

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125261

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125261 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DDDP PDUFA Goal Date: 12/29/08 Stamp Date: 11/29/2007

Proprietary Name: Stelara

Established/Generic Name: ustekinumab

Dosage Form: solution for subcutaneous injection

Applicant/Sponsor: Centocor Ortho Biotech, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s) 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

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

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

- # Not feasible:
 - Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s)

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__wk. __mo.	__wk. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	0 yr. 0 mo.	11 yr. 11 mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	12 yr. 0 mo.	16 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__yr. __mo.	__yr. __mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): <u>December 1, 2022</u>							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

 9/24/09

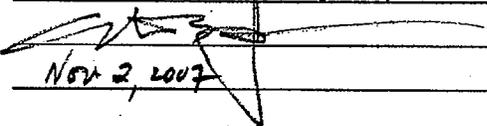
Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Debarment Certification

Centocor, Inc. hereby certifies that it 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 this application.

Name	<u>Stella S. Jones, Ph.D</u>
Title	<u>Vice President, Worldwide Regulatory Affairs</u>
Signature	
Date	<u>Nov 2, 2007</u>



Centocor Ortho Biotech Inc.

August 17, 2009

Dr. Susan Walker
Director, Division of Dermatology and Dental Products
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

**REFERENCE: STELARA™ (ustekinumab): Liquid in Vial
STN 125261/0
eCTD 125261, Sequence No. 0069**

**SUBJECT: PMR/PMC: Response to Postmarketing Requirements and
Commitments – Clinical Pharmacology and Clinical**

Dear Dr. Walker:

Reference is made to Centocor's Biologics License Application (STN 125261/0) submitted on 29 November 2007. Additional reference is made to the FDA's 14 August 2009 correspondence containing updated clinical pharmacology and clinical PMRs/PMCs for STELARA (Attachment 1).

The purpose of this submission is to provide Centocor's proposed revisions to the above-referenced PMRs/PMCs. Accordingly please find enclosed the following:

- Centocor's proposed revisions to the PMRs/PMCs listed in the FDA fax dated 14 August (Attachment 2)
- Proposed PMRs and PMCs – clean version of entire PMR/PMC list for STELARA (Word format)

We note that a duplicate copy of this submission has also been sent to Sue Kang (RPM, DDDP) via secure email in an effort to facilitate the Division's review.

The information is certified to be virus free. Please note that the information contained in this submission is considered CONFIDENTIAL unless otherwise disclosed by Centocor.

Should you have any questions or require additional information, please do not hesitate to contact me at 610-889-4486. In my absence please contact Susan Popma at 610-889-4738. For technical questions concerning this submission, please contact Michael Stevens at 610-651-6678. The Regulatory Department facsimile number is 610-651-6123.

STELARA™ (ustekinumab)
Psoriasis

Module 1.2
Cover Letter

Sincerely,

KIMBERLY SHIELDS-TUTTLE

Digitally signed by KIMBERLY SHIELDS-TUTTLE
DN: cn=US, o=RII, ou=Employees, ou=168176, cn=KIMBERLY SHIELDS-
TUTTLE, email=KShields@rii.com
Reason: I am approving this document
Date: 2009.08.17 15:46:55 -04'00'

Kim Shields-Tuttle
Senior Director, Global Regulatory Affairs, Immunology



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

FACSIMILE TRANSMITTAL SHEET

DATE: August 14, 2009

To: Kim Shields-Tuttle	From: Sue Kang Regulatory Project Manager
Company: Centocor Ortho Biotech, Inc.	Division of Dermatology & Dental Products
Fax number: (610) 651-6123	Fax number: (301) 796-9895
Phone number: (610) 889-4486	Phone number: (301) 796-4216
Subject: BLA 125261	

Total no. of pages including cover: 3

Comments: We have attached the postmarketing requirements and commitments for this application. Propose dates for final protocol submission, study completion, and final report submission for each postmarketing requirement and commitment.

Please confirm receipt of the fax by phone or email (sue.kang@fda.hhs.gov).

Thank you.

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.

Postmarketing Requirements

Clinical Pharmacology

1. Conduct an *in vitro* study to assess whether IL-12 and/or IL-23 modulate expression of major CYP enzymes (i.e., CYP 3A4, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 2D6). If, upon review, there is no significant modulation of any of the major CYP enzyme(s) observed, further exploration would not be necessary.

Final Protocol Submission: <<insert date>>
Study Completion Date: <<insert date>>
Final Report Submission: <<insert date>>

Trial Completion Date: <<insert date>>
Final Report Submission: <<insert date>>

3. As an alternative to the *in vitro* study (discussed under Item #1) and the clinical drug interaction trial (discussed under Item #2) above, conduct a clinical trial to determine the potential of ustekinumab to alter CYP substrate metabolism in psoriasis patients (e.g., using a cocktail of CYP probe drugs).

