Y N	
includes data demonstrating consistency of manufacture	<input checked="" type="radio"/> Y N	
includes complete description of product lots and manufacturing process utilized for clinical studies	<input checked="" type="radio"/> Y N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y <input checked="" type="radio"/> N	NA
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y <input checked="" type="radio"/> N	NO - significant changes
certification that all facilities are ready for inspection	<input checked="" type="radio"/> Y N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	<input checked="" type="radio"/> Y N	
if not using a test or process specified by regulation, data is provided to show the	Y N	

Examples of filing issues	Yes?	If not, justification, action & status
alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility <input type="checkbox"/> <input type="checkbox"/>	Y <input checked="" type="radio"/> Y <input checked="" type="radio"/> Y <input checked="" type="radio"/> <input type="radio"/> <input type="radio"/>	Tests are adequate
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y <input checked="" type="radio"/>	Not required.
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y <input checked="" type="radio"/>	Not required.
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	<input checked="" type="radio"/> Y N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y <input checked="" type="radio"/>	Same as approved product
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	<input checked="" type="radio"/> Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

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Recommendation (circle one)  File RTF

Reviewer: Gregory Grill-Sampson Type (circle one):  Product (Chair) Facility (DMPQ)  
 (signature/ date)

Concurrence:  
 Branch/Lab Chief: Patricia Swann 6/4/07 Division Director: \_\_\_\_\_  
 (signature/ date) (signature/ date)

## Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y N	
Clinical overview [2.5]	<input checked="" type="radio"/> Y N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	Y N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	Y N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Clinical Safety	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="radio"/> Y N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="radio"/> Y N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="radio"/> Y N	
Study Reports and related information [5.3]	Y N	
<input type="checkbox"/> Biopharmaceutic	Y N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
<input type="checkbox"/> Pharmacokinetics (PK)	Y N	
<input type="checkbox"/> Pharmacodynamic (PD)	Y N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Postmarketing experience	Y N	
<input type="checkbox"/> Case report forms	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> Individual patient listings (indexed by study)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="radio"/> Y N	
Literature references and copies [5.4]	<input checked="" type="radio"/> Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> English (or certified translation into English)	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y N	

Examples of Filing Issues	Yes?		If not, action & status
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	N	
<input type="checkbox"/> protocols for clinical trials present	Y	N	
<input type="checkbox"/> all electronic submission components usable	Y	N	
statement for each clinical investigation:			
<input type="checkbox"/> conducted in compliance with IRB requirements	Y	N	
<input type="checkbox"/> conducted in compliance with requirements for informed consent	Y	N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	Y	N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y	N	NR.
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y	N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y	N	NR.
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y	N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y	N	
drug interaction studies communicated as during IND review as necessary are included	Y	N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y	N	
comprehensive analysis of safety data from all current world-wide knowledge	Y	N	

Examples of Filing Issues	Yes?	If not, action & status
of product		
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (product number)	Phase 1 study (submitted?)		Financial disclosure or certification (submitted?)			SAS & other electronic datasets (complete & usable?)		BIMOs sites (identified?)		
	Y	N	Y	N	NR	Y	N	Y	N	NR
M02-528	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
M02-529	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
M02-538	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
M03-596	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
M03-656	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
M04-716	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
M03-658	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Lined area for providing reasons for not filing the BLA/BLS.

Is clinical site(s) inspection (BiMo) needed?

Lined area for response to clinical site inspection question.

Is an Advisory Committee needed?

Lined area for response to Advisory Committee question.

Recommendation (circle one): File RTF

Reviewer: [Signature] 6/4/07 Type (circle one): Clinical Clin/Pharm Statistical  
(signature/ date)

Concurrence:

TL Mohammed Al-Ashu 6/6/07  
Branch Chief: (signature/ date) Division Director: (signature/ date)

**Owens, Margo**

**From:** Owens, Margo  
**Sent:** Tuesday, June 05, 2007 4:47 PM  
**Subject:** FW: Therapeutic Biological Establishment Request for BLA125057/110 (Attachment B)  
**Attachments:** ScanDoc.pdf

FYI - the latest current status from the TB-EER review for sBLA 125057/110.

Margo

**From:** Kiel, Hea S  
**Sent:** Tuesday, June 05, 2007 4:45 PM  
**To:** Owens, Margo  
**Cc:** CDER-TB-EER  
**Subject:** FW: Therapeutic Biological Establishment Request for BLA125057/110 (Attachment B)

Margo,

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the TB-EER request below. There are no pending or ongoing compliance actions to prevent approval of Application BLA# - 125057/110 at this time. The following is the latest current status for the submitted site:

FDA Form 356h (Attachment B)

Manufacturer	FEI #	Profile(s) Status	EIR Classification
Abbott GmbH & Co., Germany	3002807401	CTR, TCM, TTR - AC on 10/4/05	NAI: 1/31 - 2/1/ 2005
Abbott Biotechnology Deutschland GmbH, Max Planck Ring- 2, Germany	No Data		
Abbott Laboratories, IL	1415939	TCM, LIQ - AC on 1/9/07	VAI: 8/07 - 9/01/ 2006

b(4)

HeaSuk Kiel  
 Consumer Safety Officer  
 FDA/CDER/OC/DMPQ/HFD-323  
 Phone: 301-827-8987  
 Fax: 301-827-9069

**From:** Owens, Margo  
**Sent:** Monday, April 30, 2007 3:47 PM  
**Subject:** CDER-TB-EER

**Cc:** Owens, Margo; Gill-Sangha, Gurpreet; Swann, Patrick G.; O'Leary, Connie  
**Subject:** Therapeutic Biological Establishment Request

Hello,

Attached is a request for a therapeutic biological establishment evaluation. The attachment, from applicant's form 356h, contains a list of the drug product and drug substance sites.

**Applicant Information:**

**Application BLA# - 125057/110**

**Sponsor - Abbott Laboratories**

**Street - Dept. PA72, Bldg. AP34-3**  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

**Due Date - January 21, 2008**

**Division - Division of Dermatology and Dental Products**

**Drug Name: adalimumab**

**Dosage - Injectable Solution Concentrate**

**Strengths - 40 mg/0.8 mL**

**Contacts:**

**Review Chemist - Gurpreet Gill-Sangha**

**Team Leader - Patrick Swann**

**Project Manager - Margo Owens**



ScanDoc.pdf  
(275 KB)

Thank you,  
Margo Owens  
Project Manager  
Division of Dermatology and Dental Products  
ph - 301-796-0966  
fax- 301-796-9895

## FDA Facsimile Memorandum

**Date:** May 29, 2007  
**To:** Meg Drew, M.P.H.  
Associate Director, Immunology Development  
Global Pharmaceutical Regulatory Affairs  
**From:** Margo Owens, Project Manager *MOB spa/07*  
**Subject:** sBLA 125057/110 Humira® (adalimumab)

Ms. Drew,

The Clinical Reviewer has the following information request for your sBLA 125057/110 Humira (adalimumab).

