CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
BLA 125057/S-381

Trade Name: HUMIRA

Generic Name: adalimumab

Sponsor: Abbott Laboratories

Approval Date: 08/07/2014

Indication:

HUMIRA is a tumor necrosis factor (TNF) blocker indicated for treatment of:
Rheumatoid Arthritis - Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease.

Juvenile Idiopathic Arthritis - reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older.

Psoriatic Arthritis - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

Ankylosing Spondylitis - Reducing signs and symptoms in patients with active disease.

Crohn's Disease - 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. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Plaque Psoriasis - The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systematic therapies are medically less appropriate.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/S-381

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APPLICATION NUMBER:

BLA 125057/S-381

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

sBLA 125057/S-381

SUPPLEMENT APPROVAL

AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Attention: Paul Helms, M.S.
Associate Director, Regulatory Affair

Dear Mr. Helms:

Please refer to your Supplemental Biologics License Application (sBLA), dated April 7, 2014, received April 7, 2014, submitted under section 351(a) of the Public Health Service Act for Humira® (adalimumab).

We acknowledge receipt of your amendment dated July 3, 2014.

This "Prior Approval" supplemental biologics application provides for a modification to the firing button component for the Humira Pen.

APPROVAL

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Sadaf Nabavian, Sr. Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BADRUL A CHOWDHURY
08/07/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/S-381

MEDICAL REVIEW(S)

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS
10903 New Hampshire Avenue; Building 22
Silver Spring MD 20993-0002

Medical Officer Review

BLA:	125057/381
Drug name:	Humira® (Adalimumab)
Sponsor:	Abbvie
Type of Submissions:	Prior Approval Supplement
Date of Submission:	April 7, 2014
Date of Receipt:	April 7, 2014
eCTD#:	285
Additional submissions:	Amendment dated July 3, 2014 (eCTD 309)
Review Date:	July 25, 2014
Reviewer:	Janet W. Maynard, M.D., M.H.S.
Dep Dir for Safety:	Sally Seymour, M.D.

1. Introduction and Executive Summary

This review evaluates proposed modifications made by the Applicant to the Humira autoinjector device in a chemistry, manufacturing, and controls (CMC) prior approval supplement. These modifications are proposed to minimize medication errors associated with use of the autoinjector.

The Applicant proposes changes to the firing button referred to as "an improved firing button component." Specifically, the changes to the firing button include a (b) (4) The (b) (4) is designed to reduce the potential for delayed or precluded actuation after pressing the firing button. The (b) (4) is designed to reduce the impact to the firing button if the autoinjector is accidentally dropped.

Importantly, the proposed firing button design changes are not visible to the patient and do not affect how the user interfaces with the device. Thus, the Applicant has not performed human factors testing.

The proposed device modifications were reviewed by CDRH-device and OBP and were felt to be reasonable. The device modifications may represent an incremental improvement in the Humira autoinjector. Thus, the recommendation is approval of this supplement.

1A. Recommendations for Regulatory Action

Recommendation is for approval of this supplement.

2. Regulatory History

Humira is a human-derived monoclonal antibody to TNFα that was initially approved on 12/31/02 to treat rheumatoid arthritis (RA). It was subsequently approved for psoriatic arthritis (11/9/06), ankylosing spondylitis (11/9/06), Crohn's disease (2/27/02), polyarticular juvenile idiopathic arthritis (2/21/08), and plaque psoriasis (1/18/08). The initial delivery of Humira was in pre-filled syringes (PFS) and liquid in vial.

On June 23, 2006, the Humira Pen, an autoinjector, was approved as part of sBLA 125057/65. Approval was based on performance, pharmacokinetics data, and safety. CDRH was involved with the approval of the Humira Pen; however a 510(k) was not submitted.

Subsequently, DMEPA received greater than 3,000 AERS reports of "accidental exposure" and partial injections for Humira Pen. Also, there were approximately 13,000 non-medical complaints.