Final Protocol Submission: <<insert date>>
Trial Completion Date: <<insert date>>
Final Report Submission: <<insert date>>

b(4)

Postmarketing Commitments

Clinical Pharmacology

Evaluate approaches to improve drug tolerance in the assay method for anti-drug antibodies (ADA). If a suitable method is developed, it will be applied to assess ADA in patient samples banked from the pivotal trials, if available, and on-going clinical trials. Alternatively, documentation will be submitted to the FDA demonstrating, with due diligence, that such an assay could not be feasibly developed.

Final Report Submission: December 31, 2012

Clinical

Provide information on maintenance of response with dosing intervals longer than every 12 weeks among relevant subpopulations (e.g. subjects whose psoriasis is cleared as measured by PGA or who have cleared or minimal psoriasis). This information will be obtained from a study of at least 300 subjects for a minimum of 1 year. A study concept sheet will be submitted to Division of Dermatology and Dental Products in March 2010. Within 9 months of protocol agreement with the FDA, a final protocol will be submitted to the BLA. Within 6 months of final protocol submission, study will commence. Within 6 months of study completion, a final report will be submitted to the FDA.

The study should not be undertaken until there is agreement with the Agency on the design of your study.

Concept Paper Submission:	March 2010
Draft Protocol Submission:	September 2010
Final Protocol Submission:	December 2010
Final Report Submission:	6 months after study completion

BLA 125261
Postmarketing Requirements and Commitments
Centocor Proposed Revisions to FDA FAX dated August 14, 2009
August 17, 2009

Postmarketing Commitments

Clinical Pharmacology

Evaluate approaches to improve drug tolerance in the assay method for anti-drug antibodies (ADA). If a suitable method is developed, it will be applied to assess ADA in patient samples banked from the pivotal trials, if available, and on-going clinical trials. Alternatively, documentation will be submitted to the FDA demonstrating, with due diligence, that such an assay could not be feasibly developed.

Final Report Submission: December 31, 2012

Clinical

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The study should not be undertaken until there is agreement with the Agency on the design of your study.

Concept Paper Submission:	March 2010
Draft Protocol Submission:	September 2010
Final Protocol Submission:	December 2010*
Final Report Submission:	6 months after study completion

*pending Sponsor/Agency agreement on study design



August 14, 2009

Dr. Susan Walker
Director, Division of Dermatology and Dental Products
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

**REFERENCE: STELARA™ (ustekinumab): Liquid in Vial
STN 125261/0
eCTD 125261, Sequence No. 0068
PMC/PMR: Response to Postmarketing Requirements and Commitments**

Dear Dr. Walker:

Reference is made to Centocor's Biologics License Application (STN 125261/0) submitted on 29 November 2007. Additional reference is made to Centocor's submission of proposed revisions to the PMR/PMC for STELARA dated 05 August 2009 (Seq. No. 0065).

The purpose of this submission is to provide the FDA with updated language for PMC #8, as discussed during the FDA/Centocor teleconference held earlier today (14 August). Accordingly please find enclosed the following:

- Proposed PMRs and PMCs (Attachment 1)
- Proposed PMRs and PMCs – (Word format)

We note that a duplicate copy of this submission has also been sent to Sue Kang (RPM, DDDP) via secure email in an effort to facilitate the Division's review.

The information is certified to be virus free. Please note that the information contained in this submission is considered CONFIDENTIAL unless otherwise disclosed by Centocor.

Should you have any questions or require additional information, please do not hesitate to contact me at 610-889-4486. In my absence please contact Susan Popma at 610-889-4738. For technical questions concerning this submission, please contact Michael Stevens at 610-651-6678. The Regulatory Department facsimile number is 610-651-6123.

Sincerely,

**KIMBERLY
SHIELDS-TUTTLE**

Kim Shields-Tuttle
Senior Director, Global Regulatory Affairs, Immunology

Digitally signed by KIMBERLY SHIELDS-TUTTLE
DN: c=US, o=JNJ, ou=Employees, ou=168176,
cn=KIMBERLY SHIELDS-TUTTLE, email=KShields@ts.
Jnj.com
Reason: I am approving this document
Date: 2009.08.14 15:05:24 -04'00'

200 Great Valley Parkway
Malvern, PA 19355

Postmarketing Requirements

Clinical

1. Continue the treatment and evaluation of subjects enrolled in the pivotal Phase 3 trials PHOENIX 1 (C0743T08) and PHOENIX 2 (C0743T09) for a total of 5 years from initial enrollment.

Safety assessments at each scheduled visit should at a minimum include:

- Vital signs (at injection visits only)
- Evaluation for tuberculosis
- Concomitant medication and adverse event review

At a minimum, the following additional evaluations should be performed every 24 weeks:

- Assessment of preinjection ustekinumab serum levels.
- Testing for antibodies to ustekinumab
- Routine laboratory testing (chemistry and hematology)

Complete physical examinations (including skin) should be performed at least annually.