**Clinical Reviewer's Information Request:**

1. For Study M03-656a, the sponsor's efficacy results tables indicate that "Centers were combined according to their rank (number of subjects enrolled)." The algorithm used to pool small centers is not specified in the study report or protocol. Please specify the definition of small centers, clarify the algorithm used to pool them, and submit a data set that includes the pooled site variable.
2. Data sets for Study M04-716 include the investigators' IDs but do not provide information to match these IDs with investigators' name. Please provide such information.
3. The Study M04-716 data set shows that 48% of the subjects (78 out of 161 subjects) were enrolled by investigator 320. However, according to the "Country" variable, these 78 subjects were from a variety of countries (e.g., France and Switzerland, Germany, Spain, Austria, and Belgium and The Netherlands). Please confirm that the "Investigator ID" (320) is correct and, if so, explain how a single investigator could enroll subjects from all of these countries.

Please submit a response to these questions by 3 PM Thursday, May 31, 2007.

Margo Owens  
Project Manager



psoriasis	Indication: Moderate to severe			
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
<b>SAFETY</b>				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?				N/A – not a new molecular entity
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?		X		CCDS update was submitted in March 2007 to Agency.
<b>OTHER STUDIES</b>				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (e.g., labeling comprehension)?				N/A
<b>PEDIATRIC USE</b>				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
<b>ABUSE LIABILITY</b>				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?				The sponsor states there is no abuse potential
<b>FOREIGN STUDIES</b>				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
<b>DATASETS</b>				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
27. Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
29. Are all datasets to support the critical safety analyses available and complete?	X			
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?				
<b>CASE REPORT FORMS</b>				

31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		X		To submit with the 120 day safety update
<b>FINANCIAL DISCLOSURE</b>				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	X			
<b>GOOD CLINICAL PRACTICE</b>				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
<b>CONCLUSION</b>				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

A safety assessment based on all current world-wide knowledge regarding this product. This should be worldwide post marketing data focusing on serious adverse events (SAEs) and labeling updates since the time of approval. A denominator reflecting numbers of patients exposed and amount of drug distributed, both world-wide and US, should be included. Provide a summary analysis of the data by June 15, 2007.

Please provide translations for any foreign labels.

Denise Cook, M.D.

Reviewing Medical Officer

*Denise Cook, MD 5/22/07*

Markham Luke, M.D., PhD

Clinical Team Leader

*M. Luke 5/22/07*

*Efficacy Supplement is renewal to  
BLA is already filed*



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125057/110

**MAY 22 2007**

Abbott Laboratories  
Attention: Meg Drew, MPH  
Associate Director, Immunology Department  
Global Pharmaceutical Regulatory Affairs  
Dept. PA72, Building AP34-3  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

Dear Ms. Drew:

This letter is in regard to your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your supplement dated March 23, 2007 for Humira<sup>®</sup> (adalimumab) Solution, 40 mg/0.8 mL to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your supplement today. The user fee goal date is January 21, 2008. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your application. Following a review of the supplement, we shall advise you in writing of any action we have taken and request additional information if needed.

We request that you submit the following information:

1. A safety assessment based on all current worldwide knowledge regarding this product. This should be worldwide post marketing data focusing on serious adverse events (SAEs) and labeling updates (translated as needed) since the time of approval. A denominator reflecting numbers of patients exposed and amount of drug distributed, both worldwide and US, should be included. Provide a summary analysis of the data by June 15, 2007.
2. Drug substance (DS) and drug product (DP) specifications and representative certificates of analysis to show that the batches used for the psoriasis clinical studies meet the approved specifications.

3. Confirmation that DS and DP expiry and container closure components for lots as used in the psoriasis clinical studies are as per approved original BLA/sBLA (provide reference and dates for approval).
4. Section 8.1.2.1 Adamilumab Samples of Study report No. **M02-528** (p. 23 of 622) states, “The analytical report for the determination of adalimumab concentrations in serum samples from Study M02-528 is presented in Appendix 14.2”. The above Appendix 14.2 provided analytical report for AAA only, not including adalimumab serum levels. Please provide the location (page and volume numbers. of the submission) for the analytical report for adalimumab serum levels.
5. You are reminded that all CRFs should be submitted in the 120 day safety update.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Margo Owens, at (301)796-2110.

---

Sincerely,



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

**Owens, Margo**

---

**From:** Kiel, Hea S  
**Sent:** Wednesday, May 09, 2007 12:48 PM  
:  
:  
**Subject:** Owens, Margo  
CDER-TB-EER  
FW: Therapeutic Biological Establishment Request

Margo,

The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the TB-EER request below. There are no pending or ongoing compliance actions to prevent approval of Application BLA# - 125057/110 at this time. The following is the current status for the submitted site:

For FDA Form 356h (Attachment A)

Manufacturer	FEI #	Profile(s) Status	EIR Classification
Abbott Bioresearch Center, Inc.  Worcester, MA	3003684386	BTP - AC on 4/2/07	VAI : 12/9 - 18/ 2004

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HeaSuk Kiel  
Consumer Safety Officer  
FDA/CDER/OC/DMPQ/HFD-323  
Phone: 301-827-8987  
Fax: 301-827-9069

**From:** Owens, Margo  
**Sent:** Thursday, May 03, 2007 4:40 PM  
**To:** CDER-TB-EER  
**Subject:** RE: Therapeutic Biological Establishment Request

Hello,  
Please confirm receipt of this request by replying to this email.

Thanks,  
Margo Owens  
Project Manager  
DDDP

---

**From:** Owens, Margo  
**Sent:** Monday, April 30, 2007 3:47 PM  
**To:** CDER-TB-EER  
**Cc:** Owens, Margo; Gill-Sangha, Gurpreet; Swann, Patrick G.; O'Leary, Connie  
**Subject:** Therapeutic Biological Establishment Request

Hello,  
Attached is a request for a therapeutic biological establishment evaluation. The attachment, from applicant's form 356h, contains a list of the drug product and drug substance sites.

**Applicant Information:**  
**Application BLA# - 125057/110**

**Sponsor - Abbott Laboratories**

**Street - Dept. PA72, Bldg. AP34-3**  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

**Due Date - January 21, 2008**

**Division - Division of Dermatology and Dental Products**

**Drug Name: adalimumab**

**Dosage - Injectable Solution Concentrate**

**Strengths - 40 mg/0.8 mL**

**Contacts:**  
**Review Chemist - Gurpreet Gill-Sangha**

**Team Leader - Patrick Swann**

**Project Manager - Margo Owens**

<< File: ScanDoc.pdf >>

Thank you,  
Margo Owens  
Project Manager  
Division of Dermatology and Dental Products  
ph - 301-796-0966  
fax- 301-796-9895

## Owens, Margo

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**From:** Owens, Margo  
**Sent:** Monday, April 30, 2007 3:47 PM  
CDER-TB-EER  
**Subject:** Owens, Margo; Gill-Sangha, Gurpreet; Swann, Patrick G.; O'Leary, Connie  
Therapeutic Biological Establishment Request  
**Attachments:** ScanDoc.pdf

Hello,

Attached is a request for a therapeutic biological establishment evaluation. The attachment, from applicant's form 356h, contains a list of the drug product and drug substance sites.