(b) (4) However, the FDA continued to receive AERS reports of medication errors. There were multiple communications between the FDA and the

Applicant to address the medication errors. The Sponsor noted plans for future changes to the device. The FDA requested a human factors study with the proposed labeling and proposed modified device. In March 2011, the FDA approved a labeling supplement that included new Patient Instructions for Use labeling (Supplement #128). (b) (4)

Given the large number of complaints associated with the Humira Pen, an FDA safety issues team (SIT) has been monitoring the reports and requesting the Sponsor address the reports. The team met with upper management at the FDA in November 2012 and February 2013 to discuss the appropriate regulatory path to address the issues with the Humira Pen. It was felt that the issues did not rise to the level of recall, but the Agency should continue to work closely with the Sponsor on incremental improvements to the Humira Pen.

Following this discussion, a teleconference was held with the Applicant on March 21, 2013, and the Agency agreed with the Applicant to (b) (4) submit a CMC supplement for the proposed Humira autoinjector changes only. Supplement 342 provided for the changes to the autoinjector, including modifications to the cap over the firing button and an alternative firing mechanism subassembly with an increased force to fire. These modifications were evaluated in human factors testing, which demonstrated some medication errors. These errors primarily involved removal of the Humira Pen prior to completion of the injection. Thus, patients might receive a single lower dose of medication than what was prescribed, which is unlikely to result in clinical consequences. Importantly, none of the errors appeared to be secondary to the proposed modifications. It was felt that the proposed device modifications represented an incremental improvement in the Humira autoinjector and they were approved on July 24, 2013 (Supplement 342).

Subsequently, the Applicant also submitted revised Pen carton labeling (side opening carton and Quick Tips), which were approved as Supplement 355 on February 26, 2014).

In the current Supplement 381, the Applicant proposes changes to the firing button design that are not visible to the patient and do not affect how the user interfaces with the device. Thus, human factors testing was not requested or performed.

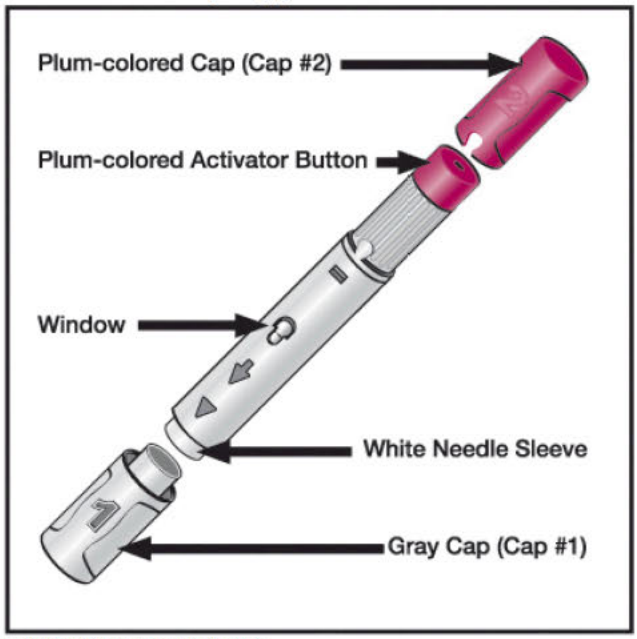
3. Overview of Changes Proposed in this Prior Approval Supplement

The Applicant proposes changes to the firing button referred to as "an improved firing button component." Specifically, the changes to the firing button include a (b) (4) is designed to reduce the potential for delayed or precluded actuation after pressing the firing button. The (b) (4) is designed to reduce the impact to the firing button if the autoinjector is accidentally dropped.

3A. Currently Approved Humira Pen

The currently approved Humira Pen is shown in Figure 1. In order to inject Humira, patients must first remove the gray cap (Cap 1) to expose the needle. Next, the plum-colored cap (Cap 2) is removed to expose the plum-colored activator button.

Figure 1: Currently Approved Humira Pen



Source: Patient Instruction's for Use

3B. Proposed Changes to the Humira Pen

The proposed changes to the Humira Pen include changes to the firing button component. Of note, changes to the subassembly were approved on July 24, 2013 in Supplement 342. These changes included an increased force to fire and changes to Cap 2 that decreased the risk of accidental firing if Cap 2 was recapped after removal. The currently proposed changes were not evaluated in human factors studies. The most recently approved changes to Cap 2 and the force to fire were reviewed in human factors testing (see my previous review of Supplement 342, dated July 15, 2013).

