

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125261

CROSS DISCIPLINE TEAM LEADER REVIEW

particulates were not observed with assay qualification and validation. In addition, conflicting data was obtained during stability testing of other samples. Because the root cause of the increase in visible particulates was not clear, the Product Quality team issued an amended review recommending a *Complete Response* in the first cycle until the issues are resolved and product potency and purity can be assured.

The following deficiencies and informational needs were conveyed in the *Complete Response* Letter of 18 Dec 2008:

Deficiencies:

1. Control procedures need to be established to validate the performance of manufacturing processes responsible for causing variability in the drug product (§ 211.110). Specifically, numerous drug product lots have recently failed the visible particulate matter assay specification at release and during stability testing. The application lacks documentation of an event that can reasonably be determined to have caused the visible particulate assay out-of-specification (OOS) results.
2. The application lacks an accurate testing and sampling method for measurement of visible particulate matter that has been developed, documented, reviewed, and approved by Centocor's Quality Control Unit (§ 211.165).

Information Needed for Resolution:

1. Identification of the root cause of the OOS results for the visible particulate assay supported by a comprehensive, consistent narrative of the investigation into the OOS events with data that strongly and directly support the conclusions. The root cause investigation should also outline corrective actions taken that ensure consistent drug product manufacture and testing.
2. Development and validation of a robust sampling and testing method for assessment of the level of visible particulates in the drug product. Development and validation results should provide assurance that the assay is able to consistently and reproducibly perform its intended function. The assay should be reviewed and approved by Centocor's Quality Control Unit.

In their complete response, the applicant provided data to establish that the _____ were indeed the root cause of the OOS results for the visible particulate assay, and proposed use of glass syringes instead. The Product Quality team found this data adequate, and concluded that, "the increased particles in the OOS results were an artifact of the _____ and do not represent particles present in the drug product," and that sufficient information was provided to support the change in process to use of glass syringes. b(4)

Additionally, the applicant provided data from the out of trend (OOT) investigation regarding the increase in appearance of visible particles in stability samples of drug product validation batches. Although a root cause for these particles was not identified, the data indicate that the particles represent the normal degradation pathway of the product. The applicant addressed this issue by proposing a shelf life of 12 months (rather than _____ as proposed with the b(4)

original submission). This shorter shelf-life of 12 months, in combination with other changes and commitments, was found acceptable by the Product Quality review team.

The Product Quality team finds that the application now demonstrates that manufacture of Stelara is well-controlled and the conditions sufficiently validated to ensure that the product is pure and potent, and they recommend *Approval*.

The applicant agreed to a number of product-related post-marketing commitments (listed at the end of this review), the dates of which are under negotiation with the applicant at the time this review closed.

4. Nonclinical Pharmacology/Toxicology

As their pivotal chronic toxicology study, the applicant conducted a 26-week subcutaneous dose study in cynomolgus monkeys with a 12-week recovery period. Toxicokinetic evaluation confirmed high exposures in excess of that required for complete pharmacologic inhibition of IL12/23 activity. One of ten monkeys developed bacterial enteritis; no other significant adverse events were noted. Histopathology did not reveal pre-neoplastic change in any organs.

Genotoxicity studies, which are not typically conducted with monoclonal antibodies due to their large size, were not conducted with ustekinumab.

The applicant submitted literature studies in lieu of conducting carcinogenicity studies. The literature studies, reviewed comprehensively by Dr. Jiaqin Yao and also in the OSE consult of October 28, 2008 (section 3.1.1), suggest that ustekinumab may present a risk for carcinogenicity. Briefly, administration of murine IL12 had an anti-tumor effect against transplanted tumors in mice, and IL12/IL23p40 knock-out mice had reduced anti-tumor host defenses, manifested as earlier development, increased frequency, and greater aggressiveness of UV-induced tumors. Both the Pharmacology/Toxicology team and the Advisory Committee recommended communication in labeling of this signal for potential risk, but did not recommend additional nonclinical carcinogenicity studies.

Stelara did not reduce male fertility in cynomolgus monkeys, although the group size was small, and an analogous murine anti-IL12/IL23p40 antibody did not reduce female fertility in mice. Teratogenicity was not observed. Embryofetal toxicity studies in cynomolgus monkeys demonstrated similar rates of fetal loss between treated and untreated animals; one neonatal loss was seen in each of two dose groups but none in control animals. Proposed wording to communicate this information has been incorporated into draft labeling.