PHOENIX 1 (C0743T08)

Final Protocol Submission:	September 2005
Trial Completion Date:	May 2011
Final Report Submission (5-Year CSR):	January 2012

PHOENIX 2 (C0743T09)

Final Protocol Submission:	December 2005
Trial Completion Date:	October 2011
Final Report Submission (5-Year CSR):	June 2012

2. Enroll 4,000 Stelara-treated subjects into the Psoriasis Longitudinal Assessment Registry, and follow for 8 years from time of enrollment.

Final Protocol Submission:	15 Jan 2010
Trial Completion Date (for ustekinumab):	01 Dec 2019
Final Report Submission:	01 Dec 2020

3. Establish a U.S.-based prospective, observational pregnancy exposure registry that compares the pregnancy and fetal outcomes of women exposed to ustekinumab during pregnancy to an unexposed control population. Outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system

development, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life.

Final Protocol Submission: 15 Jan 2010
Trial Completion Date: 15 Jul 2013
Final Report Submission: 15 Jul 2014

4. Conduct a lactation study in women who are breastfeeding while exposed to ustekinumab. This study may be conducted in a subset of women enrolled in the U.S.-based pregnancy registry, who choose to breastfeed their infants and should assess for the presence of ustekinumab in breast milk and potential effects in nursing infants.

Final Protocol Submission: 15 Jan 2010
Trial Completion Date: 15 Jul 2013
Final Report Submission: 15 Jul 2014

5. Submit data analyses from the Nordic Database Initiative annually for the duration of the study (proposed for conduct in Sweden); submit an interim summary report after 5 years, and a final study report upon completion of the study.

Final Protocol Submission: 15 Jan 2010
Trial Completion Date: 15 Dec 2019
Final Report Submission: 15 Dec 2020

6. Submit data analyses from the Pregnancy Research Initiative (study C0168T71) annually for the duration of the initiative (underway in Sweden and Denmark for infliximab); submit an interim summary report after 5 years, and a final study report upon completion of the study.

Final Protocol Submission: 15 Jan 2010
Trial Completion Date: 15 Dec 2020
Final Report Submission: 15 Dec 2021

7. Conduct studies to evaluate the safety and efficacy of ustekinumab in pediatric subjects. Such studies are deferred pending analyses of safety data from adults in the trials C0743T08 (PHOENIX 1) and C0743T09 (PHOENIX 2) and the PSOLAR registry once completed. These safety analyses must establish that there are no safety issues that would preclude study of pediatric subjects. Pediatric studies should not be undertaken until there is agreement with the Agency on the design of such studies.

Pediatric Plan Proposal due: 01 Dec 2020

The following are requests for postmarketing commitments for ustekinumab. Please provide your written agreement to conduct these studies to include timelines of protocol submission, study initiation and completion and final report submission.

Postmarketing Commitments

Clinical

8. Provide information on maintenance of response with dosing intervals longer than every 12 weeks among relevant subpopulations (e.g. subjects whose psoriasis is cleared as measured by PGA or who have cleared or minimal psoriasis). This information will be obtained from a study of at least 300 subjects for a minimum of 1 year. A study concept sheet will be submitted to Division of Dermatology and Dental Products in March 2010. Within 9 months of protocol agreement with the FDA, a final protocol will be submitted to the BLA. Within 6 months of final protocol submission, study will commence. Within 6 months of study completion, a final report will be submitted to the FDA.

Clinical Pharmacology

9. Evaluate approaches to improve drug tolerance in the assay method for anti-drug antibodies (ADA). If a suitable method is developed, it will be applied to assess ADA in on-going trials. Alternatively, documentation will be submitted to the FDA demonstrating, with due diligence, that such an assay could not be feasibly developed.

Final Report Submission: 31 Dec 2012

10. Conduct an in vitro investigation to assess whether IL-12 and/or IL-23 would modulate expression of major CYP enzymes (i.e., CYP 3A4, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 2D6). Results will be submitted to the FDA. If no significant modulation in any of the major CYP enzyme(s) is observed, Centocor Ortho Biotech Inc. believes that further exploration would not be necessary. If significant findings emerge, Centocor Ortho Biotech Inc. will work with the FDA to plan an appropriate path forward.

Final Report Submission: December 2010

Product Quality

11. Establish quantitative Drug Product release and stability specifications for the non-reduced cSDS assay when sufficient commercial experience with the assay has been gained. A proposed specification including justification based on

supporting data will be submitted as a Prior Approval Supplement by September 2011.

Final Report Submission: September 2011

12. Collect Drug Product release and stability data to reassess and lower the allowable number of sub-visible particles as determined by the sub-visible particulate assay. A proposed specification including justification based on supporting data will be submitted as a CBE-0 Supplement by September 2010.

