

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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

**CHEMISTRY REVIEW(S)**



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

Office of Biotechnology Products  
Division of Monoclonal Antibodies  
Rockville, MD 20852  
Tel. 301-827-0850

## Memorandum of Review

**Date:** September 5, 2007

**To:** File for STN: 125057/110  
RPM: Margo Owen

**From:** Gurpreet Gill-Sangha, Ph.D., Product Reviewer,  
DMA/OBP/OPS/CDER, HFD-123 *Gurpreet Gill-Sangha*  
*9/26/07*

**Through:** Patrick Swann, Ph.D., Deputy Division Director,  
DMA/OBP/OPS/CDER, HFD-123 *Patrick Swann*  
*9-26-07*

**Subject:** STN: 125057/110 is an efficacy supplement that provides for labeling changes to Humira® (adalimumab) package insert, including the addition of a new indication for treatment of moderate to severe chronic plaque psoriasis.

**Applicant:** Abbott Labs, 200 Abbott Park Rd., Abbott Park, IL 60064

**Product:** Humira® (adalimumab)

**Submission Date:** March 23, 2007

**Filing Action Date:** May 22, 2007      **Status:** Filed

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

**Sections Reviewed:** Overview of product information.

### Review Comments:

#### Overview:

The original submission for this supplement dated March 23, 2007 contained only a categorical exclusion for environmental assessment for CMC review. Abbott was requested in information request letter dated May 22, 2007 to provide drug substance, drug product batches and the container closure used in the psoriasis trial. Information provided was reviewed and refer to details in the review comments section below. The information was found to be adequate and the supplement is recommended for approval from the CMC perspective.

Conclusions:

I. Recommendation: Approval from CMC perspective

II. Sections Deferred to other reviewers: None

III. Post-marketing commitments:

b(4)

cc:

Gill-Sangha/Swann

HFD-123

OBP Drive:

via M. Welschenbach

DMA Drive

BLA (STN: 125057/110)

DMA Paper Files

BLA (STN: 125057/110)

Revision History:

Prepared by you

09/05/07

Comments by Team Leader

09/25/07

**Review Comments:**

Humira is a currently licensed product, and no additional CMC information is presented in this supplement. The following information regarding environmental assessment was presented:

**Environmental Assessment:** Abbott claimed a categorical exclusion from the requirement to environmental assessment and is aware of no extraordinary circumstances that could significantly affect the quality of the environment. Since Humira is a well characterized antibody and consists of commonly found amino acids and carbohydrate components, the proposed action is not expected to significantly alter the concentration or distribution of these substances, their metabolites, or degradation products in the environment and meets the exemptions under 21 CFR 25.31 (c). A categorical exclusion based on 21 CFR 25.31 (c) is acceptable and therefore granted.

The following CMC information was requested from Abbott in the May 22, 2007 filing/information request letter:

1. 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.

*Abbott response on June 15, 2007 (110-02): Some of the drug substance lots utilized in the production of drug product used in psoriasis clinical trials were manufactured prior to the approval of BLA 125057 (December 2002), however all lots met specification. Similarly, some of the drug product lots utilized in clinical trials were manufactured prior to the approval of BLA 125057. [*

*[ All other met specifications. The CoAs provide the result for sterility of the filled drug product. Sterility of formulated bulk drug [*

*[ 7 [*

**Evaluation:** CoAs for three drug substance (24002BF, AYP06F, and AYP21H) and three drug product lots (24264HK, 25270HK, and 25272K) are provided. Abbott refers to a minor deviation for one drug product batch 128004. However, all other lots met specifications. Sterility data for formulated bulk product is also provided and is acceptable.

2. Confirmation that DS and DP expiry and container closure components for lots used in the psoriasis clinical studies are as per approved original BLA/sBLA (provide reference dates for approval).

*Abbott response on June 15, 2007 (110-02):*

*Drug Substance: The shelf life of DS was [ as originally approved in December 2002. The shelf-life has been extended as follows:*

- [ 7 months in 2004 as reported in BLA annual report February 2005,

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☐ ☐ months in 2005 as reported in BLA annual report February 2006,  
and

- To 60 months in 2006, as reported in BLA annual report February 2007. All DS lots for the production of DP for clinical trials were within the expiry dating in effect at the time.

Drug Product: The shelf-life of DP was ☐ ☐ as originally approved in December 2002. The shelf-life has been extended as follows:

☐ ☐ months in 2003, as reported in BLA annual report February 2004. The initial retest period is ☐ ☐ Extensions are allowed for an additional ☐ ☐ In practice, retest date extensions are based on stability studies and not actual retesting. Data are available from several stability studies of drug product manufactured at both ☐ ☐ ☐ ☐ that support 36 month dating.