There are no outstanding nonclinical pharmacology/toxicology issues. The Pharmacology/Toxicology team recommended an approval action from the nonclinical perspective. No nonclinical postmarketing studies are recommended or required.

5. Clinical Pharmacology/Biopharmaceutics

Stelara is a liquid-in-vial dosage form intended for subcutaneous injection administered initially in two doses four weeks apart followed by repeat dosing every 12 weeks. The median time to reach the maximum serum concentration (t_{max}) in subjects with psoriasis was 13.5 days and 7 days respectively after a single subcutaneous administration of 45 mg and 90 mg of ustekinumab. The median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in psoriasis subjects, ranging from 15 to 32 days across all psoriasis studies.

The applicant studied two doses, 45mg and 90mg, in their pivotal trials, which included population pharmacokinetics. Serum concentration was inversely proportional to body weight; serum concentrations for heavier subjects were lower than for lighter subjects. The applicant performed an exposure-response analysis which identified a clear dose-response: both IGA and PASI 75 correlated with serum concentration or AUC. For a given dose, subjects lighter than 100kg demonstrated a better response than subjects heavier than 100kg. The applicant based their dosing paradigm, 45mg for patients less than 100kg and 90 mg for patients ≥ 100 kg, on this analysis.

Dr. Pravin Jadhav conducted a pharmacometric analysis to determine whether the applicant's proposal represented the best dosing regimen; the reader is referred to his and Dr. Abi Adebawale's reviews for full discussion. The applicant studied two doses, 45mg and 90mg, across all body weights. Both doses demonstrated effectiveness, although the higher dose was more effective in heavier subjects. Dose-response was not seen for adverse events. Using pharmacometric modeling, six dosing paradigms were explored: 45mg for all, 90 mg for all, the applicant's two-step proposal, a three-step proposal, a five-step proposal, and a semi-continuous proposal. The results are presented in Table 1.

Table 1: Predicted response rates under different dosing regimens based on the AUC-proportion of PASI75 responders model

Dosing strategy	Dose	Predicted Response Rate (%) (Overall and by weight cut-offs)			
		Overall	<70kg	70-<100kg	≥ 100 kg
1 dose for all	45mg	65	80	68	54
1 dose for all	90mg	75	84	76	70
Weight-based dosing adjustments					
2-step	<100kg: 45mg ≥ 100 kg: 90mg	70	80	68	70
3-step	<70kg: 45mg 70kg-<100kg: 67.5mg(0.75mL) ≥ 100 kg: 90mg	73	80	74	70
5-step	<45kg: 45mg 45kg-<60kg: 54mg(0.6mL) 60kg-<75kg: 67.5mg(0.75mL) 75kg-<90kg: 81mg(0.9mL) ≥ 90 kg: 90mg	75	82	75	70
Semi-continuous	<45kg: 45mg 45kg-90kg: 1mg/kg	75	82	75	70

	$\geq 90\text{kg}$: 90mg				
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Source: adapted from Pharmacometrics Review (31 July 2008), BLA 125261, Dr. Pravin Jadhav, pp.29-30.

The dosing paradigms were presented to the Advisory Committee, who voted as follows:

- 2-step dosing: 7 votes
- 3-step dosing: 3 votes
- abstain: 1 vote

The committee expressed the following concerns about the 3-step paradigm: (1) lack of data at 67.5 mg (2) possible delays in generating stability data for 67.5 mg and (3) lack of availability of information on the lowest effective dose. Regarding the first concern, lack of data at 67.5mg, the applicant provided safety and effectiveness data that fully bracket this dose. Regarding the second concern, delays in generating stability data for the 67.5mg dose, it appears that the committee members did not realize that the 3-step regimen would not require a production of 67.5mg vial prior to marketing; the applicant could market their proposed dose configurations, 45mg and 90mg, and prescribers could use the 90mg vial for patients receiving either the 67.5mg dose or the 90mg dose until stability data allowed marketing of a 67.5mg vial. The third concern, the lack of information regarding the lowest effective dose, reflects the desire for dose optimization for the small minority of patients who weigh less than 45kg; this concern, when applied to the much larger population of patients who weigh 70-100kg, *supports* the 3-dose paradigm, which would optimize the dose for this much larger segment of the population in whom the drug will be used.