Final Report Submission: September 2010

13. Reassess release and shelf-life specifications for Ustekinumab drug substance and drug product as appropriate. Data and specifications reassessment will be provided within 2 years from the time of approval and reported in an annual report.

Final Report Submission: Annual Report 2011

14. Conduct end of life concurrent validation of _____ at the manufacturing scale. The studies will include an assessment of yield, chromatographic profile, and impurities where appropriate. Data will be submitted as a CBE-0 Supplement by September 2011.

b(4)

Final Report Submission: September 2011

15. Perform reduced scale end-of-life viral removal studies for the _____ Study conditions will adequately reflect the manufacturing scale process. Data will be provided by September 2010.

b(4)

Final Report Submission: September 2010

16. Revise the _____ SDS-PAGE and IEF stability specifications upon review of available stability data. The proposed specifications, including justification based on supporting data, will be submitted as a CBE-0 Supplement by September 2010.

Final Report Submission: September 2010

17. Develop and validate the Microflow Digital Imaging assay and incorporate this assay into the annual stability testing program with appropriately justified specifications. Alternately, documentation can be submitted to FDA demonstrating with due diligence that this assay could not be feasibly developed. A final report will be submitted by September 2011.

STELARA™ (ustekinumab) BLA 125261
Postmarketing Requirements and Commitments
Centocor Proposal Incorporating Changes to PMC#8 per 14 August 2009 FDA teleconference
Date: 14 August 2009

Final Report Submission: September 2011

18. Perform both IEF and cIEF in parallel for future batches as part of the commercial stability program until sufficient data have been submitted to demonstrate that the cIEF is as stability indicating as the IEF. Data will be submitted as a CBE-30 Supplement by September 2011.

Final Report Submission: September 2011

19. Perform an extensive qualification study for multi-use of the glass syringes, which are used for _____ for the visible particle assay to ensure continued effectiveness of the cleaning procedure. Data will be provided within one year of approval in an annual report. b(4)

Final Report Submission: Annual Report 2010

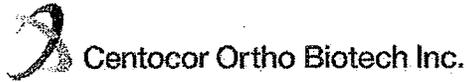
20. Continue the root cause investigation to identify the causative factor(s) that led to increased visible particle counts on stability for the clinical and validation drug product batches. The final report will be provided within one year of approval in an annual report.

Final Report Submission: Annual Report 2010

21. Develop and implement a bioburden test method that uses an increased sample volume for the determination of bioburden in the pre-harvest _____ and harvest samples. The acceptance criteria for bioburden in-process controls should be consistent with historical data and reported as CFU/volume tested. b(4)

The revised test method and acceptance criteria including justification based on supporting data will be submitted as a Prior Approval Supplement by September 2011.

Final Report Submission: September 2011



August 5, 2009

Dr. Susan Walker
Director, Division of Dermatology and Dental Products
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

**REFERENCE: STELARA™ (ustekinumab): Liquid in Vial STN 125261/0
eCTD 125261, Sequence No. 0065**

**SUBJECT: PMC/PMR : Response to Post Marketing Requirements and
Commitments Request Dated 29 July 2009**

Dear Dr. Walker:

Reference is made to Centocor's Biologics License Application (STN 125261/0) submitted on 29 November 2007. Further reference is made to the FDA's fax communication dated 29 July 2009 (Attachment 1) containing the proposed Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs) for the above-referenced BLA.

As requested by the FDA, Centocor is hereby proposing milestone dates for each of the PMRs and PMCs. Accordingly please find enclosed the following:

- Proposed PMRs and PMCs – red line version showing Centocor proposals(Attachment 2)
- Proposed PMRs and PMCs – clean version (Word format)

Please note that Centocor is respectfully requesting to modify the content of the FDA's original text for PMR #1, PMC #8, PMC #9, PMC #10, and PMC #21. The rationale for requesting these changes is provided in the enclosed Response Document (Attachment 3). The Response Document also includes a specific proposal for obtaining data from the long-term extension of Study C0743T09 (PHOENIX 2) and the PSOLAR registry to address PMC #8 as was discussed during our teleconference with DDDP on 3 August 2009.

This information is certified to be virus free. Please note that the information contained in this submission is considered CONFIDENTIAL unless otherwise disclosed by Centocor.



Centocor Ortho Biotech Inc.

Should you have any questions or require additional information, please do not hesitate to contact me at 610-889-4486. In my absence please contact Susan Popma at 610-889-4738. For technical questions concerning this submission, please contact Michael Stevens at 610-651-6678. The Regulatory Department facsimile number is 610-651-6123.