**Applicant Information:**

**Application BLA# - 125057/110**

**Sponsor - Abbott Laboratories**

**Street - Dept. PA72, Bldg. AP34-3**  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

**Due Date - January 21, 2008**

**Division - Division of Dermatology and Dental Products**

**Drug Name: adalimumab**

**Dosage - Injectable Solution Concentrate**

**Strengths - 40 mg/0.8 mL**

**Contacts:**

**Review Chemist - Gurpreet Gill-Sangha**

**Team Leader - Patrick Swann**

**Project Manager - Margo Owens**



ScanDoc.pdf  
(275 KB)

Thank you,  
Margo Owens  
Project Manager  
Division of Dermatology and Dental Products  
ph - 301-796-0966  
fax- 301-796-9895

FDA Form 356h (Attachment A)

Drug Substance and Establishment Information				
Site Name	Site Address	Establishment Identification (FEI) or Registration Number (ORN)	Drug Master File Number	Manufacturing Steps or Types of Testing
Abbott Bioresearch Center	100 Research Drive Worcester, MA 01605 USA	3003684386	☐ ☑	Manufacture, testing, release and stability testing of drug substance.

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Appears This Way  
On Original

FDA Form 356h (Attachment B)

Drug Product Description Information BIOA 12503 - Products - Drug Product				
Site Num	Site Address	Registered Establishment Title (NDA) or Registration Number (CFR)	Drug NDC/ATC Code Number	Manufacturing Site/US Agent

Abbott GmbH & Co. KG	Knollstrasse 67061 Ludwigshafen Germany	3002807401	N/A	Release testing of unlabeled pre-filled syringes and vials, stability testing of pre-filled syringes and vials, testing of excipients.
Abbott Biotechnology Deutschland GmbH	Max-Planck-Ring 2 65205 Wiesbaden Germany	N/A	N/A	Release of unlabeled pre-filled syringes and vials for labeling and packaging in the US; release of labeled product for the US if labeled and packaged
Abbott Laboratories	200 Abbott Park Rd. Abbott Park, IL 60064 - USA	1415939	N/A	Labeling and packaging of vials and pre-filled syringes, release of labeled product.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 10811

Abbott Laboratories  
Attention: Meg Drew, Associate Director  
200 Abbott Park Road  
Abbott Park, IL 60064-6188

Dear Ms. Drew:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adalimumab (D2E7) for psoriasis.

We also refer to the meeting between representatives of your firm and the FDA on February 7, 2007. The purpose of the meeting was to discuss the supplemental BLA application.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Sincerely,

*{See appended electronic signature page}*

Susan Walker, M.D.  
Division Director  
Division of Dermatologic and Dental Drug  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING MINUTES**



**Meeting Date:** February 7, 2007      **Time:** 10:30 A.M.  
**Location:** WO 1311      **Meeting ID:** 20428  
**Topic:** IND 10811, Adalimumab (D2E7) for Psoriasis  
**Subject:** Pre-sBLA meeting  
**Sponsor:** Abbott Laboratories  
**Meeting Chair:** Susan Walker, M.D./Division Director, DDDP

**Meeting Recorder:** Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

**FDA Attendees:**

Susan Walker, M.D./Division Director, DDDP  
Stanka Kukich, M.D./Deputy Division Director, DDDP  
Markham Luke, M.D., Ph.D./Team Leader, Clinical, Dermatology, DDDP  
Jill Lindstrom, M.D./ Team Leader, Clinical, Dermatology, DDDP  
Kenneth Katz, M.D./Clinical Reviewer, DDDP  
Paul Brown, Ph.D./Supervisor, Pharmacology, DDDP  
Kurt Brorson, Ph.D./Product Reviewer, DMA  
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII  
Kathleen Fritsch, Ph.D./Biostatistian, DBIII  
Abimbola Adebowale, Ph.D./Pharmacokinetics Reviewer, DCPIII  
Zei-Pao Huang/Regulatory Information Specialist, OBPS  
Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

**Sponsor Attendees:**

**Abbott Laboratories**

Meg Drew, M.P.H./Associate Director, Global Development Regulatory Affairs  
Rebecca Drummond, M.S./Senior Regulatory Affairs Specialist, Global Development Regulatory Affairs  
Yihua Gu, M.S./Manager, Global Statistics and Data Management  
Thomas Harris, R.Ph./Senior Director, Global Development Regulatory Affairs  
Lauren Hetrick/Senior Director, Regulatory Intelligence  
Rebecca Hoffman, M.D./Divisional Vice President, Immunology Development Center  
Martin Kaul, M.D./Global Project Head, Immunology Development Center  
Joanna Peng, Ph.D./Group Leader, Clinical Pharmacology and Pharmacometrics

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Mary Kaye Willian, Dr. P.H., M.P.H., M.S./Associate Director, Global Health Economic and Outcomes Research

**Purpose:**

To provide general guidance on the content and format of the Biologics Licensing Application. The pre-meeting briefing document (submitted November 21, 2006) provides background and questions (p 9) for discussion. The sponsor requests input from the Agency on their upcoming supplemental BLA application.

**Clinical Pharmacology and Biopharmaceutics:**

**Sponsor's Question 8:**

Does the Agency agree that the proposed format and content for the planned sBLA is adequate and appropriate as presented in Appendix A?

**Agency's Response:**

There were no specific clinical pharmacology or biopharmaceutics comments included in this briefing package. We have the following comments:

Please include all pertinent reports (e.g. Reports of Bioanalytical and Analytical Methods for Human Studies and Population PK Study Reports) under Item 6 for Human Pharmacology and Bioavailability.

Please consider changing the position of the Annotated Labeling from "Item 3 Summary" to "Item 2 Labeling" for consistency.

**Clinical and Biostatistics:**

Marketing of this product for a psoriasis indication will be acceptable only if supported by a very robust safety database and by a favorable balance of risks and potential benefits, which differs in psoriasis compared to other diseases for which this product is indicated. Development of a risk management approach for pre-marketing development is very important. For more information, please see the FDA Guidance Document entitled "Development and Use of Risk Minimization Action Plans."

*The sponsor will propose a registry protocol in the sBLA to capture safety information, especially regarding potential long-term safety risks in addition to their routine pharmacovigilance activities and communication of risks via labeling. The Agency requested that the sponsor include a complete protocol for the proposed registry.*

**Sponsor's Question 1:**

Abbott believes that the scope of the clinical program is sufficient to support the planned sBLA for the following psoriasis indication:

Humira® is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Pivotal Study M03-656 was discussed with the FDA at the EOP2 meeting followed by multiple teleconferences to ensure agreement was reached on study design in order to provide adequate efficacy and safety to evaluate the proposed target indication and dosing regimen.

It has been noted that the recent FDA approved indication for infliximab is restricted (i.e., severe plaque psoriasis only) and includes incremental monitoring language in the indication compared to another TNF-blocker (i.e., etanercept) and systemic biological agents (i.e., efalizumab, alefacept). In light of this recent outcome, Abbott would like to ensure that the adalimumab sBLA provides the analyses necessary to allow consideration for the approval of an indication that is consistent with approved agents such as etanercept, efalizumab, and alefacept, that have similar benefit/risk profiles. Therefore, Abbott plans to provide additional subgroup analyses in both the CSE and CSS (see SAPs in Appendix E) to compare the efficacy and safety of adalimumab in both moderate and severe psoriasis patients as defined by PGA. Are there additional analyses that the Agency would like to see in this sBLA in order to evaluate the proposed indication and be assured of the favorable benefit/risk profile for adalimumab in both moderate and severe chronic plaque psoriasis patients, similar to previously approved biological therapies?