The current supplement proposes two changes to the firing button component: (1) a (b) (4) to reduce the potential for delayed device actuation after pressing the firing button and (2) a (b) (4) to reduce impact to the button if the autoinjector is accidently dropped. The current supplement does not propose changes to the currently approved, alternative firing mechanism subassembly.

The Applicant notes that subsequent to the approval of the alternative firing mechanism subassembly, complaints were received regarding delayed delivery of adalimumab from the Humira Pen. These complaints are described by the complainant as having pressed the firing button but actuation of the device does not immediately occur. As the plum

colored firing button is pushed downwards by the user, [redacted] (b) (4) which decreases the potential impact on the button if the pen is dropped prior to use. An enlarged view of the firing button illustrating the [redacted] (b) (4) of the improved design is provided in Figure 2.

An amendment was made on July 3, 2014 that clarified additional changes to the device that were omitted from the drawing provided in the initial supplement submission (Figure 3). The amendment noted that the additional changes included changes to the [redacted] (b) (4) of the firing button component to improve robustness of the manufacturing process. The design verification testing provided in sBLA 125057/381 supporting the firing button [redacted] (b) (4) were inclusive of all the design modifications and all acceptance criteria were met.

[redacted] (b) (4)

(b) (4)

The Applicant submitted device testing data related to the originally approved autoinjector and recent changes to the autoinjector. All device related data were reviewed by CDRH-device and were felt to be reasonable from a CDRH engineering review perspective. To support the proposed device changes, the sponsor performed device testing related to the force to fire and free-fall conditioned autoinjectors. For all device testing, the results were within the device specifications. Relevant specifications include:

(b) (4)

Performance Testing: Force to Fire

Design verification testing was performed on 210 autoinjectors with the improved firing button and alternative firing mechanism subassembly. This testing demonstrated that the firing button design changes did not impact the force to fire functionality of the Pen (i.e., the force required to press the firing button and actuate the device). Testing was performed under three different conditions: room temperature, 2-8^{o}C (Humira Pen recommended storage temperature) and 20-40 minutes after removal from the recommended storage temperature. The mean force to fire ranged from (b) (4) across

the three test conditions, which is within the design verification specification of (b) (4). In addition, this was similar to the required force to fire noted in Supplement 342, were the proposed force to fire was (b) (4) Thus, the proposed device changes do not result in a change in the required force to fire to the currently approved Humira Pen.

(b) (4)

Performance Testing: Free-Fall Conditioned Autoinjectors
The Applicant evaluated 60 autoinjectors with the modified firing button design for delivery time and volume after free fall pre-conditioning even though the proposed design changes are not anticipated to impact the dispensing performance of the Humira Pen. All acceptance criteria were met for these performance tests.

Since the firing button design changes are not visible to the patient and do not affect how the user interfaces with the device, no Human Factors study was conducted on this proposed change.

The Office of Biological Products (OBP) reviewed the proposed device modifications and did not have any concerns with the proposed changes. The device changes would not be anticipated to affect the product itself. Thus, OBP recommended approval of this supplement.

Reviewer's comments: The completed device testing indicates that the proposed device changes maintain device performance within the device specifications. Further, the force to fire the device is similar to the currently approved device. There does not appear to be device changes that affect how the user interfaces with the device. Thus, human factors testing does not appear to be necessary to support the proposed changes. While it is unclear whether the slight decrease in the time to initiate injections and the decreased risk of accidental firing with device dropping represent significant device improvements, these may represent minor improvements that may decrease use related errors.

4. Summary of Changes and Recommendations
The Applicant proposes modifications to the Humira Pen to minimize medication errors associated with its use. The proposed modifications may help mitigate some of the device-associated medication errors and user complaints. There may be other categories of autoinjector-related injection issues that are not mitigated by the Sponsor's proposed changes. However, the proposed changes may provide incremental

improvement in the use of the Humira Pen autoinjector. Further, the Sponsor has worked closely with the Agency on incremental improvements in the Humira Pen and has a long-term plan to redesign the autoinjector. Thus, we recommend approval of this supplement.