Sincerely,

**KIMBERLY SHIELDS-
TUTTLE**

Digitally signed by KIMBERLY SHIELDS-TUTTLE
DN: cn=US, o=JNJ, ou=Employees, ou=168176, cn=KIMBERLY
SHIELDS-TUTTLE, email=KShields@its.jnj.com
Reason: I am approving this document
Date: 2009.08.05 14:15:50 -0400

Kim Shields-Tuttle
Senior Director,
Global Regulatory Affairs, Immunology

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]
Sent: Wednesday, July 29, 2009 9:28 AM
To: Shields, Kim [CNTUS]
Subject: FW: PMCs/PMRs for BLA 125261
Importance: High

Hi Kim,

Please find attached a revised version of the fax sent yesterday regarding the PMCs/PMRs for BLA 125261. PMC #21 needed to be revised. Please let me know if you have any questions or concerns,

<<Fax_Postmarketing Requirements(2).pdf>>
Kind regards,

Sue Kang
Regulatory Project Manager

Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 5185
10903 New Hampshire Avenue
Silver Spring, MD 20993

Tel: 301-796-4216
fax: 301-796-9895
Email: sue.kang@fda.hhs.gov

From: Kang, Sue
Sent: Tuesday, July 28, 2009 1:19 PM
To: 'Shields, Kim [CNTUS]'
Subject: PMCs/PMRs for BLA 125261

Hi Kim,

Attached is an electronic courtesy copy of the PMCs/PMRs for BLA 125261. A copy was also sent via fax to 610-651-6123. Confirm receipt of attachment.

Also, just as a reminder, a teleconference has been scheduled for Monday, August 3rd, from 4-4:30PM. Please send me a call-in number for this meeting.

If you have any questions or concerns, please do not hesitate to contact me.

Kind regards,

Sue Kang
Regulatory Project Manager

Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 5185
10903 New Hampshire Avenue
Silver Spring, MD 20993

Tel: 301-796-4216
fax: 301-796-9895
Email: sue.kang@fda.hhs.gov

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: Provide information on maintenance of response with dosing intervals longer than every 12 weeks among relevant populations (e.g., subjects whose psoriasis is cleared as measured by PGA and PASI or who have minimal psoriasis). This information will be obtained from a study of at least 300 subjects treated with Stelara™ (ustekinumab) for a minimum of one year.

PMR/PMC Schedule Milestones:

Concept Paper Submission:	03/2010
Draft Protocol Submission:	09/2010
Final Protocol Submission:	<u>12/2010</u>
Final Report Submission:	6 months after completion of study

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

long-term data needed and theoretical concern ; *only feasible to conduct post-approval;*

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- If the PMR is a FDAAA safety study/clinical trial, describe the risk

- If the PMR is a FDAAA safety study/clinical trial, does it:

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

- 3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

- 4. If not required by regulation, characterize the review issue leading to this PMC

Information is needed on maintenance of response with dosing intervals longer than every 12 weeks

5. What type of study or clinical trial is required or agreed upon (describe)?

A study in relevant populations (e.g., subjects whose psoriasis is cleared as measured by PGA and PASI or who have minimal psoriasis). This information will be obtained from a study of at least 300 subjects treated with Stelara™ (ustekinumab) for a minimum of one year. Concept paper to be submitted March 2010

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

For Time Oussou

(Signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: Evaluate approaches to improve drug tolerance in the assay method for anti-drug antibodies (ADA). If a suitable method is developed, it will be applied to assess ADA in patient samples banked from the pivotal trials, if available, and on-going clinical trials. Alternatively, documentation will be submitted to the FDA demonstrating, with due diligence, that such an assay could not be feasibly developed.

PMR/PMC Schedule Milestones: Final Report Submission: 12/31/2012

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The true incidence rate of antibodies to ustekinumab in psoriasis subjects could not be determined from the data provided due to the limitations of the immunogenicity assay method used (i.e. the potential for assay interference by ustekinumab itself). Specifically, a low incidence of antibody – positive subjects were observed in the clinical studies (~ 3% to ~ 5 %), however, a high percentage (~ 48% to ~ 90 % of subjects had inconclusive antibody status due to the presence of ustekinumab in the patients samples at the time of antibody sampling. The PMC requested will enable us to characterize the true incidence rate of immunogenicity.

This issue is appropriate for a PMC because the immunogenicity information provided by the applicant is not optimal but acceptable to inform the label on the possible incidence rate of immunogenicity, and the current database on efficacy and safety does not indicate that immunogenicity precludes efficacy nor does it appear to be a safety concern (e.g. increased development of injection site reactions).

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this PMC

The true incidence rate of antibodies to ustekinumab in psoriasis subjects could not be determined from the data provided due to the limitations of the immunogenicity assay method used (i.e. the potential for assay interference by ustekinumab itself). The PMC requested will enable us to characterize the true incidence rate of immunogenicity (i.e. the actual percentage of subjects that had a positive antibody status).

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

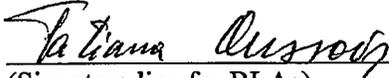
- Other
Develop a more selective immunogenicity assay method

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.



(Signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: Establish quantitative drug product release and stability specifications for the non-reduced cSDS assay when sufficient commercial experience with the assay has been gained. A proposed specification including justification based on supporting data will be submitted as a prior approval supplement.