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Primary Container Closure: The primary packaging used for drug substance in Psoriasis clinical trials was described in the original approved BLA. The pre-filled syringe (PFS) primary packages used for drug product in these clinical trials conform to original approved BLA. PFS lots produced after April 2005 may have utilized ☐ ☐

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Evaluation: The sponsor was requested to provide the following information on July 12, 2007:

**Please provide the approved stability protocols for drug substance and drug product.**

On August 9, 2007 Abbott provided the following stability protocols for DS and DP via email to Margaret Kober, RPM:

Appears This Way  
On Original

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Abbott provided the DS and DP stability protocols and the updated expiry dating.

**The clinical team had a concern that no psoriasis clinical studies were performed using the pen as the container closure and only Humira in pre-filled syringe was used. Please refer to the following exchange of emails to clarify that since Humira is approved in the pre-filled syringe and a pen. Therefore, from the CMC perspective the two container closures are comparable as per previous supplement BLA approvals for Humira as dated in the emails.**

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**From:** Swann, Patrick G.

**Sent:** Tuesday, August 28, 2007 8:19 AM

**To:** Luke, Markham C; Gill-Sangha, Gurpreet

**Cc:** Owens, Margo; Kober, Margaret; Siegel, Jeffrey; Cook, Denise

**Subject:** RE: Humira sBLA 125057/110 - DS and DP stability protocols  
Markham,

As you probably know, we have had a great deal of discussion lately about sponsors' proposals to perform the clinical trials with one drug product configuration and license another. Sponsors don't always agree with our concerns but I think this issue deserves high scrutiny to minimize the risk of inaccurate labeling.

In this case as I understand it, Abbott performed the psoriasis clinical trial with a pre-filled syringe and would like FDA to approve the use of Humira Pen for this indication. From the CMC review of 125057.

The Humira Pen autoinjector is a single use, disposable drug product in which the functional secondary packaging is integrated with the current adalimumab PFS, which is the primary container closure system for the product.

The concerns DMA has had with other products (e.g. change in product quality due to new primary container/closure) are not applicable here. CDRH provided a consult for 125057 found the pen in compliance with current standards. Therefore, I agree with Gurpreet that the product quality issues have been adequately addressed.

Patrick

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**From:** Luke, Markham C

**Sent:** Sunday, August 26, 2007 8:01 PM

**To:** Cook, Denise

**Cc:** Owens, Margo; Kober, Margaret; Swann, Patrick G.; Gill-Sangha, Gurpreet; Siegel, Jeffrey

**Subject:** RE: Humira sBLA 125057/110 - DS and DP stability protocols

For Clinical to consider: If the pen is truly advantageos over a syringe and facilitates adherence to therapy, would not patients receiving the pen get a higher dose over the course of therapy. Denise please address in clinical review together with anything that CMC comes up with.

Jeff may have considered this in his review of the original pen application and we should look into what his thoughts on this were.

See device article below.

Thanks,  
Markham

Expert Review of Medical Devices

March 2007, Vol. 4, No. 2, Pages 109-116

(doi:10.1586/17434440.4.2.109)

HUMIRA<sup>®</sup> Pen: a novel autoinjection device for subcutaneous injection of the fully human monoclonal antibody adalimumab

Alan Kivitz<sup>†</sup> and Oscar G Segurado

<sup>†</sup> *Author for correspondence*

The HUMIRA<sup>®</sup> (adalimumab) Pen is a novel, integrated, disposable autoinjection delivery system for the subcutaneous injection of adalimumab. Adalimumab is a biological disease modifier for the treatment of rheumatoid arthritis and other chronic debilitating diseases mediated by tumor necrosis factor. Sustaining long-term efficacy with a biological therapy is influenced by patient adherence to the therapeutic regimen, which is often affected by the route of drug administration. Self-administered injectables offer several advantages over intravenous injections (i.e., portability, convenience and flexible scheduling). In particular, patients with chronic, debilitating diseases may need a self-administered medication available in an easy-to-use and convenient delivery device that minimizes pain and facilitates adherence to therapy. The adalimumab Pen offers these benefits and recent evidence indicates that patients overwhelmingly prefer the adalimumab Pen to the prefilled syringe.