4.1 Recommended Regulatory Action

The recommended regulatory action is approval of this supplement.

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/s/

JANET W MAYNARD
08/04/2014

SALLY M SEYMOUR
08/04/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/S-381

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: July 23, 2014
From: Lana Shiu, M.D.
General Hospital Devices Branch, DAGRID, ODE, CDRH
To: Dr. Janet Maynard and Sadaf Nabavian
Division of Pulmonary and Rheumatologic Products, CDER
Via: Keith Marin and Ryan McGowan
Combination Products Team Leaders, GHDB, DAGRID, CDRH

Rick Chapman
Branch Chief, General Hospital Devices Branch, DAGRID, ODE, CDRH

Subject: BLA 125057/381 Humira Pen Injector /Applicant: AbbVie
CDRH Tracking: ICC1400414

Indication: Treatment for Rheumatoid Arthritis
Background:

Humira/Adalimumab was approved for the treatment of rheumatoid arthritis in 2002 and is currently marketed in the configuration of single use 40mg vial, prefilled syringe and prefilled syringe in an autoinjector.

The Humira Pen, containing 40 mg adalimumab solution for injection, is a pre-filled syringe (PFS) presentation that is administered via the functional secondary packaging (autoinjector) that serves as a drug delivery system for the product. The Humira Pen autoinjector is a single use, disposable drug product in which the functional secondary packaging components (the syringe housing subassembly and the firing mechanism subassembly) are integrated with the current adalimumab PFS, which is the primary container closure system for the product

Device Description
The Humira Pen autoinjector was initially developed by (b) (4) but not commercialized. Prior to the pivotal bioequivalence study (b) (4) several modifications were made to these subassemblies. The syringe housing and firing mechanism subassemblies were (b) (4)

Other modifications (post bioequivalence study) included:

1. The addition of a safety cap to cover the firing mechanism button to prevent accidental misfiring.
2. The addition of a yellow colored band on the firing mechanism (b) (4) to indicate completeness of injection through the window of the autoinjector.
3. A (b) (4) was also added to the (b) (4), which (b) (4) to help prevent accidental needlestick injury under normal use.

Changes to the autoinjector <u>after the approval</u> (the reason for this supplement submission):
**An alternative <u>firing mechanism subassembly</u> was developed after the original approval of the Humira Pen to help prevent accidental firing and adjust the required force to fire the Humira Pen.
**After approval of the alternative firing mechanism, an improvement to the <u>firing button</u> on the alternative firing mechanism was developed.

(b) (4)

(b) (4)

Since the original approval of the Humira Pen, two areas of improvement to the user interface have been developed for the <u>firing mechanism subassembly</u> accomplished by adjustment of the <u>Force to Fire</u> and an alternative (b) (4) <u>(Cap 2) design</u>.

<u>Force to fire</u> is the force required to press the plum colored button on the Humira Pen to initiate the injection once Cap 1 and the (b) (4) (Cap 2) have been removed. The design specification for force to fire is (b) (4). Trending of manufacturing test results indicate that the average force to fire for the originally approved firing mechanism is at the lower end of the specification, approximately (b) (4) A force to fire at the lower end

of the design specification range may lead to inadvertent firing of the autoinjector if the plum colored firing button is accidentally pressed before the user is ready for injection.

A design improvement has been made in which the average force to fire has been readjusted to (b) (4) This was accomplished by (b) (4)

(b) (4)

The (b) (4) was improved to prevent accidental firing if Cap 2 is recapped after removal. The Humira Pen is activated and ready for injection once Cap 1 and Cap 2 have been removed. If a patient/caregiver removes or partially removes Cap 2 and attempts to recap the Humira Pen with the originally approved firing mechanism design, the pen may accidentally fire. Within the originally approved Cap 2, (b) (4)

Subsequent to the approval of the alternative firing mechanism subassembly, changes in the design of the firing button were made to reduce the observation of delayed delivery complaints. These complaints are described by the complainant as having pressed the

firing button but actuation of the device does not immediately occur.