**Agency's Response:**

The study synopses submitted in the meeting package appear sufficient for sBLA filing and review, but the acceptability of the study reports and the data themselves will be review issues, especially regarding Study M04-716, which was not discussed at the EOP2 meeting. The sponsor is referred to the EOP2 meeting minutes, which state as follows: "Two adequate and well-controlled studies might be sufficient for demonstrating the short-term efficacy of the product (e.g. response at 3-6 months of treatment)." The sBLA submission should provide evidence that the safety and efficacy of adalimumab have been demonstrated for the proposed indication. For demonstrating efficacy the Agency will be considering both PASI-75 (the primary endpoint in the protocol) and success on the PGA (the endpoint generally recommended by the Division of Dermatology and Dental Products). The Agency does not have recommendations for additional subgroup analyses. Only subgroup analyses pre-specified in the protocol with adequate error control can be used to support efficacy claims. The indication could be restricted if the benefit-risk ratio is not acceptable across the entire population studied in the clinical trials. Labeling of adalimumab, including the indication, will be a review issue under the sBLA.

*The sponsor acknowledged that approvability of the proposed indication depends on the risk-benefit assessment in the entire moderate to severe disease population studied.*

**Sponsor's Question 2:**

Abbott believes that the number of subjects in the clinical program and the length of time for subject follow-up to be included in the planned sBLA (clinical database cut-off of 29 June 2006) follows ICH Guideline E1A and will provide adequate characterization of the safety of adalimumab in psoriasis, particularly in view of the large safety database in RA patients treated with adalimumab. Does the Agency agree?

Adalimumab Exposure in Psoriasis Controlled Studies	N=1696 n (%)
>4 weeks	1659 (97.8)
>12 weeks	1608 (94.8)
>24 weeks	1417 (83.5)
>36 weeks	1165 (68.7)
>48 weeks	810 (47.8)
>60 weeks	446 (26.3)
>72 weeks	224 (13.2)
>84 weeks	163 (9.6)
>96 weeks	154 (9.1)
>108 weeks	142 (8.4)
>120 weeks	117 (6.9)
>132 weeks	89 (5.2)
>144 weeks	82 (4.8)
>156 weeks	60 (3.5)
>168 weeks	15 (0.9)

Total exposure to adalimumab: 1654.9 PY

**Agency's Response:**

While the number of subjects may fulfill ICH E1a guidelines, a specific determination of the adequacy of the safety database for adalimumab for this indication will be a review issue under the sBLA.

**Sponsor's Question 3:**

During Abbott's EOP2 discussion with the FDA on 24 February 2004, we agreed that Studies M02-528 and M03-656 would form the basis for US approval. However, Study M04-716 was subsequently initiated and represents a third placebo-controlled confirmatory trial in patients with psoriasis. Therefore, Abbott intends to include results from this clinical study in our sBLA submission with plans to incorporate the clinical study results into the labeling. Does the Agency agree?

**Agency's Response:**

There was no concurrence in the EOP2 discussion that Studies M02-528 and M03-656 would form the basis for US approval. The Agency will review all submitted data to determine which data may be potentially suitable for incorporation into labeling.

**Sponsor's Question 4:**

Abbott proposes that the 120-day safety update, based on a 23 March 2007 submission date, will contain safety data from subjects with cumulative exposure to adalimumab from the date of the initial dose given in the clinical program through 23 February 2007. Does the Agency agree with the proposed period for the 120-day safety update?

**Agency's Response:**

No. The 120-day safety update should include data on subjects through approximately 90 days after submission of the sBLA.

*The sponsor originally proposed submitting a periodic safety update that would include data on all subjects through February 23, 2007. The update would include data that were queried*

*and reconciled and quality-assurance reviewed, and would be in the same format as the text and all tables in the safety summary submitted in March 2007 with the sBLA. The sponsor stated that they cannot provide the same quality of data for the period up to 90 days post submission. The sponsor proposed that they provide database information as of June 24, 2007. Data in this proposed update will be non-reconciled and non-queried and will not be reviewed by quality assurance. Key tables from the original sBLA safety summary will be updated,*

*The Agency responded that the sponsor's proposal is acceptable.*

**Sponsor's Question 5:**

To meet FDA requirements for the Integrated Summary of Efficacy, Common Technical Document (CTD) Module 2.7.3 format will be used; and for the Integrated Summary of Safety, CTD Module 2.7.4 format will be used with additional safety tables provided, where appropriate, in the Summary of Clinical Safety. Human pharmacokinetics will be addressed in the Summary of Clinical Pharmacology, CTD Module 2.7.2. Abbott believes that the planned structure and content of these documents, in accordance with the ICH M4E CTD Guidance, should provide reviewers with complete analyses of key safety parameters, and a thorough evaluation of any identified safety issues, as well as the protocol-driven primary efficacy endpoints. Does the Agency agree?

**Agency's Response:**

Yes, this appears acceptable. A final determination on acceptability will be a review issue.

**Sponsor's Question 6:**

Abbott proposes to summarize new safety findings that resulted in labeling changes identified from spontaneous reports and other available post-marketing sources since approval of HUMIRA® in the US on 312 December 2002 in the CSS (Section 2.7.4.6, Module 2, CTD-format). Does the Agency agree?

**Agency's Response:**

Yes, this appears acceptable. A final determination on acceptability will be a review issue. Postmarketing data include US as well as foreign data.

**Sponsor's Question 7:**

Abbott will be requesting a partial waiver for the evaluation of adalimumab use in pediatric psoriasis patients given the low prevalence of disease in pediatric patients less than 4 years of age and a deferral for patients 4 to 17 years of age (inclusive). <

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**Agency's Response:**

The Pediatric Research Equity Act (PREA) requires all applications submitted under section 351 of the Public Health Service Act for a new active ingredient contain a pediatric assessment unless the applicant has obtained a waiver or deferral. As described in the draft Guidance Document entitled "How to Comply with the Pediatric Research Equity Act," the Agency may grant a full or partial waiver of PREA requirements, or a deferral of these requirements, under certain conditions. If it believes a full or partial waiver or deferral is justified, the sponsor may apply for such according to a process outlined in the Guidance Document cited above. Without a review of prevalence data in patients less than 4 years of age or a rationale for a deferral for patients 4 to 17 years of age, however, the Agency cannot make a commitment regarding waiving or deferring PREA requirements. The Agency does note that the sponsor's previously advanced rationale for postponing pediatric studies rested on waiting for data from JRA studies, as captured in the EOP2 meeting minutes. If the sponsor submits a request for PREA waiver and/or deferral, the sponsor should describe the status of these JRA studies. The sponsor should await future discussion with the Agency on pediatric studies before their initiation. The sponsor's justification for risk vs. benefit in the pediatric population to be studied will be required.

**Sponsor's Question 8:**

Does the Agency agree that the proposed format and content for the planned sBLA is adequate and appropriate as presented in Appendix A?