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**From:** Gill-Sangha, Gurpreet

**Sent:** Sunday, August 26, 2007 3:47 PM

**To:** Luke, Markham C; Swann, Patrick G.

**Cc:** Owens, Margo; Cook, Denise; Kober, Margaret

**Subject:** RE: Humira sBLA 125057/110 - DS and DP stability protocols

Markham:

The pen is also an approved container as of STN 125057 **b(4)** Humira. So from CMC perspective it is an approved container.

Patrick: Do you have any thoughts if additional CMC information is needed if pen is not used in the psoriasis studies?

Thanks  
Gurpreet

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**From:** Luke, Markham C  
**Sent:** Sunday, August 26, 2007 11:58 AM  
**To:** Gill-Sangha, Gurpreet; Swann, Patrick G.  
**Cc:** Owens, Margo; Cook, Denise; Kober, Margaret  
**Subject:** RE: Humira sBLA 125057/110 - DS and DP stability protocols

If the studies were done with the pre-filled syringe and they want to market the pen, is there any concern from CMC?

Markham

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**From:** Gill-Sangha, Gurpreet  
**Sent:** Sunday, August 26, 2007 11:35 AM  
**To:** Luke, Markham C; Swann, Patrick G.  
**Cc:** Owens, Margo; Cook, Denise; Kober, Margaret  
**Subject:** RE: Humira sBLA 125057/110 - DS and DP stability protocols

Markham:

We had a similar conversation earlier during the clock and I am referring to those emails attached below. If this still does not satisfy your question we can talk more and see if we need to get additional information from Abbott. I will unfortunately not be able to attend the meeting tomorrow due to a conflict.

And in the latest CMC amendment we have received information on drug substance and drug product batches used for psoriasis study to meet the acceptance criteria approved for the BLA.

Thanks  
Gurpreet

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**From:** Luke, Markham C  
**Sent:** Tuesday, April 17, 2007 3:01 PM  
**To:** Gill-Sangha, Gurpreet  
**Cc:** Brorson, Kurt; Cook, Denise  
**Subject:** RE: Load Notice for Humira STN125057/110

Thanks Gurpreet. See you at the next team meeting.

Markham

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**From:** Gill-Sangha, Gurpreet  
**Sent:** Tuesday, April 17, 2007 2:22 PM  
**To:** Luke, Markham C; Brorson, Kurt  
**Cc:** Bauerlien, Melinda; Swann, Patrick G.; Fuchs, Chana; Clouse, Kathleen A; Cook, Denise  
**Subject:** RE: Load Notice for Humira STN125057/110

Markham:

As far as my understanding there is no change in formulation for the psoriasis versus the marketed product. The marketed product is 40 mg in 0.8 mL buffer formulation and it is approved in the vial, Pre-filled syringe and pen injector. The package insert for the psoriasis indicates only use of the pen or pre-filled syringe.

The only CMC information in this sBLA is the environmental assessment since there are no changes to the formulation from the approved marketed form. I also understand from Kurt that a 20 mg dose is proposed for JRA indication for which a package is to be submitted in April 2007. Kurt, feel free to add anything if I have missed.

Thanks  
Gurpreet

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**From:** Luke, Markham C  
**Sent:** Tuesday, April 17, 2007 9:28 AM  
**To:** Brorson, Kurt  
**Cc:** Bauerlien, Melinda; Gill-Sangha, Gurpreet; Swann, Patrick G.; Fuchs, Chana; Clouse, Kathleen A; Cook, Denise  
**Subject:** RE: Load Notice for Humira STN125057/110

Dear Kurt,

Thank you.

Looking forward to discussions with Gurpreet. She appeared to be very enthusiastic and knowledgeable in our discussions yesterday.

Need clarification from you regarding the following for the Humira psoriasis studies:

1) What was the formulation used in clinical studies?

2) How different was this formulation from those formulations proposed for marketing?

Thanks,  
Markham

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**From:** Luke, Markham C

**Sent:** Sunday, August 26, 2007 6:15 AM

**To:** Gill-Sangha, Gurpreet; Swann, Patrick G.

**Cc:** Owens, Margo; Cook, Denise; Kober, Margaret

**Subject:** RE: Humira sBLA 125057/110 - DS and DP stability protocols

Of note, we do have the question regarding whether the product to-be-marketed is the product that was studied in the psoriasis studies. If it is not, please identify the products that was studied and how similar/different from the to-be-marketed product they are.

Please identify whether the dosing pen is of any additional concern. My understanding is that this product is new since the psoriasis studies.

Please address this concern.

Thanks,  
Markham

Therefore, **this supplement is acceptable from the CMC perspective.**