PMR/PMC Schedule Milestones: Final Report Submission: 09/2011

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The cSDS assay is a new assay implemented by the sponsor. The cSDS assay will eventually replace the SDS-PAGE assay. Long term data are needed to establish quantitative acceptance criteria for the non-reduced cSDS assay. The quantitative acceptance criteria are needed to adequately control for purity. The sponsor agreed to this PMC in eCTD sequence #65, received by the agency on 8/5/2009.

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC

The acceptance criteria used for non-reduced cSDS currently being used by the sponsor at release are "_____ compared to reference" and for stability "no new peak _____ compared to reference standard". This does not provide sufficient control over purity/impurity levels in the drug product as there could be unspecified amounts of impurities as long as no single impurity band was over _____ compared to reference. Because the cSDS assay is new, there is insufficient data available to establish quantitative acceptance criteria.

b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: Collect drug product release and stability data to reassess and lower the allowable number of sub-visible particles. A proposed specification including justification based on supporting data will be submitted as a CBE-0 supplement.

PMR/PMC Schedule Milestones: Final Report Submission: 09/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The sponsor needs to revise the specifications for sub-visible particles to more accurately reflect manufacturing and clinical usage. Currently, the sponsor has specifications that meet or are tighter than compendial limits. This is a PMC to allow the sponsor to acquire more data on sub-visible particle levels so that specifications can be further tightened. The sponsor agreed to this PMC in eCTD sequence #65, received by the agency on 8/5/2009.

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

– **Describe the particular review issue leading to the PMR**

– **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC

The compendial USP and EP sub-visible particle limits are

- For $\geq 10 \mu\text{m}$, ≤ 6000 particles per vial
- For $\geq 25 \mu\text{m}$, ≤ 600 particles per vial

The sponsor is using the compendial limits to monitor stability, but has tightened the compendial acceptance criteria for release to:

- _____

The actual manufacturing experience would indicate limits of _____

_____ The sponsor needs to adjust the specifications to more accurately reflect manufacturing experience.

b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

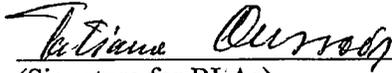
- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.



(Signature for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: Reassess release and shelf-life specifications for the ustekinumab drug substance and drug product within 2 years from the date of this letter and submit in an annual report.

PMR/PMC Schedule Milestones: Final Report Submission: Annual Report 2011

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

An assessment of release and stability specifications requires long-term data. This is a standard post-approval assessment that needs to be done as part of the life cycle approach to manufacturing. The sponsor agreed to this PMC in eCTD sequence #65, received by the agency on 8/5/2009.

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC

An assessment of specification is part of the normal life-cycle approach to manufacturing. However, as the sponsor is planning to replace the _____, _____, respectively, an assessment of specifications after 2 years is further warranted.

b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

 - Registry studies
 - Primary safety study or clinical trial (list risk to be evaluated)

 - Subpopulation (list type)

 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing studies
 - Additional data or analysis required for a previously submitted or expected study (provide explanation)

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
 - Dose-response study performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Other
-

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Taiana Ousry

(Signature for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for *each* PMR/PMC in the Action Package.

PMR/PMC Title: Conduct end-of-life concurrent validation of _____, _____ at the manufacturing scale. The studies will include an assessment of yield, chromatographic profile, and impurities where appropriate. Data will be submitted as a CBE-0 supplement.

b(4)

PMR/PMC Schedule Milestones: Final Report Submission: 09/2011

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

This is only feasible as a post-approval commitment. The sponsor needs to acquire additional data, at manufacturing scale, to support the proposed life-times of the chromatography resins used during drug substance purification. The sponsor agreed to this PMC in eCTD sequence #65, received by the agency on 8/5/2009.

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- Which regulation?

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- Describe the particular review issue leading to the PMR

[Empty box for describing the review issue]

- If the PMR is a FDAAA safety study/clinical trial, describe the risk

[Empty box for describing the risk]

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC

In the BLA, there were end-of-life time studies done for chromatography resins. These studies were done at reduced scale. The reduced scale studies, however, used mostly non-product containing cycles. This does not accurately reflect manufacturing conditions, in which product containing cycles predominate. There is a concern that multiple cycles of antibody or impurities binding to the resins could impact the resin life-times. The reduce scale studies used by the sponsor do not address this concern and, therefore, may not accurately reflect resin life-times. The use of concurrent lifetime studies at manufacturing scale has already been agreed to by the sponsor. This is a typical approach used to monitor resin lifetimes.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

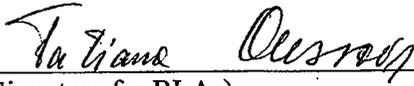
- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.