**Agency's Response:**

The sponsor's proposal to include the clinical summaries, clinical study reports, and case report tabulations (including SAS transport files, data definition files, annotated CRFs and analysis-ready data sets) appears to be appropriate from a biostatistics perspective. In particular the sponsor should note that the clinical study reports should include:

- a. the study protocols with the statistical analysis plan and any protocol amendments (with dates)

*The sponsor responded that they will include all study protocols, with SAPs and amendments.*

- b. the generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials

*The sponsor responded that the treatment assignments are included in all data listings (i.e., they will not be a separate list). The actual treatment was the same as the assigned treatment for all patients that received the study drug.*

- c. all case report forms generated during the studies. These should be hyperlinked and cross-classified by seriousness (e.g., deaths, SAEs), type of adverse event (e.g., malignancy, infection, hypersensitivity reaction), study, and treatment arm.

*The sponsor responded that they plan to submit the CRFs for deaths, SAEs and discontinuations due to AEs according to ICH E3. All CFRs for deaths, SAEs and AEs leading to discontinuation will be hyperlinked and cross-classified by*

*seriousness. They will provide treatment assignment (by randomized/received treatment arm) list and actual treatment allocations. They will also provide a separate listing indicating types of AE of special interest (including malignancy, infection, allergic reaction, and others) for deaths, SAEs and discontinuations due to AEs. The list will be hyperlinked to the respective CRF.*

*The Agency responded that they would like to have all CRFs submitted to the sBLA. The sponsor asked if they could submit what they have and then submit the rest at the 120 day safety date. The Agency stated that the sponsor's proposal is acceptable.*

- d. A report on the rates and titers of anti-adalimumab antibody (AAA) formation, including an evaluation of AAA on efficacy and safety. The report should include a description of the assay used to measure and quantify AAA. The report should also describe the timing of serum sample collection for AAA measurement relative to the last infused dose.

*The sponsor responded that the assay is concentration-based (not titer-based). The sBLA will include adalimumab and AAA Analytical Methodology Validation Reports in Item 6, along with study-specific analytical reports in PK Report appendices. The sponsor stated that they will provide AAA formation rates in M02-528 and M03-656 PK reports. The M03-656 report will include evaluation of AAA formation impact on safety and efficacy. The Agency stated that the sponsor should include AAA data for all studies for which these data are available, including M02-528.. The M03-656 PK Report also includes actual dose and sampling times and the M02-528 PK report includes planned dose and sampling times.*

The proposal for analysis-ready data sets in Appendix F appears to be generally acceptable. Please be sure to design the separate analysis data sets so they can be easily merged. A final determination on acceptability will be a review issue. The applicant is referred to ICH M4 (Common Technical Document for the Registration of Pharmaceuticals for Human Use) for further information on format and content of the submission.

**Sponsor's Question 9:**

For the planned sBLA, Abbott plans to provide CTD-formatted documents mapped to an electronic Biologics License Application (eBLA) structure. The planned sBLA will conform to the FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format-General Considerations (January 1999, IT2) and FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format-New Drug Applications (NDAs) (January 1999). Does the Agency agree with the proposed format and structure for the planned sBLA?

**Agency's Response:**

Yes, this appears acceptable presently, although standards for sBLA submissions may change in the future. A final determination on acceptability of the submission will be a review issue.

**Sponsor's Question 10:**

Draft labeling will be submitted in accordance with the final rule amending labeling format and content requirements (21 CFR 201.56 and 201.57). A separate sBLA is currently under review by the Division of Gastroenterology Products for the indication of Crohn's disease (CD) with approval

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**Agency's Response:**

Yes, this appears acceptable. Please also include previous versions of approved labeling and any foreign labeling with translations as part of the review package.

*The sponsor responded that labeling will include the last approved version of USPI, the current USPI (if different than last approved), and foreign labeling which will include the current approved version of European Union Summary of Product Characteristics.*

*The Agency responded that any foreign labeling that includes concerns not captured in U.S. or European labeling should also be submitted.*

**Sponsor's Question 11:**

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**Administrative Comments**

1. 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).
2. The Sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires 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 waived or deferred.
3. Comments shared today with the sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. The comments are not meant to be viewed as commitments from the Agency. Review of the information submitted to the sBLA might identify additional comments or informational requests.
4. The sponsor is reminded that effective June 30, 2006 all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).
5. We note that SPL should be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf>], you are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format. During the initial implementation phase of the PLR (until the end of 2006), FDA advises applicants to make a good faith effort to provide PLR-compliant SPL with their marketing applications or efficacy supplements. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email [spl@fda.hhs.gov](mailto:spl@fda.hhs.gov) for individual assistance.

Please submit the completed Highlights Data Element Table. To complete the Highlights data elements, please refer to the following two documents at the FDA Data Standards Council website (<http://www.fda.gov/oc/datacouncil>) under Structured Product Labeling: "Companion Document for SPL Release 2 Implementation Guide for Highlights DRAFT" and "SPL Highlights Data Element Table." The companion document provides information on the appropriate terminology standards. If you need assistance completing the Highlights data elements portion of your application, please contact [spl@fda.hhs.gov](mailto:spl@fda.hhs.gov). Structured Product Labeling (SPL):

The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

IND 10811 2/7/07 meeting

Minutes Preparer: \_\_\_\_\_  
Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

Chair Concurrence: \_\_\_\_\_  
Susan Walker, M.D./Division Director, DDDP



Our Reference: BB-IND 10811

Food and Drug Administration  
Rockville, MD 20852

Abbott Labs Pharmaceutical Products Division  
Attention: Bagyashree Sundaram  
Senior Regulatory Affairs Associate  
200 Abbott Park Road  
D491 AP30 1E  
Abbott Park, IL 60064-6157

Dear Ms. Sundaram:

Please refer to your **Investigational New Drug Application (IND)** for "Adalimumab" and to the meeting held on February 24, 2004, between representatives of your firm and this agency. As requested in your letter of January 15, 2004, a copy of our memorandum of that meeting is attached for your information.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see <http://www.fda.gov/cber/transfer/transfer.htm> and <http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html>. Until further notice, however, all correspondence regarding this IND should continue to be addressed to:

CBER Document Control Center  
Attn: Office of Therapeutics Research and Review  
HFM-99, Room 200N  
1401 Rockville Pike  
Rockville, Maryland 20852-1448

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

Cristi L. Stark, MS  
Regulatory Project Manager  
Division of Review Management and Policy  
Office of Drug Evaluation VI  
Office of New Drugs  
Center for Drug Evaluation and Research

Enclosure: Meeting Summary



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

Memorandum

**Date:** MAR 24 2004  
**From:** Cristi Stark, DRMP, ODEVI, HFM-589  
**To:** IND 10811  
**Subject:** Type B Meeting Summary

**Meeting or Teleconference Date:** February 24, 2004      **Time:** 1:00-2:30pm

**Location:** WOC 2, Conference Room G

**Meeting Requestor/Sponsor:** Abbott Labs Pharmaceutical Products Division

**Product:** Adalimumab [Human Monoclonal Antibody   , Abbott) to Tumor Necrosis Factor] b(4)

**Proposed Use:** Treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

**Type of meeting:** End of Phase 2

**Meeting Purpose:** To present the Phase 2 psoriasis study results to-date and discuss the proposed Phase 3 clinical program

**Sponsor questions and FDA response:**

1. *As supportive of the results of the Phase 2 study, M02-528, Abbott believes that the proposed single Phase 3 study (M03-656) will support approval for the target indication:*

*Adalimumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in patients who are candidates for systemic therapy or phototherapy.  
Does the FDA agree?*

No. Two adequate and well-controlled studies might be sufficient for demonstrating the short-term efficacy of the product (e.g. response at 3-6 months of treatment). However, the most important flaw in the proposed Phase 3 clinical program is the absence of adequate and well-controlled study of long-term administration of adalimumab as treatment of plaque psoriasis.