As the plum colored firing button is pushed downwards by the user, (b) (4)

(b) (4)

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(b) (4)

[redacted]

Shelf Life-subassembly changes did not impact shelf life

Biocompatibility-subassembly changes did not impact biocompatibility

Sterility-subassembly changes did not impact sterility

Human Factors-LCDR Quynh-Nhu Nguyen of the Human Factor's team is already consulted by DPARP on the changes to the Humira Pen (alternative firing subassembly and improved firing button). We will defer to her expertise.

Autoinjector Functional Performance Testing

The performance testing for autoinjectors assembled from both (b) (4) [redacted] included the following elements:

- (b) (4) [redacted]

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Free-Fall Conditioned Autoinjectors

Autoinjectors were dropped from a distance of 1meter and were allowed to fall directly onto the syringe needle ([redacted] end, dropped onto the opposite [redacted] end, and allowed to fall in a horizontal attitude. After the falls, the autoinjectors were subjected to the following tests to ensure correct performance of the autoinjector in the delivery of the intended drug.

- All ejection times into air were within specification.
- All delivered volumes were greater than or equal to the 0.8 mL minimum specification.
- All exposed needle length measurements were within specification.
- All [redacted] depth measurements were within specification.
- All measured dose efficiencies were within specification.
- All [redacted] removal operations were successful in removing the [redacted] from the syringe.
- All [redacted] removal operations were successful.
- The autoinjector fired successfully in all tests.
- No wet injections occurred for any of the tests.
- The yellow indicator was displayed in the window at the end of all injections.
- The [redacted] successfully activated after all injections.

Free-fall performance testing was done for autoinjectors with the alternative Cap 2 and [redacted] and all acceptance criteria were met.

Even though the design modifications to the [redacted] and button do not impact dispensing functionality after actuation, sixty (60) autoinjectors with the improved firing button design were still tested for delivery time and volume after free-fall pre-conditioning and all acceptance criteria were met.

[redacted]

Two hundred (200) non-conditioned firing mechanism subassemblies, stored at room temperature were tested with the originally-approved [redacted] (Cap 2) design. The mean measured force required to remove the [redacted] at room temperature from these subassemblies was approximately [redacted] The results ranged from approximately [redacted], meeting the design verification specification of [redacted]. Other tests showed that at 2 to 8°C, a force as high as [redacted] (with mean forces in two tests at approximately [redacted] could be required to remove the [redacted].

For the alternative design for the [redacted] (Cap 2), two hundred ten (210) firing mechanism subassemblies were tested. Testing was performed under three different conditions: room temperature, 2-8 °C (the Humira Pen recommended storage temperature) and 20-40 min after removal from the recommended storage temperature. The mean results over the different conditions tested ranged from [redacted], meeting the design verification specification of [redacted]

(b) (4)

Force to Fire with Improved Firing Button

Design verification testing was performed on two hundred ten (210) autoinjectors with the improved firing button and alternative firing mechanism subassembly to demonstrate that the firing button design changes have no impact on the force to fire functionality of the Pen. Testing was performed ((b) (4) across the three test conditions, which is within the design verification specification of (b) (4) under three different conditions: room temperature, 2-8 °C (the Humira Pen recommended storage temperature) and 20-40 min after removal from the recommended storage temperature.

(b) (4)

Review and Comments:

Per the most recent drug label, the Humira drug autoinjector has a volume of 0.8ML containing 40mg drug in a 1ML glass syringe. The overall results from the testing performed demonstrated adequate force to fire, dose accuracy and ejection time as defined within the performance specifications. The design changes to the firing subassembly and fire button have been adequately tested and do not impact on the safety/efficacy of the device in the functional delivery of the drug per the bench tests.

Recommendation:

No further issues from the CDRH engineering review perspective.

Lana Shiu, M.D.