(Signature for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: Perform reduced scale end-of-life viral removal studies for the _____
_____ Study conditions will adequately reflect the manufacturing scale process.

b(4)

PMR/PMC Schedule Milestones: Final Report Submission: 09/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The sponsor needs to do additional viral removal studies for the _____

b(4)

The sponsor agreed to this PMC in eCTD sequence #65, received by the agency on 8/5/2009.

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- Which regulation?

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- Describe the particular review issue leading to the PMR

- If the PMR is a FDAAA safety study/clinical trial, describe the risk

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

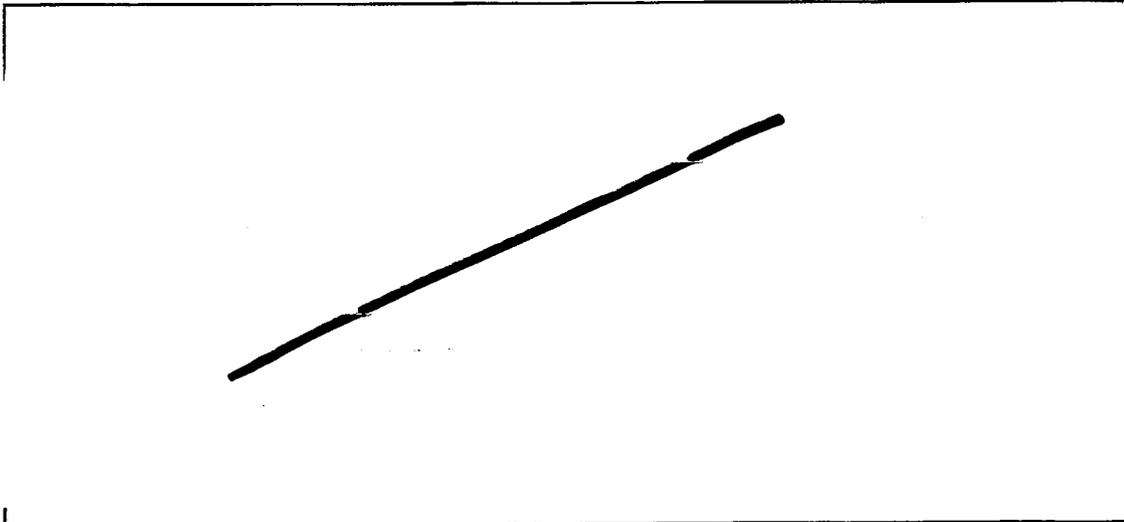
 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC



b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoeconomic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

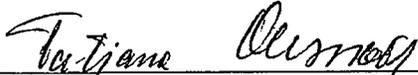
- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
 - Dose-response study performed for effectiveness
 - Nonclinical study, not safety-related (specify)
 - Other
-
-

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.



(Signature for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

b(4)

PMR/PMC Title: Revise the _____, SDS-PAGE and IEF stability specifications upon review of available stability data. The proposed specifications, including justification based on supporting data, will be submitted as a CBE-0 supplement.

PMR/PMC Schedule Milestones: Final Report Submission: 09/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Updated SDS-PAGE and IEF stability specifications for a drug substance manufacturing _____ are needed to provide assurance that there is adequate control over product quality. The sponsor needs to generate, review and analyze stability data. There are long term data required. The sponsor agreed to this PMC in eCTD sequence #65, received by the agency on 8/5/2009.

b(4)

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC

The ~~stability~~ stability acceptance criteria proposed by the sponsor for SDS-PAGE and IEF are ~~reference~~ reference standard. It is unclear how these criteria could be used to monitor stability. The sponsor was asked to modify the criteria to ensure that product degradation could be identified.

b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Tatiana Ousrop

(Signature for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for *each* PMR/PMC in the Action Package.

PMR/PMC Title: Develop and validate the Microflow Digital Imaging assay and incorporate this assay into the annual stability testing program with appropriately justified specifications. Alternately, documentation can be submitted to FDA demonstrating with due diligence that this assay could not be feasibly developed.

PMR/PMC Schedule Milestones: Final Report Submission: 09/2011

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

This was a PMC proposed by the sponsor. The sponsor recently implemented an alternate assay to measure visible particles. The sponsor needs additional data so that this assay can be validated and commercial specifications established. As long-term data will be needed, this is an appropriate PMC. This PMC was originally proposed by the sponsor in eCTD # 39, received by the Agency on 9/24/2008.

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC

The sponsor had out of trend (OOT) and out of specification visible particle results for drug product. As part of the investigations into these results, an alternate assay capable of measuring visible particles, Microflow Digital Imaging, was used by the sponsor. The sponsor proposes to develop this assay as an orthogonal method to detect visible particles.

5. What type of study or clinical trial is required or agreed upon (describe)?

--

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

 - Registry studies
 - Primary safety study or clinical trial (list risk to be evaluated)

 - Subpopulation (list type)

 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing studies
 - Additional data or analysis required for a previously submitted or expected study (provide explanation)

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
 - Dose-response study performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Other
-

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Tatiana Oussouf

(Signature for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: Perform both IEF and cIEF in parallel for future batches as part of the commercial stability program until sufficient data demonstrate that the cIEF is as stability indicating as the IEF. Data will be submitted as a CBE-30 supplement.