For a product intended for chronic therapy, rigorous evidence of long-term (at least 1 year) efficacy will be required. In addition, potent systemic anti-psoriatic drugs might be used intermittently or as rotational therapy. The safety (and ideally the efficacy) of retreatment in patients who achieve clinically significant treatment responses should be assessed.

Recommended study designs will be provided.

You propose a 4:1 (active: placebo) treatment allocation for the 12-week trial. This unbalanced allocation may lead to problems with interpretation of results across patient subgroups. We recommend a more balanced allocation (2:1 or more preferably 1:1). Imbalance randomization has the potential to weaken the ability to draw conclusions from the exploratory subset analyses performed during the BLA review. A small placebo group increases the risk that there will be fluke occurrence of a seemingly non-consistent result for safety or efficacy when the subsets are examined, due to a chance occurrence in the small placebo group subset. Thus the Agency may be unable to determine whether it is a chance occurrence of bad luck, or if it is a real signal. If it relates to efficacy with a risky product, or if it relates to a serious adverse event (AE), then we may not be able to just write it off to chance occurrence, and it has the potential to hold up approval or to appear in labeling. Therefore, we advise that 1:1 randomization will provide more robust data.

b(4)

Please include a plan for assessment of center effects.

Abbott stated that they will be providing long-term follow-up data for prolonged efficacy. However, it is a problem to acquire blinded data for a period longer than 12 weeks because of the harshness on the patients in the study. Abbott will also be providing information on retreatment and capture effects.

FDA responded that rigor is a problem, which will be addressed in question number two.

- 2. At the time of the initial submission, the psoriasis safety database will consist of ~750 subjects who have been exposed to adalimumab (at least 600 subjects will have had at least 6 months exposure to adalimumab). This number plus the PsA safety database at the time of filing (~400 subjects) and the current RA safety database (~3300 subjects) will comprise a total of ~4450 subjects. Abbott believes that the size of the safety database generated in the Phase 2 and proposed Phase 3 psoriasis study in combination with the existing RA and PsA safety databases will be adequate to support an approval for continuous treatment of psoriasis subjects.*

*Does the FDA agree?*

No. To support an indication for continuous treatment of psoriasis subjects will require a safety database comprising a larger number of subjects with moderate to severe psoriasis as well as a greater number of subjects treated continuously for a full year.

Safety data in patients with rheumatoid arthritis and psoriatic arthritis may not be fully extrapolated to patients with psoriasis because of potential differences between these patient populations in:

- Incidence of serious adverse events (e.g. neoplasia, susceptibility to infections, autoimmune disease, anti-drug antibody responses).
- Use of concomitant immunosuppressive therapies on study (e.g. methotrexate).
- Interactions between the product and the disease (e.g. potential for psoriasis rebound following discontinuation of study therapy).

It should also be noted that a number of the patients with psoriatic arthritis may have had insufficient involvement with psoriasis to be informative.

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Abbott responded that it is their intention to provide data on all patients. Also they asked what the FDA had in mind for a longer-term study, which moved the discussions to question number six.

6. *Abbott believes that the overall development program is adequate to support the approval of adalimumab for continuous therapy of moderate to severe chronic plaque psoriasis patients.*

*Does the FDA have any other comments or proposals to the development program?*

To obtain labeling for efficacy for maintenance of long-term treatment will require demonstration of durable (at least 1 year) efficacy and safety via a rigorous long-term treatment clinical trial. We recommend a Phase 3 study in which patients who respond (using a clinically significant measure of response) to induction therapy and maintain response for 9 months of continuous therapy are randomized to receive an additional 3 months of study treatment (adalimumab or placebo). Subjects who maintain a response would be considered treatment successes.

Abbott responded that they will study patients as long as needed. However, the 658 trial has already started to answer the question FDA is seeking. What issue in terms of efficacy and safety still needs to be addressed by Abbott? Also why was 9 months chosen? Is there anything that we are unaware of?

FDA responded that to answer safety and efficacy concerns Abbott must have patients maintain a response on treatment. This means that patients must undergo a rigorous long-term trial in which they should be treated/maintained for 9 continuous months and then rerandomized, to show rigor, to placebo or adalimumab to see if treatment is still maintained. The 9-month time period is derived from a 1-year study in which you backtrack the 12-week treatment to arrive at 9 months.

FDA feels that if we are asked to consider a life-long therapy, it is important to understand the safety and efficacy. Therefore, data is needed that will give us a reasonable amount of confidence that we can extrapolate for the rest of the patients lives. A 12-week time period is not enough time to extrapolate. FDA believes that data for the course of 1-year is extrapolatable and will show the product provides extended safety and efficacy.

Abbott asked if the response to off-adalimumab therapy is found to be more durable, would a randomized observation period longer than 12 weeks combined with a shorter duration of continuous adalimumab therapy be worth looking into? They were told it would be appropriate.

Abbott replied that they will make a sustained commitment for the safety and efficacy of the product. It was then asked if a compromise could be reached between providing access of the drug to the population before submitting further data regarding long-term use.

FDA responded that for a disease that is chronic, long-term, and not generally life threatening, adequate labeling must be provided that describes the maintenance of this product. It is not appropriate in a BLA supplement to only describe induction of response. Therefore, rigorous evidence of efficacy after some long-term use is required (the re-randomized withdrawal study will fulfill this). It is important to understand how a product fits a disease.

Abbott then inquired how many patients should be included in the database.

FDA replied that there is not a set number; just use a slightly larger population than what is currently proposed. Also know that RA patients cannot be applied as a 1:1 basis for the safety database.

3. *Abbott considers the appropriate target patient population for the proposed Phase 3 study to be adult moderate to severe chronic plaque psoriasis subjects with at least 5% body surface area (BSA) affected by psoriasis and a minimum Psoriasis Area and Severity Index (PSAI) score of 8, based on the literature.*

*Does the FDA agree?*

No. For the purpose of eligibility in the clinical trials we recommend that you define adults with moderate to severe chronic plaque psoriasis as patients who meet all the following criteria:

- $\geq 10\%$  body surface area (BSA) affected by psoriasis
- Psoriasis Area and Severity Index (PASI)  $\geq 12$ ,

- Physician's Global Assessment  $\geq$  moderate
  - History of or candidate for anti-psoriatic systemic therapy or phototherapy
4. *Abbott considers the PASI to be the primary efficacy variable for treatment of moderate to severe chronic plaque psoriasis. The primary efficacy analysis in the proposed Phase 3 study will be the proportion of subjects with clinical response defined as at least a 75% reduction in PASI score ( $\geq$  PASI 75) at the end of treatment (Week 12) relative to the Baseline PASI score.*

*Does the FDA agree?*

FDA agrees that a proportion of patients achieving a PASI 75 response is acceptable as primary efficacy variable in patients with moderate to severe chronic plaque psoriasis for induction, and for maintenance of the therapeutic response. We strongly suggest that the proportion of patients who achieve a rating of "clear" or "nearly clear" by a validated static Physician's Global Assessment scale be used as the principal secondary efficacy outcome. We consider PGA to be a very important and meaningful efficacy endpoint. We would be comfortable with the PGA being used as a primary efficacy endpoint, if you prefer. Please provide a standard definition for the severity of the signs of disease (induration, erythema and scaling). We do not view a reduction in the PASI score  $\geq$  50% as an acceptable demonstration of treatment response.