Lana L. Shiu -S

Digitally signed by Lana L. Shiu -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lana L. Shiu -S, 0.9.2342.19200300.100.1.1=1300389268
Date: 2014.07.25 12:02:31 -04'00'

Team Leader

Ryan J. Mcgowan -S

Digitally signed by Ryan J. Mcgowan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000352462, cn=Ryan J. Mcgowan -S
Date: 2014.07.25 12:47:23 -04'00'

Branch Chief

Digitally signed by Richard C. Chapman -S
Date: 2014.07.28 08:22:33 -04'00'

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/s/

SADAF NABAVIAN
08/04/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125057/S-381

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OBP			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Sadaf Nabavian, OND, DPARP, 301-796-2777	
DATE: July 3, 2014	IND NO.	NDA NO.: sBLA 125057/S-381	TYPE OF DOCUMENT: Prior Approval Supplement	DATE OF DOCUMENT: April 7, 2014
NAME OF DRUG: Humira (adalimumab)	PRIORITY CONSIDERATION: Yes		CLASSIFICATION OF DRUG: TNF Blocker	DESIRED COMPLETION DATE: July 25, 2014

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This Prior Approval Supplement is for the use of an improved firing button component for the Humira Pen presentation. Per the Sponsor the proposed design changes will [redacted] (b) (4) The change in the [redacted] (b) (4) is being implemented to address the complaint category "Delayed Delivery" and the change in the [redacted] (b) (4) is being introduced to address the complaint category "Autoinjector Broken/Damaged." the sponsor has updated Section 3.2.P.2.4, Pharmaceutical Development, with design verification testing demonstrating that the new button does not impact the functioning of the Pen (see attached). The sponsor has also included Force-to-Fire testing under standard, warm, and cool conditions to demonstrate that the force to press the button is still within the filed specification, and additional performance testing after a pre-conditioning free-fall to further demonstrate that the functionality of the pen is not affected. DPARP is requesting for OBP's review in this change.
STN 381, Seq 285, submission dated April 7, 2014:
http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea68137a058>
The PDUFA due date for this supplement is August 7, 2014.

SIGNATURE OF REQUESTOR: Sadaf Nabavian	METHOD OF DELIVERY (Check all that apply): ☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

SADAF NABAVIAN
07/03/2014

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--Originating Center: When the consult request is initiated.
--Consulting Center: When the consult is completed.
Email: combination@fda.gov or FAX: 301-427-1935

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH/ODE/DAGID/GHDB
Division:
Mail Code: HF
Consulting Reviewer Name: LCDR Keith Marin
Building/Room #: Bldg 66, Rm 2567
Phone #: 6-2462
Fax #:
Email Address: Keith.Marin@fda.hhs.gov
RPM/CSO Name and Mail Code: Keith Marin

From (Originating Center):
Center: CDER/OND
Division: DPARP
Mail Code: HF
Requesting Reviewer Name: Dr. Janet Maynard
Building/Room #: Bldg 22, Room 3232
Phone#: 6-2978
Fax #:
Email Address: Janet.Maynard@fda.hhs.gov
RPM/CSO Name and Mail Code: Sadaf Nabavian/6-2777
Requesting Reviewer's Concurring Supervisor's Name: Ms. Ladan Jafari

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: July 3, 2014

Requested Completion Date: July 25, 2014

Submission/Application Number: BLA 125057/381
(Not Barcode Number)

Submission Type: BLA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ✓ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: April 7, 2014

Official Submission Due Date: April 7, 2014

Name of Product: Humira Pen

Name of Firm: AbbVie

Intended Use: Rheumatoid Arthritis

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

This Prior Approval Supplement is for the use of an improved firing button component for the Humira Pen presentation. Per the Sponsor the proposed design changes will (b) (4) . DPARP is requesting for CDRH's review in this change. Submission link: Seq 285,Supplement 381, April 7, 2014:http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea68137a058>

Documents to be returned to Requesting Reviewer? ☐ Yes ✓ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ✓ Consultative Review ☐ Collaborative Review

The change in the (b) (4) is being implemented to address the complaint category "Delayed Delivery" and the change in the (b) (4) is being introduced to address the complaint category "Autoinjector Broken/Damaged." the sponsor has updated Section 3.2.P.2.4, Pharmaceutical Development, with design verification testing demonstrating that the new button does not impact the functioning of the Pen (see attached). The sponsor has also included Force-to-Fire testing under standard, warm, and cool conditions to demonstrate that the force to press the button is still within the filed specification, and additional performance testing after a pre-conditioning free-fall to further demonstrate that the functionality of the pen is not affected.

Reference ID: 3536788

32 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

SADAF NABAVIAN
07/03/2014