The exposure-response relationship for efficacy, the bracketing provided by the safety and efficacy data from the 45mg and 90mg doses, and the absence of dose-response for adverse events at these doses support the three-step dosing regimen. In addition, inclusion of this dosing regimen in labeling would be useful should applicant proceed with their plans to market a prefilled syringe presentation, which would be less flexible than the current liquid-in-vial presentation and would preclude incremental adjustments in dose. However, because the applicant did not study the intermediate dose, and the studies may not have been adequately powered to ascertain a dose-response for adverse events, the applicant's proposal for a two-step dosing regimen is acceptable.

The applicant did not conduct a thorough QT/QT_c study. The CDER DCRP QT Interdisciplinary Review Team (QT-IRT) advised that no such study was needed because ustekinumab, as a monoclonal antibody, could not access the hERG pore via the intracellular side, and QT prolongation has not been observed with any other monoclonal antibody.

Immunogenicity rates were relatively low; however, the presence of ustekinumab interfered with antibody assessment in a large proportion of subjects. The presence of increased amounts of particulates did not appear to result in increased immunogenicity. An improved immunogenicity assay method that can measure anti-drug antibodies (ADA) without interference from levels of ustekinumab that are expected to be present in patients' serum at the time of ADA sampling should be developed as a postmarketing commitment.

Ustekinumab is not metabolized by CYP450 enzymes. However, because the formation of CYP450 enzymes can be altered by increased levels of cytokines during chronic inflammation, a molecule such as ustekinumab that antagonizes cytokine activity may affect the formation of CYP450 enzymes. This potential effect and resulting need to monitor concomitant medications upon initiation of Stelara should be addressed in labeling. Additionally, the Clinical Pharmacology team recommended the following postmarketing commitment:

Conduct an in vitro study or studies to determine whether IL-12 and/or IL-23 modulate CYP enzyme expression and whether ustekinumab is able to reverse the effects of IL-12/IL-23 on CYP expression (e.g., in vitro hepatocyte study). An alternative in vivo approach would be to determine the potential of ustekinumab for the alteration of CYP substrate metabolism in psoriasis patients (e.g., a cocktail study with CYP probe drugs).

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The applicant submitted data from two pivotal trials, T08 and T09, to establish the effectiveness of Stelara, either 45mg and 90mg, in the treatment of moderate to severe psoriasis in patients who are candidates for phototherapy or systemic therapy. Subjects were dosed on week 0, week 4, and then every 12 weeks after that. The trials, which are ongoing, are similar in design (identical through week 28) and will follow subjects for five years. The primary timepoint was at 12 weeks, after which subjects on placebo were crossed-over to active treatment. The primary efficacy endpoint was PASI75, and a major secondary endpoint was Clear or Minimal on the Physician's Global Assessment Scale. The results for the above endpoints for both T08 and T09 are presented in the table below:

Table 2: Week 12 Efficacy Results

	Stelara 45 mg	Stelara 90 mg	Placebo
Study 08	N=255	N=256	N=255
PASI 75 response	171 (67%) p<0.001	170 (66%) p<0.001	8 (3%)
PGA Cleared/Minimal	154 (60%) p<0.001	158 (62%) p<0.001	10 (4%)
Study 09	N=409	N=411	N=410
PASI 75 response	273 (67%) p<0.001	311 (76%) p<0.001	15 (4%)
PGA Cleared/Minimal	278 (68%) p<0.001	302 (73%) p<0.001	20 (5%)

Source: Biostatistical Review (28 July 2008), BLA 125261, Dr. Kathleen Frisch, pp.31.

The initial application included data to week 52 for T08 and to week 28 for T09, and the Complete Response resubmission provided data through week 100 for T09. The reader is referred to the reviews by Drs. Brenda Carr and Kathleen Fritsch for a full discussion of the trial designs and results.

The results from T08 and T09 demonstrate that Stelara is superior to placebo in the treatment of moderate to severe psoriasis. I concur with the conclusions of Clinical reviewer and Biostatistical team that the data support a determination of efficacy for both doses.

8. Safety

Initial application

The safety database, comprised of pooled data from the two pivotal studies and a phase 2 study and including 2,226 ustekinumab-exposed subjects, 372 of who received ustekinumab for at least one year, is adequate to characterize adverse events. Four deaths were reported, three of which were determined to be unlikely due to ustekinumab exposure; the fourth death occurred in a subject with metastatic kidney (transitional cell) cancer, and relatedness to ustekinumab was considered possible. The rates of serious and non-serious adverse events were similar across all arms. The most frequently reported adverse events were nasopharyngitis and respiratory infection. Laboratory parameters were generally comparable across ustekinumab and placebo-treated groups. No effect of ustekinumab on lymphocyte parameters was identified.