5. *Abbott believes it prudent to postpone pediatric psoriasis studies until sufficient safety data and dosing information are available from ongoing juvenile RA (JRA) study (contingent upon the date of availability of JRA data).*

*Does the FDA agree?*

Yes.

#### **FDA questions/comments and Sponsor response:**

1. Optimization/titration of dose to response is an important objective for potent therapies that may be associated with life-threatening adverse events. Have you considered studying induction and/or maintenance therapy at lower dosages? In a clinical trial in patients with RA (Study DE009), 20 mg eow demonstrated a 35% response over placebo by ACR 20 criteria at Week 24.

Abbott stated that in general they feel the dose range studied is appropriate.

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3. The Agency requests confirmation of the percentage of the psoriatic arthritis subjects from among the subjects in psoriatic arthritis trials who manifested moderate to severe level of plaque psoriasis.
4. Treatment response in the rheumatoid arthritis trials was not affected by body weight. Analysis of efficacy by body weight will be required to assess if fixed dosing is appropriate for the psoriatic group of patients.

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6. Please provide data on anti-drug antibody development in the phase 2 studies.
7. Please adequately examine the issue of fixed dosing versus body weight. This is a very important issue as your psoriasis patients are in a different weight range when compared to your RA patients. You need to make sure this fixed dose is appropriate.

Abbott stated they will do PK modeling and other analyses similar like their RA study to make sure the dose is appropriate.

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On Original

**FDA Attendees:** Beverly Conner, PharmD, ODEVI, DRMP  
Scheldon Kress, MD, ODEVI, DTBIMP  
Louis Marzella, MD, ODEVI, DTBIMP  
Cristi Stark, MS, ODEVI, DRMP  
Marc Walton, MD, ODEVI, DTBIMP  
Bo-Guang Zhen, PhD, OPaSS, BTSS

**Sponsor Attendees:** M. Shamsul Alam, PhD, Director of Scientific Data, Global  
Pharmaceutical Research and Development  
Alejandro A. Aruffo, PhD, President Abbott Bioresearch Center,  
Divisional Vice President, Pharmaceutical Discovery Research  
Diana Chen, MD, Associate Medical Director, Global Pharmaceutical  
Research and Development  
Meg Doherty, MPH, Senior Regulatory Administrator, Global  
Pharmaceutical Regulatory Affairs  
Tom Harris, RPh, Director, Global Pharmaceutical Regulatory Affairs  
Rebecca Hoffman, MD, Global Project Head, Global Pharmaceutical  
Research and Development  
James Lefkowitz, MD, Divisional Vice President, Global  
Pharmaceutical Research and Development  
Bagyashree Sundaram, MS, Senior Regulatory Associate, Global  
Pharmaceutical Regulatory Affairs

Appears This Way  
On Original

## Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Non-clinical overview [2.4]	N	No new non-clinical information. Drug is already approved for other indications. See above.
Non-clinical summary [2.6]	N	
Pharmacology	N	
Pharmacokinetics	N	
Toxicology	N	

CTD Module 4 Contents	Present?	If not, justification, action & status
Module Table of Contents [4.1]	N	See above.
Study Reports and related info. [4.2]	N	
Pharmacology	N	
Pharmacokinetics	N	
Toxicology	N	
Literature references and copies [4.3]	N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	N/A	See above.
legible	N/A	
English (or translated into English)	N/A	
compatible file formats	N/A	
navigable hyper-links	N/A	
interpretable data tabulations (line listings) & graphical displays	N/A	
summary reports reference the location of individual data and records	N/A	
protocol-specified (as opposed to a different, post-hoc analysis) and other critical statistical analyses included	N/A	
all electronic submission components usable	N/A	



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**REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES**

**Product:** Adalimumab  
**IND No.:** BB-IND 10,811  
**Sponsor:** Abbott Laboratories  
**Indication:** Psoriasis

- (a) **Is the indication for a life-threatening condition that occurs in the pediatric population?**  
No.
- (b) **If yes, are there approved therapies labeled for use in the pediatric population?**  
No.
- (c) **If yes, list the approved therapies and labeled pediatric age group(s) of approval.**  
Not applicable.

1. **What ages are included in your deferral request?**  
4-17 years

**Reason for not including the entire pediatric population in the studies or in the deferral request?**

Requesting a partial waiver for pediatric patients 0 up to 4 years of age.

2. **Reason(s) for deferring pediatric studies:**

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**3. Have pediatric drug development plans been submitted to the Agency?**

Yes.

If yes, date submitted: A request for a pre-phase 3 meeting with the Agency was submitted on 18 December 2006 during which the pediatric development program. Abbott proposed dates for a mid-March 2007 face-to-face meeting.

Reference is made to the pre-sBLA meeting held with the Agency (DDDP) on 07 February 2007, during which it was requested that the status of the juvenile rheumatoid arthritis (JRA) program be provided in the Ps deferral request. Abbott is evaluating the safety and efficacy of adalimumab in the treatment of JRA in Study DE038. One hundred and seventy one pediatric patients (4-17 years of age)

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## REQUEST FOR PARTIAL WAIVER OF PEDIATRIC STUDIES

**Product Name:** Adalimumab  
**IND No.:** BB-IND 10,811  
**Sponsor:** Abbott Laboratories  
**Indication:** Plaque Psoriasis

**1. What age ranges are included in your waiver request?**

The Sponsor requests a partial waiver for pediatric patients 0 up to 4 years of age.

**2. Reasons for waiving pediatric studies:**

(a) Studies are impossible or highly impractical because the number of patients is so small, and the disease may be difficult to accurately diagnose.

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**3. Justification for waiver:**

Due to the unavailability of precise incidence data but evidence for the very low numbers of chronic plaque psoriasis, the uncertainty around the napkin psoriasis/psoriatic diaper rash diagnosis and the degree of maturity of the immune system, it was determined that children under the age of 4 should not be included in this study:

- The incidence of psoriasis increases until the age of 69 for both sexes. The lowest average annual incidence rate per 100,000 is seen in patients less than 20 years of age with a rate of 30.9 in comparison to 130.6 in adults at the age of 70 or above.<sup>3</sup> In the Stanford Psoriasis Life History Survey, the percentages for onset of psoriasis decreased with age: 27% of patients reported the onset before the age of 16, 10% before the age of 10, 6.5% before the age of 5 and 2% before the age of 2.<sup>1</sup>
- Psoriasis in childhood and adolescents manifests in many forms, most commonly as plaque and guttate psoriasis.<sup>4</sup> The most common type of psoriasis seen among very young children (less than two years of age) is napkin psoriasis/psoriatic diaper rash. This type can be present in the first



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days of life.<sup>1</sup> However, there is controversy regarding whether or not psoriatic diaper rash represents true psoriasis as the diagnosis is clinical and may be confused with other dermatologic conditions.<sup>2</sup>

- It is anticipated that some physicians may be hesitant to administer an immune response modifier to patients under the age of 4, since there is some evidence to suggest that the immune system in this youngest age bracket is not yet mature.<sup>5</sup>

Based on these considerations, the Sponsor requests a partial waiver for pediatric patients 0 up to 4 of age.