PMR/PMC Schedule Milestones: Final Report Submission: 09/2011

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

The sponsor is planning to replace the IEF assay with the cIEF assay. It is unclear if the cIEF assay is as stability indicating as the IEF assay. Additional stability data, from additional lots, is required so that an adequate assessment can be made of the stability indicating properties of the cIEF assay. The sponsor agreed to this PMC in eCTD sequence #65 received by the Agency on 8/5/2009.

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC

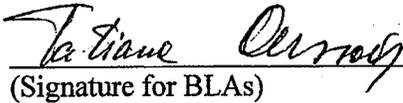
IEF was determined to be a very stability indicating assay for Ustekinumab. The sponsor proposed replacing the IEF assay with a cIEF assay. However, from the data submitted by the sponsor, it was unclear if the cIEF assay was as stability indicating. There were multiple communications between the Agency and the sponsor on this issue. It was determined that the sponsor needs additional data with the cIEF assay to support its use to monitor Ustekinumab stability.

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.



(Signature for BLAs)

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoeconomic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Fatima Oussay

(Signature for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: Perform an extensive qualification study for multi-use of the glass syringes which are used for pooling of vials for the visible particle assay to ensure continued effectiveness of the cleaning procedure. Data will be provided within one year of the date of this letter in an annual report.

PMR/PMC Schedule Milestones: Final Report Submission: 09/2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

This was a PMC proposed by the sponsor to address the introduction of glass syringes into the _____ that is part of the analytical procedure to monitor visible particles. The sponsor proposed this PMC in eCTD sequence #56 received by the Agency on 3/27/2009.

b(4)

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- Which regulation?

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- Describe the particular review issue leading to the PMR

- If the PMR is a FDAAA safety study/clinical trial, describe the risk

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC

The sponsor had out of specification (OOS) results for visible particles in post-validation drug product (DP) batches. The root cause of these particles was determined to be _____, as part of test sample preparation for the visible particle analytical procedure. As a corrective action, the sponsor introduced glass vials to be used for _____. The sponsor provided qualification data for the glass syringes. The sponsor intends to use the glass syringes multiple times, with a cleaning procedure in place between each use. While the sponsor provided data demonstrating the effectiveness of the cleaning procedure, the data were limited in term of the number of cleanings that were done with each syringe. The sponsor has proposed a commitment to a more extensive qualification study to monitor the effectiveness of the cleaning procedure. It is expected that this more extensive study will allow for a shelf-life to be established for the glass syringes.

b(4)

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoeconomic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.



(Signature for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: Continue the root cause investigation to identify the causative factor(s) that led to increased visible particle counts on stability for the clinical and validation drug product batches. The final report will be provided within one year of the date of this letter in an annual report.

PMR/PMC Schedule Milestones: Final Report Submission: Annual Report 2010

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

This was a PMC proposed by the sponsor to address out of trend (OOT) results for visible particles in stability samples. The investigation into these OOT results is still on-going. This PMC was originally proposed by the sponsor in eCTD #46, received by the Agency on 11/4/2008.

2. If required, characterize the PMR. Check all that apply and add text where indicated.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

[Empty box for describing the particular review issue leading to the PMR]

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

[Empty box for describing the risk if the PMR is a FDAAA safety study/clinical trial]

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC

The sponsor had out of trend (OOT) visible particle results for stability samples stored at the recommended storage temperature of 2-8⁰C. The OOT investigation focused on the increased appearance of visible particles in drug product validation batches compared to batches used in clinical trials. To date, the sponsor has not been able to determine a root cause for the OOT results. The results to date support that the validation batches 1) demonstrate an increased appearance on stability of visible particles, compared to the batches used clinically, and 2) these particles represent the normal degradation pathway of the product. As result of the OOT results the sponsor has changed to shelf-life of the drug product to 12 months and has made additional changes and commitments which have adequately addressed CMC quality and safety concerns. However, the sponsor should continue the investigation to try and assign a root cause to the OOT stability results.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoeconomic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

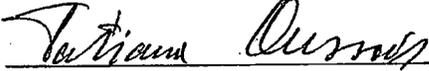
- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.



(Signature for BLAs)

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
 - Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

 - Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

 - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

 - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable

4. If not required by regulation, characterize the review issue leading to this PMC

The current bioburden test method for pre-harvest and harvest samples do not use sufficient sample volumes. A bioburden method with increased sensitivity needs to be developed for these samples.

5. What type of study or clinical trial is required or agreed upon (describe)?

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)
Develop a bioburden method with increased sensitivity.

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

6. Is the PMR/PMC clear and feasible?

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(Signature for BLAs)