No cases of active tuberculosis or non-tuberculous mycobacterial infection were reported. Of note, diagnosis of latent tuberculosis did not preclude enrollment if the subject initiated treatment; 68 such subjects were enrolled. No cases of systemic fungal infection or salmonellosis were reported.

The rate of injection site reactions was low, and no cases of anaphylaxis or serum sickness were reported. As previously mention, immunogenicity rates were relatively low, and did not correlate with increased particulate levels; however, the presence of ustekinumab interfered with antibody assessment in a large proportion of subjects.

Eight solid malignancies (prostate [two], kidney, thyroid, breast, colon, tongue, and malignant melanoma in situ) were reported in 8 subjects, fewer than would be expected by comparison with the SEER database (per subject year exposure, adjusted for age, gender and race). No lymphomas were reported. Eighteen ustekinumab-treated subjects developed nonmelanoma skin cancer: 5 squamous cell carcinomas and 14 basal cell carcinomas. The rate and types of solid tumor malignancies, as well as the ratio of basal to squamous cell carcinomas of the skin, do not suggest a malignancy signal related to immunosuppression.

Cardiovascular events were uncommon, and rates were not increased over expected background rates.

The applicant did not provide sufficient data to establish the safety of self-administration. Subjects were permitted to administer self-administer study agent after the second dose,

however this took place at the study site under observation by study personnel. Unsupervised self-administration at home was not permitted. Because the infrequency of dosing could impede mastery of injection technique, it will be important to understand the impact of true self-administration (at home, without study personnel oversight) on safety and effectiveness and to ascertain whether subjects are able to successfully self-administer the drug without the benefit of professional oversight.

Complete Response:

The Complete Response resubmission provided additional safety data from T09 through week 100, and T12 (active control study w/etanercept) through week 24. Total deaths in the development program increased to 10, although no additional deaths were attributed to ustekinumab. In T09, 14 additional malignancies were reported in 14 subjects, 3 nonmelanoma skin cancers and 11 solid tumors. There were no new safety signals that were identified from the additional safety data provided.

9. Advisory Committee Meeting

The application was presented to the Dermatologic and Ophthalmologic Drugs Advisory Committee on June 17, 2008. The Committee unanimously agreed that the applicant had demonstrated the effectiveness of ustekinumab in the treatment of psoriasis and had provided sufficient information to support the dosing regimen, and the committee unanimously recommended approval. The committee also expressed unanimous concern about the potential for malignancy demonstrated by nonclinical studies and unanimously recommended that these findings be communicated to prescribers. The committee unanimously agreed that subjects had been followed for an insufficient amount of time, and were in near unanimous agreement that an insufficient number of subjects had been studied. The committee's vote regarding a two-step or three-step dosing paradigm is presented in section 5 of this review. The committee voted 4 (for) to 7 (against) against self-administration. The committee unanimously agreed that the applicant's risk assessment proposals were insufficient.

10. Pediatrics

The applicant conducted studies in subjects 18 years of age and older. The applicant's pediatric assessment included a request for deferral for all pediatric populations. The applicant's pediatric plan proposed years of age after completion of the 5-year extensions of the adult pivotal trials, pending an adequate safety profile from the trial extensions and postmarketing data. Progression into younger pediatric subpopulations would be dependent upon an adequate safety profile in adolescents and adults. The deferral request and pediatric plan were presented to the Pediatric Review Committee; the committee concurred with the deferral request and the proposed plan.

b(4)

11. Other Relevant Regulatory Issues

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted.

12. Labeling

Review by the Division of Medical Error Prevention and Analysis found the proposed tradename, Stelara, to be acceptable.

At the time this review closed, labeling negotiations with the applicant regarding the package insert are ongoing, and the carton and container labels are still under review.

The applicant provided a Medication Guide as part of their REMS.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: *Approval*

Risk Benefit Assessment

The applicant demonstrated the effectiveness of their product for the treatment of moderate to severe psoriasis in patients who are candidates for phototherapy or systemic therapy. No clear safety signals for infection, malignancy, cardiovascular events, or immunogenicity emerged during the development program. The applicant studied sufficient numbers of subjects to adequately characterize common adverse events. However, because of the chronic nature of psoriasis and the consequent likelihood of long-term use of Stelara, as well as the theoretical concern for infectious or malignant adverse events based the mechanism of action of the drug, a multi-pronged approach to postmarketing risk assessment is needed to elucidate potential low-frequency or long-latency signals. Additionally, because of the potential risks, health care provider and patient education (regarding potential risks, mitigation measures, and the need for adverse event reporting) is necessary.

The applicant initially proposed additional risk assessment via 5-year continuation of pivotal trials T08 and T09 (ongoing), continuation of a 64-week, active-comparator trial against etanercept, addition of a ustekinumab arm to the existing PSOLAR postmarketing registry for serious adverse events, a prospective 5-year observational cohort study (Nordic Database Initiative), a 5-year pregnancy registry, and datamining, in addition to routine pharmacovigilance, and the applicant initially proposed a specialty pharmacy provider to address prescriber and patient education needs. In the first review cycle, the OSE review team recommended that in addition to the applicant's proposals, a Risk Evaluation and Mitigation Strategy (REMS) consisting of a Medication Guide and a Communication plan was needed; this was communicated to the applicant in the Complete Response action letter. In their Complete Response resubmission and subsequent amendments, the applicant provided a REMS consisting of a Medication Guide, Communication Plan, and Timetable for Assessments. Although the final DRISK consultation response is pending at the time of closure of this review, the REMS appears adequate from a clinical perspective to ensure that the benefits of Stelara outweigh potentials risks.

Recommendation for Postmarketing Risk Management Activities

In addition to the REMS, postmarketing safety studies are needed.

Recommended Postmarketing Requirements (dates not finalized at the time this review closed)

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

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

- Vital signs
- Evaluation for tuberculosis
- Routine laboratory testing (chemistry and hematology)
- Concomitant medication and adverse event review
- Testing for antibodies to ustekinumab

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

- Pre-injection ustekinumab serum levels should be obtained for pharmacokinetic analysis at each scheduled visit.
- Complete physical examinations (including skin) should be performed at least annually.

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

2. Enroll Stelara-treated patients into the Psoriasis Longitudinal Assessment Registry.

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

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: <<insert date>>
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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: <<insert date>>
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5. Submit data analyses from the Nordic Database Initiative annually for the duration of the study (proposed for conduct in Sweden) and final study report upon completion of the study.

Final Protocol Submission: <<insert date>>
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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) and final study report upon completion of the study.

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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.

Final Protocol Submission: <<insert date>>
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Recommended Postmarketing Commitments (dates not finalized at the time this review closed)

Clinical

1. Evaluate other maintenance dosing regimens (e.g. longer intervals, lower doses).

Final Protocol Submission: <<insert date>>
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Clinical Pharmacology

2. Develop an immunogenicity assay method that can measure anti-drug antibodies (ADA) without interference from levels of ustekinumab that are expected to be present in patients' serum at the time of ADA sampling. This new assay should be used to assess ADA in patient samples banked from the pivotal trials and/or to assess ADA in on-going clinical trials.

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

3. Conduct an in vitro study or studies to determine whether IL-12 and/or IL-23 modulate CYP enzyme expression and whether ustekinumab is able to reverse the effects of IL-12 or IL-23 on CYP expression (e.g., in vitro human hepatocyte study). You may need to conduct a drug interaction study or studies in patients based on the results of the in vitro study. An alternative in vivo approach would be to determine the potential of ustekinumab for the alteration of CYP substrate metabolism in psoriasis patients (e.g., a cocktail study with CYP probe drugs).

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Product Quality

4. 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 Protocol Submission: <<insert date>>
Trial Completion Date: <<insert date>>
Final Report Submission: September 2011

5. 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 Protocol Submission: <<insert date>>
Trial Completion Date: <<insert date>>
Final Report Submission: September 2010

6. 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.

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7. 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 Protocol Submission: <<insert date>>
Trial Completion Date: <<insert date>>
Final Report Submission: September 2011

8. 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 Protocol Submission: <<insert date>>
Trial Completion Date: <<insert date>>
Final Report Submission: September 2010

9. 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. **b(4)**

Final Protocol Submission: <<insert date>>
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Final Report Submission: September 2010

10. 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.

Final Protocol Submission: <<insert date>>
Trial Completion Date: <<insert date>>
Final Report Submission: September 2011

11. 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 Protocol Submission: <<insert date>>
Trial Completion Date: <<insert date>>
Final Report Submission: September 2011

12. Perform an extensive qualification study for multi-use of the glass syringes, which are _____ vials 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 Protocol Submission: <<insert date>>
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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 Protocol Submission: <<insert date>>
Trial Completion Date: <<insert date>>
Final Report Submission: <<insert date>>

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

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