**b(4)**

#### References

1. Marcoux D, de Prost Y Pediatric Psoriasis Revisited. J Cutan Med Surg 2002; 22-28
2. Lewkowicz D, Gottlieb A Pediatric Psoriasis and Psoriatic Arthritis. Dermatologic therapy 2004; Vol 17, 364-375.
3. Bell L M et al. Incidence of Psoriasis in Rochester, Minn. 1980-1983. Arch Dermatol, Aug 1991
4. Li-Chung W & Rogers M Psoriasis: Varied presentations, individualized treatment, Contemporary Pediatrics, Jan 2006
5. Bellanti JA et al Developmental immunology: clinical application to allergy-immunology, Ann Allergy Asthma Immunol 2003

## ACTION PACKAGE CHECKLIST

BLA # NDA #	BLA STN# 125057/110 NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Humira® Established Name: Adalimumab Dosage Form: Solution, 40 mg		Applicant: Abbott Laboratories	
RPM: Tamika White		Division: DDDP (HFD-540)	Phone # (301) 796-2110
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b></p> <p><input type="checkbox"/> Confirmed      <input type="checkbox"/> Corrected</p> <p>Date:</p>	
❖ User Fee Goal Date		January 21, 2008	
❖ Action Goal Date (if different)		January 16, 2008	
❖ Actions			
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR	
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None	
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed	

❖ Application Characteristics

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:

- Fast Track
- Rolling Review
- CMA Pilot 1
- CMA Pilot 2

Orphan drug designation

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
  - Restricted distribution (21 CFR 314.520)
- Subpart I
- Approval based on animal studies

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
  - Restricted distribution (21 CFR 601.42)
- Subpart H
- Approval based on animal studies

NDAs and NDA Supplements:

OTC drug

Other: N/A

Other comments:

❖ Application Integrity Policy (AIP)

• Applicant is on the AIP

Yes  No

• This application is on the AIP

Yes  No

• Exception for review (*file Center Director's memo in Administrative Documents section*)

Yes  No

• OC clearance for approval (*file communication in Administrative Documents section*)

Yes  Not an AP action

❖ Public communications (approvals only)

• Office of Executive Programs (OEP) liaison has been notified of action

Yes  No

• Press Office notified of action

Yes  No 1/11/08

• Indicate what types (if any) of information dissemination are anticipated

- None
- FDA Press Release
- FDA Talk Paper
- CDER Q&As
- Other Note to Correspondence

❖ <b>Exclusivity</b>	
<ul style="list-style-type: none"> <li>• NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>	<input type="checkbox"/> Included <input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity?</li> <li>• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> <li>• NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> <li>• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>)</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes  <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____  <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____  <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____  <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
❖ <b>Patent Information (NDAs and NDA supplements only)</b>	
<ul style="list-style-type: none"> <li>• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> <li>• [505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>• [505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews).</i>)</li> <li>• [505(b)(2) applications] For <b>each paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for <b>each</b> paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified          <input type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<ul style="list-style-type: none"> <li>❖ BLAs: Facility-Related Documents               <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Requested <input checked="" type="checkbox"/> Accepted <input type="checkbox"/> Hold
<ul style="list-style-type: none"> <li>❖ NDAs: Methods Validation</li> </ul>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
<ul style="list-style-type: none"> <li>❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)</li> </ul>	<del>11/8/07</del> 1/14/08 P/T Supervisor Memo
<ul style="list-style-type: none"> <li>❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No carc
<ul style="list-style-type: none"> <li>❖ ECAC/CAC report/memo of meeting</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Nonclinical inspection review Summary (DSI)</li> </ul>	<input checked="" type="checkbox"/> None requested
<ul style="list-style-type: none"> <li>❖ Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	<del>12/14/07</del> ✓
<ul style="list-style-type: none"> <li>❖ Financial Disclosure reviews(s) or location/date if addressed in another review</li> </ul>	See page 19 of the clinical review.
<ul style="list-style-type: none"> <li>❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)</li> </ul>	<input type="checkbox"/> None OSE/DDRE Review of 6 Deaths 1/10/08 Phase 4 Registry 11/4/07, 1/11/08 SEALD 8/24/07
<ul style="list-style-type: none"> <li>❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> Not needed
<ul style="list-style-type: none"> <li>❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)</li> </ul>	See page 85 of the clinical review.
<ul style="list-style-type: none"> <li>❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> Not needed
<ul style="list-style-type: none"> <li>❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)</li> </ul>	<input type="checkbox"/> None requested
<ul style="list-style-type: none"> <li>• Clinical Studies</li> </ul>	6/15/07
<ul style="list-style-type: none"> <li>• Bioequivalence Studies</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Clin Pharm Studies</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Statistical Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None Review completed 12/4/07; Addendum 12/13/07 ✓
<ul style="list-style-type: none"> <li>❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None      12/3/07 ✓

<p>within the 45-day period).</p> <p>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</p> <p>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</p>		
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)		Division Director Review <u>  </u> / <u>  </u> / <u>  </u> Team Leader Review 1/10/08
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)		
❖ Package Insert		
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>		
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>		1/15/08
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>		3/23/07
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>		
❖ Patient Package Insert		
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>		N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>		N/A
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>		N/A
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>		N/A
❖ Medication Guide		
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>		
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>		
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>		10/5/07 Final Approved Medication Guide in Patient Insert
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>		
❖ Labels (full color carton and immediate-container labels)		
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>		N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>		1/2/08
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)		<input type="checkbox"/> DMETS N/A <input checked="" type="checkbox"/> DSRCS 11/04/07 <input checked="" type="checkbox"/> DDMAC 12/04/07 <input checked="" type="checkbox"/> SEALD 12/14/07 <input checked="" type="checkbox"/> Other reviews 1/16/08 <input type="checkbox"/> Memos of Mtgs

✓ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	1/10/08
❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input type="checkbox"/> Included N/A
❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If AP: OC clearance for approval</li> </ul>	N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. ( <i>Include certification.</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
• Outgoing Agency request for post-marketing commitments ( <i>if located elsewhere in package, state where located</i> )	1/16/08
• Incoming submission documenting commitment	1/16/08
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	
❖ Internal memoranda, telecons, email, etc.	12/10/08
❖ Minutes of Meetings	
• Pre-Approval Safety Conference ( <i>indicate date; approvals only</i> )	N/A
• Pre-NDA/BLA meeting ( <i>indicate date</i> )	<input type="checkbox"/> No mtg 2/07/07
• EOP2 meeting ( <i>indicate date</i> )	<input type="checkbox"/> No mtg 3/24/04
• Other (e.g., EOP2a, CMC pilot programs)	N/A
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	<del>9/26/07</del> ✓
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• <input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See page 3 of the product review.
• <input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
• <input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation