APPLICATION NUMBER:

125545Orig1s000

OTHER ACTION LETTERS
BLA 125545

Hospira Inc., a Pfizer company
Attention: Tracy Dianis
Director, Global Regulatory Affairs Biologics
275 N. Field Drive, Building H2
Lake Forest, IL 60045

Dear Ms. Dianis:

Please refer to your Biologics License Application (BLA) dated December 16, 2014, received December 16, 2014, and your amendments, submitted under section 351(k) of the Public Health Service Act for “Epoetin Hospira”.

We acknowledge receipt of your amendment dated December 22, 2016, which constituted a complete response to our October 16, 2015, action letter.

We also acknowledge receipt of your amendment dated June 2, 2017, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During a recent inspection of the Hospira, Inc. (FEI #1925262) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

**CARTON AND CONTAINER LABELING**

We acknowledge receipt of your container labels and carton labeling submission dated and received December 22, 2016. We reserve comment on the proposed container labels and carton labeling until the application is otherwise adequate.

**MEDICATION GUIDE**

We reserve comment on the proposed labeling until the application is otherwise adequate.

**PROPRIETARY NAME**

Please refer to correspondence dated March 20, 2017 which addresses the proposed proprietary name, Retacrit. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

We acknowledge receipt of your submission dated January 23, 2017 of a revised proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for “Epoetin Hospira” to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

**SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.
   - Present tabulations of the new safety data combined with the original BLA data.
• Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

6. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Drug Substance
1. The data provided in response to FDA Comment 2 (sequence 0057 dated May 22, 2017) do not address microbial control during storage of the used during the drug substance (DS) manufacturing process. Complete a storage verification study for the used in the “Epoetin Hospira” DS manufacturing process, to include . Update section 3.2.S.2.5 accordingly.

Drug Product
2. In-process endotoxin testing was implemented at the sampling point ; however, action limits have not been provided. Establish an in-process endotoxin action limit for the step of “Epoetin Hospira” drug product manufacturing process based on 20 lots per dose strength. Update section 3.2.P.3.3 and 3.2.P.3.4 accordingly.

3. In-process bioburden testing was implemented at the sampling point ; however, action limits have not been provided. Establish an in-process bioburden action limit for the...
The endotoxin spike recovery study for “Epoetin Hospira” drug product held at 2-8°C, presented in section 3.2.P.5.3, is incomplete. Additional studies are necessary to ensure that endotoxin can be detected in “Epoetin Hospira” drug product. These additional studies should be conducted to show that at least 50% of the spiked endotoxin in the drug product can be detected by USP <85>. Quantify the amount of recovered endotoxin from each sample by titration to an endpoint using the gel clot method (see USP <85>). This is independent of the ability to detect within 2-fold of the detection limit (λ), which you have shown. Include a range of dilutions of the standard endotoxin, prepared prior to spiking undiluted product, that cover the range of endotoxin concentrations used in the standard series in water. The endotoxin recovery levels can be calculated based on the theoretical spike level or the LAL reagent water controls. Two consecutive and consistent data points (that is, within or outside the accepted range of 50-200% recovery) should be obtained for data analysis. Include results from the negative control (LAL reagent water) and time zero. A bracketing approach including representative lots of 2000 U/mL, 10,000 U/mL and 40,000 U/mL “Epoetin Hospira” is acceptable. Should low endotoxin recovery (LER) be observed, provide for an alternative release testing strategy.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "RESUBMISSION" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, “Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants,” November 2015 at https://www.fda.gov/downloads/drugs/guidances/ucm345649.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.
If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
06/21/2017
Dear Ms. Dianis:

Please refer to your Biologics License Application (BLA) dated December 16, 2014, received December 16, 2014, submitted under section 351(k) of the Public Health Service Act for “Epoetin Hospira.”

We also refer to your amendments dated January 16, 20, 23, 27, 28, February 06, 13, 18, 19, 20, March 2, 4, 6, 13, April 15, 16, 20, 29, May 2, 7, 22, 29, June 12, 29, July 2, 9 (Document Number 28), 20, and 27, 2015.

We also acknowledge receipt of your amendments dated July 9 (Document Number 29) and August 28, 2015, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**CLINICAL**

We have identified Good Clinical Practice (GCP) compliance issues with clinical studies EPOE-10-01 and EPOE-10-13. We also note that the BLA submission did not include complete auditing reports for the clinical sites for studies EPOE-10-01 and EPOE-10-13. Hence, the final analysis populations to support the demonstration of no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit cannot be determined based on the information provided in the BLA submission.

In order to address this deficiency, you will need to submit the following:

A. Full auditing reports for studies EPOE-10-01 and EPOE-10-13. The reports must include a description of the GCP compliance issues that you identified and measures taken to address the GCP compliance issues. For sites closed due to GCP compliance issues, you must include the details of the GCP compliance issues.
B. Additional sensitivity analyses for efficacy and safety that excludes the patients from sites closed due to GCP compliance issues. You will need to submit amended clinical study reports and datasets for studies EPOE-10-01 and EPOE-10-13.

**PRODUCT QUALITY**

**Analytical Similarity**

1. Your analytical similarity assessment shows that “Epoetin Hospira” drug product has approximately 4% higher erythropoietin content as compared to US-licensed Epogen/Procrit. This difference in erythropoietin content raises concerns regarding exposure when the proposed erythropoietin content release specification for your drug product are considered. An ~4% difference in erythropoietin content between “Epoetin Hospira” and the reference product combined with the proposed release acceptance criterion of ±90% for the erythropoietin content could potentially allow for an unacceptably large difference between the two products. You previously indicated that the failed legacy PK study (EPOE-10-08) may have resulted from differences in erythropoietin content of approximately 10% between “Epoetin Hospira” and the US-licensed reference product. Thus, while revising the acceptance criteria for the erythropoietin content of your drug product is necessary, revised erythropoietin content specifications alone will not be sufficient to address the concerns related to exposure.

To address the differences in erythropoietin content between your proposed product and the reference product, you should adjust the erythropoietin content of “Epoetin Hospira” drug product to be in agreement with the erythropoietin content of the US-licensed reference product that you determined in your analytical similarity assessment. To support the adjusted drug product formulation, you should evaluate the impact of adjusting erythropoietin content on other process and product parameters, including an assessment of in-vivo and in-vitro potency. In addition, you should tighten the erythropoietin content release and stability specification for “Epoetin Hospira” drug product to a more appropriate range, and provide a justification for the revised acceptance criterion.

2. Inconsistencies were noted in the information provided in your 351 (k) BLA regarding the “Epoetin Hospira” drug product lots used in the single dose PK/PD similarity study, EPOE-12-02. In amendment 20 to the BLA received on May 4, 2015, you stated that “Epoetin Hospira” lot CL2-309 was used for PK/PD study EPOE-12-02. However, in section 3.2. P.2 Pharmaceutical Development (page 31), you listed lots CL1-044, CL1-048 and CL1-438 as the drug product (“DP”) lots used in PK/PD study EPOE-12-02. Your analytical similarity assessment suggested that lots CL1-044, CL1-048 and CL1-438 have different protein content than other “Epoetin Hospira” DP lots including lot CL2-309. Thus, it is not clear which “Epoetin Hospira” lots were used in this comparative study. Clarify the “Epoetin Hospira” lots used in the PK/PD similarity study EPOE-12-02.

3. Figure 1 in Section 3.2.R.5.6.4 of your 351(k) BLA provides representative dose-response curves for the in vivo bioassay comparing “Epoetin Hospira” and the US-licensed reference product. The data used to plot the curves were not provided. Our review of these plots suggested that the dose response curves for the two products appeared to be generated from
an identical dataset, which raised questions regarding the accuracy and identity of the data used to generate them. During inspection of the drug substance manufacturing facility conducted on [date], we evaluated primary analytical similarity data, including the in-vivo biological activity data provided by representatives from Hospira. At that time, Hospira confirmed that the same dataset was inadvertently used to generate the representative in vivo biological activity plots for “Epoetin Hospira” and the US-licensed reference product and provided records of the correct datasets. Update your submission with the correct primary data and plots for the representative in-vivo biological activity data described in section 3.2.R.5.6.4.

4. The chromatograms for native N-linked glycan analysis of “Epoetin Hospira” drug substance (e.g. Figure 47, Section 3.2.S.3.1) obtained by High Performance Anion Exchange Chromatography with Pulsed Amperometric Detection (HPAEC-PAD) show unlabeled peaks between 52 and 60 min. In the HPAEC-PAD method validation report, you refer to these peaks as “pentasialylated” species; however no additional information was provided regarding the origin and identity of these species and whether they are observed in the US-licensed reference product. Provide data to support the identity of these species. In addition, provide data for the analysis of native N-linked glycans in the reference product by HPAEC-PAD and address whether these “pentasialylated” species are present in the US-licensed reference product.

5. The trypsin peptide map of “deformulated” Epogen (Figure 2, Section 3.2.R.5.6.1.1) shows small peaks between 21 and 23 minutes that are not observed in “Epoetin Hospira”. Please clarify the identity of these peaks. In addition, comparison of the representative “Epoetin Hospira” trypsin peptide maps in Section 3.2.R.5.6.1.1 (Figures 1 and 2) to the peptide maps of “Epoetin Hospira” Drug substance (DS) lots 410340 and 410637 in the method qualification report (Figure 1 in Report LF-194-R-222-14) shows differences in peak intensities, resolution and retention times that suggest differences in method performance between the qualified method and the method used in the similarity assessment. Please explain the differences in peak intensities, resolution, and retention times observed between the “Epoetin Hospira” trypsin peptide maps provided in the method qualification report and in Section 3.2.R.5.6.1.1.

Drug Substance

6. Characterization of process-related impurities in “Epoetin Hospira” drug substance (“DS”) detected the presence of an olfactory receptor protein from Cricetulus griseus (Chinese hamster). This protein was detected as a low abundance early eluting peak by RP-HPLC. The identity of this species was confirmed by LC-MS tryptic peptide mapping. You reported that the levels of this impurity in 13 “Epoetin Hospira” drug substance lots ranged from 0.2 to 0.3% by RP-HPLC. Provide data to demonstrate that the host cell protein (HCP) assay used to quantify HCP as a release method of “Epoetin Hospira” drug substance is able to detect and quantify the olfactory receptor protein detected by RP-HPLC.

7. Based on the information provided throughout your 351(k) BLA, we are unable to determine your final designation of several product related species identified in ‘Epoetin Hospira” (e.g.
Asn deamidation, and Asp isomerization species) as either product-related substances or product-related impurities. In Table 1 of Section 3.2.S.3.2, you stated that “product related species are assigned as product related impurities pending completion of studies to evaluate the bioactivity of samples...”. Provide information as to whether the product related species identified in “Epoetin Hospira” under acceptable conditions of use, storage, and potential excursions are product-related substances or product-related impurities. Data to support their designation as product-related substances or product-related impurities based on both biological activity and safety should also be provided.

8. In Section S.2.S.2.5 of the BLA, you provided the process performance qualification (PPQ) results for the five PPQ lots. One of the lots, lot 410638 showed lower production yield starting at the [step] step and in subsequent downstream manufacturing steps. At the [stage], this lot had approximately [percentage] lower protein content compared to the other four PPQ lots. While lower protein content may not impact product quality, it may be a measure of process consistency. Provide clarification regarding the root cause of the low product yield of lot 410638 and provide a justification as to why the results from your PPQ exercise, with respect to product yield are supportive of consistent manufacture.

9. Your proposed action limit for controlling [parameter] at different steps of the drug substance upstream and downstream manufacturing processes is “report results”. This action limit does not allow adequate control of [parameter]. Revise your action limit to define a range of [reference] that will ensure control and consistency of protein content in the drug substance manufacturing process.

10. For all the [steps] involved in the manufacture of “Epoetin Hospira” drug substance including [steps], you state that alternative or equivalent [parameters] from those listed in your 351(k) BLA may be used. The identity of the alternative/equivalent [parameters] was not stated and it is not clear whether they were validated for use in the “Epoetin Hospira” drug substance manufacturing process. In addition, for the [step], the master and executed batch records submitted in your 351(k) BLA suggest that there are additional [parameters] used for this step that are not listed in the description of the manufacturing process. For example, page 364 of the executed batch record for lot 410637 shows a list of [parameters] some of which are not discussed in your description of the manufacturing process. Clarify the [parameters] used in each step of the manufacturing process and provide information as to whether they were validated for use in the manufacture of “Epoetin Hospira” drug substance.

11. For qualification of future working cell banks (WCB), you propose to perform functional testing of the new working cell bank [step] of the drug substance manufacturing process. This testing is insufficient to confirm the suitability of the new working cell bank for manufacture of “Epoetin Hospira” drug substance. Following the manufacture of a new WCB, at least one lot of “Epoetin Hospira” drug substance should be manufactured and characterized to confirm the suitability of the new WCB. Revise your qualification protocol for qualification of future WCBs to include the manufacture and
complete characterization of at least one lot of “Epoetin Hospira” drug substance to confirm the suitability of future WCBs.

12. The drug substance manufacturing process allows the acceptance criteria for concurrent validation of the step are inadequate because the proposed acceptance criterion of ≤ is inconsistent with the drug substance release specification of total by (NMT %). This would result in drug substance lots failing the release specification. Revise your acceptance criteria for validation to be consistent with the release specification of “Epoetin Hospira” drug substance and provide a justification for the revised criteria.

13. Concurrent validation of used in the “Epoetin Hospira’ DS manufacturing process at commercial scale is currently underway. Provide any finalized or interim validation reports for the at commercial scale, including trending data of the parameters evaluated.

14. In addition to reclassification of process parameters, you implemented additional changes to the drug substance manufacturing process following process validation. The changes included:

Provide trending lot release data for all quantitative quality attributes for all the drug substance lots manufactured to date to support your at commercial scale.

15. The small-scale studies used to support chemical stability of used in the manufacture of “Epoetin Hospira” drug substance are not adequate because the containers used for these studies, i.e., are not representative of the commercial scale containers. For example, the are not representative of the because the introduce an additional material not present in the commercial scale process. Provide chemical stability data to support chemical hold times of used in the manufacture of “Epoetin Hospira” drug substance using containers representative of commercial manufacture.

16. The protocols for annual requalification of the analytical reference standard and qualification of future analytical reference standards are deficient. Because this reference standard is used to calculate the erythropoietin content of the drug product using the RP-UPLC method, you
should specify how the standard is calibrated for erythropoietin content and how this value is verified over time. The re-qualification acceptance criteria of [blurred text] mg/mL for erythropoietin content may be acceptable provided the erythropoietin content is properly calibrated. Revise your protocol for qualification of the analytical reference standard to specify how the standard is calibrated for erythropoietin content and how this value is verified over time. In addition, the reference standard is used in the comparative acceptance criteria for DS and DP identity testing by trypsin peptide mapping and the gel based identity assays. Therefore, the qualification acceptance criteria for the identity of the analytical reference standard should be revised to state that no new species should be observed by these methods.

17. You state that the leachables risk assessment for the [blurred text] used to store your drug substance considered the manufacturer’s extractables data, the storage conditions of the DS, and the fact that the material of construction conforms to USP [blurred text]. However, you did not provide details on the risk assessment including the potential leachates and their toxicology assessment. Provide a detailed risk assessment of the potential leachables from the container closure components used to store “Epoetin Hospira” drug substance.

18. You state in your 351 (k) BLA that the [blurred text] used in the manufacture of “Epoetin Hospira” drug substance remains to be determined. Provide any finalized or interim validation reports for the [blurred text] at commercial scale.

19. In section 3.2.S.2.5, you provided a description of the scaled-down studies conducted to support the proposed [blurred text] used in the downstream drug substance manufacturing process. However, you did not provide the data or study reports from these studies. To support the proposed [blurred text], provide the results of the scaled-down studies, including control charts that show the trends of the measured attributes with the increasing number of [blurred text] step. In addition, for the [blurred text] steps validated for [blurred text] at small scale, please specify the number of [blurred text] prior to use in the [blurred text] experiments.

20. Section 3.2.S.2.1 of the 351 (k) BLA indicates that [blurred text] is the primary release and stability testing site of “Epoetin Hospira” drug substance, with the exception of the potency assay. [blurred text] is listed as an alternative stability testing site for “Epoetin Hospira” drug substance. The validation reports provided in your 351(k) BLA for the drug substance stability assays were generated by [blurred text]. Method validation and/or method transfer reports to [blurred text] were not provided. Provide method validation or method transfer reports to support use of all the relevant methods at [blurred text].

21. You propose to discontinue testing for the non-human sialic acid form N-Glycolylneuraminic acid (Neu5Gc) species in the drug substance because the species are observed in low quantities (<1.3%) in all drug substance lots tested to date. You classified Neu5Gc as a high criticality CQA due to its potential to elicit an immune response in humans. Your overall
control strategy does not include specific controls for these species. Provide a control strategy for Neu5Gc.

22. For assessment of adventitious agents in the unprocessed bulk, you used a 14 day in vitro virus assay (IVV) in place of an IVV 28 day assay that utilizes an additional amplification step for detection of slow growing viruses. The risk associated with use of the 14 day IVV assay is the inability of the assay to detect adventitious or endogenous agents that may replicate slowly in the assay’s indicator cell lines. Provide a risk assessment to evaluate the risk of using a 14-day assay instead of an extended assay to detect adventitious agents in your unprocessed bulk. The assessment should consider risks including, but not limited to, animal-sourced raw materials used in your manufacturing process, raw material testing requirements, the sensitivity of your assay to detect specific viruses that may have been introduced, and the consideration that growth of wild type viruses may be less robust compared to laboratory virus stocks accustomed to growth in cultured cells.

**Drug Product**

23. You propose to manufacture the 40,000 U/mL presentation on filling line in a batch size range of L using a L tank. Validation of the manufacturing process for the 40,000 U/mL presentation was conducted using three drug product lots manufactured at the L scale in a L tank on filling line. These process validation data support a L scale. However, it is not clear how these data support scales larger than L. Provide validation data to support the proposed batch size range of L for the 40,000 U/mL drug product presentation on filing line.

24. Validation of the drug product manufacturing process utilized a bracketing strategy for the 2000–10,000 U/mL presentations. Two lots each of the 3000 U/mL and 4000 U/mL drug product presentations were included in the validation exercise to assess process consistency and stability of the drug product. In your process validation report, the results obtained to demonstrate consistency for the 3000 and 4000 U/mL lots, i.e. the results of the Critical Process Parameters (CPP), In Process Controls (IPCs) and In Process Tests (IPTs) were not provided. It is not clear if these lots were evaluated for these parameters as stated in Table 3 of Section 3.2.P.3.5. Provide the CPPs, IPCs and IPTs results for the 3000 and 4000 U/mL lots included in the PPQ exercise.

25. The protocol provided in Section 3.2.P.5.5 of the 351 (k) BLA for qualifying the performance of the commercial transportation of drug product includes evaluation of two parameters; temperature and physical integrity of the shipment. This protocol is deficient because it does not include assessment of product quality. Revise the commercial shipping validation protocol to include assessment of product quality.

26. The information provided in your 351 (k) BLA indicates that all drug product release and stability testing except testing for endotoxins, sterility and potency, is conducted at L. The validation report for the trypsin peptide mapping method used for analyzing the oxidized species in drug product during release and stability monitoring (method validation report LF-194-R-251-10) indicates that validation of the method was
conducted by Hospira. Therefore, we are unable to determine if the method was validated for its intended use at use of this method at

27. The results of your compatibility study of “Epoetin Hospira” drug product with plastic syringes from different vendors showed a significant increase in sub-visible particles when syringes are used. We are concerned about the increased levels of sub-visible particles when syringes are used due to potential link between sub-visible particles and safety, particularly immunogenicity. Provide justification to support the use of syringes. In addition, in this study you evaluated the compatibility of “Epoetin Hospira” drug product with plastic syringes ranging in volume from 1 mL to 3 mL. The extractable/deliverable volume data used to support the fill of your drug product were based on extractable volume using a 1.5 mL syringe with a low void volume. It is unclear if a 3 mL syringe will deliver the appropriate volume for accurate dosing. If syringes larger than 1.5 mL will be used to deliver your drug product, you should provide extractable volume data from the syringe volume sizes that you proposed for use. Consider revising your product labeling to include specific information that will ensure safe use of your product.

**Drug Substance and Drug Product**

28. Revise your DS and DP post-approval stability protocols to include testing of pH. Consider including additional purity tests (such as SDS-PAGE) in the post approval stability protocols for DS and DP. Measurement of pH and additional purity tests may provide information not otherwise provided by the proposed purity/impurity assays.

29. Revise your release and stability specifications for “Epoetin Hospira” DS and DP to address the following:

   a. Your proposed release and stability acceptance criteria for the potency of the DS of U/mg) are not supported by your clinical and manufacturing experience and do not consider the results from the analysis of the reference product. The specific activities observed for your clinical and commercial DS lots ranged from 112,000 – 133,000 U/mg. For the reference product, the in vitro specific activity results also ranged from 112 – 133 U/µg (112000 – 133000 U/mg). Revise your release and stability specifications for potency of DS to be consistent with the clinical and manufacturing experience of your product and with your analysis of the reference product.

   b. The “Epoetin Hospira” DP release and stability specification for potency should also be evaluated following adjustment of the erythropoietin content in your DP. Determination of appropriate potency acceptance criteria should take into consideration the results obtained from your analysis of the reference product.

   c. The impurities assessment in Section 3.2.S.3.2 of your 351(k) BLA using both SEC and SV-AUC suggest that SEC may underestimate the levels of dimers and HMWS in your product. The average level of dimers determined by SEC in “Epoetin Hospira” DS was 0.2±0.1% and HMWS larger than the dimer were not detected. Assessment of HMWS by SV-AUC shows results ranging from 0.7 – 2.6% for dimers.
and up to 0.3% for HMWS larger than the dimer. SEC is used for release and stability testing of DS and DP. SEC is also used to establish the % HMWS standard used in the Western blot method. You should optimize the SEC used in release and stability testing of DS and DP or provide data to support that SEC provides an accurate assessment of dimers and HMW species. In addition, provide data to support that the amount of HMWS species of the % HMWS standard used in the Western blot method is accurate.

d. The DS and/or DP release acceptance criteria for your identity assays including trypsin peptide mapping and the gel-based methods are not adequate because they do not address the presence of new peaks/bands that are not observed in the reference standard. You should revise your identity assays SOPs to state that no new peaks/bands should be present in the peptide maps and gels and provide a definition of a new peak/band.

e. Your proposed release and stability acceptance criterion for the pH of “Epoetin Hospira” DS is not supported by your clinical and manufacturing experience. Although your development studies showed that the DS is stable at significantly lower pH values, the pH observed in your clinical and proposed commercial DS lots ranged from 7.5 – 7.8. Revise the pH release and stability specifications for ‘Epoetin Hospira” DS to reflect your clinical and manufacturing experience.

f. Analysis of erythropoietin content in “Epoetin Hospira” by RP-UPLC (Method ATM-0813-4) shows a single main peak between 22 and 26 minutes with a tailing shoulder, which is integrated with the main peak for the determination of erythropoietin content. The identity of the tailing shoulder is not addressed in your 351 (k) BLA application. Clarify the identity of the species in the shoulder peak.

g. Your proposed DP release and stability acceptance criterion of % for Met 54 oxidation for all strengths is not supported by the clinical and manufacturing experience. Revise the DP release and stability specifications for Met 54 oxidation to reflect your clinical and manufacturing experience. You may need to establish different acceptance criteria for release and stability, and for the different strengths.

h. The “Epoetin Hospira” DS release and stability acceptance criteria for N-linked Native glycans by HPAEC-PAD and isoform distribution by Capillary Zone Electrophoresis (CZE) are generally wider than your clinical and manufacturing experience and may potentially allow for combinations of N-linked native glycans and charged isoform distribution levels that may be different from those observed in your clinical lots and in the analysis of the reference product. Revise your DS release and stability acceptance criteria for N-linked native glycans by HPAEC-PAD and isoform distribution by CZE to be consistent with your clinical and manufacturing experience and with the results of the analysis of the reference product.

i. The proposed release acceptance criterion for sialic acid content of NLT % mol/mol is not supported by your clinical and manufacturing experience and the results from the analysis of the reference product. Revise your release acceptance criteria for sialic acid content for “Epoetin Hospira” DS to be consistent with your clinical and
manufacturing experience and with the results of the analysis of the reference product.

j. Your release and stability specification for extractable volume of “Epoetin Hospira” DP is \( mL \). Revise your acceptance criterion for extractable volume to include two decimal places. In addition, specify the rounding procedures applied to extractable volume data.

k. Describe your control strategy for the Cys29-Cys33 trisulfide species and the N-linked glycan lactosamine repeats in “Epoetin Hospira” DS and DP.

30. Section 3.2.P.6 of your 351(k) BLA describes the approach used to establish and qualify the Hospira internal primary and secondary biological reference standards PBRS-EPO-101 and BRS-EPO-101, respectively. Please address the following comments related to the information provided in this section:

a. You described the approach used to establish and qualify BRS-EPO-101 and align the potency results of “Epoetin Hospira” measured against International Biological Reference Preparation 3 (BRP3) in IU/mL with US-licensed reference product labeled potency in U/mL. This approach relies on the premise that the specific activity of “Epoetin Hospira” and the US-licensed reference product measured both in U/\( \mu \)g and IU/\( \mu \)g is the same. You provided data supporting that the in-vitro specific activity measured in U/\( \mu \)g is the same in both products. However, we are unable to locate the data in your 351 (k) BLA that supports the claim that in vitro specific activity measured in IU/\( \mu \)g between the two products is the same.

In the November 2012 Type C meeting package for IND 100685, you showed that there were statistically significant differences in in vitro specific activity (IU/\( \mu \)g) between “Epoetin Hospira” drug product formulated based on erythropoietin content and the US-licensed reference product. You attributed these differences to an overestimation of the erythropoietin content in the US-licensed reference product due to residual HSA and provided model adjusted specific activity data that accounted for the contribution of residual HSA. We communicated at that meeting and in a CMC post-meeting comment to the June 12, 2014 Type 3 BPD meeting minutes that we do not agree with the use of model adjusted data to quantify erythropoietin content.

To support the use of BRS-EPO-101 and PBRS-EPO-101 as bioassay reference standards and any potency conversions from IU to U, provide data from the analysis of a sufficient number of “Epoetin Hospira” and US-licensed reference product lots to demonstrate that in vitro specific activity of the two products experimentally measured in IU/\( \mu \)g is the same. A comparison of specific activity in IU/\( \mu \)g eliminates any biases that could result from the assumptions made and subsequent manipulation/adjustment of the data to obtain bioactivity results in Units.

b. You stated in your 351(k) BLA that you conducted in vitro potency testing against the USP Erythropoietin reference standard for bioassays and the results obtained confirm that the USP/WHO international Unit (IU) is different from the U.S. Amgen
Unit (U); however these data were not included in your 351(k) BLA. To further support your claim that the IU is different from the Amgen Unit, provide the results from this study and discuss how the results obtained with the USP Erythropoietin reference standard in IU compare to those obtained with BRP3 in IU.

c. You intend to use BRS-EPO-101 to calculate the potency of “Epoetin Hospira” drug substance and drug product. Accurate and precise determination of the declared erythropoietin content and declared potency of BRS-EPO-101 and PBRS-EPO-101 is important to prevent drift in these attributes of the reference standard and your product over time. BRS-EPO-101 (and by association PBRS-EPO-101) has a theoretically defined potency of \( \text{U/mL} \), which was based on an erythropoietin content of \( \mu\text{g/mL} \). You recently determined that the defined potency of the BRS-EPO-101 should be \( \text{U/mL} \) based on a re-measured erythropoietin content of \( \mu\text{g/mL} \) using a more accurate method (RP-UPLC). You determined that the \( \% \) difference in biological activity is a minor difference and therefore retained the defined potency of \( \text{U/mL} \). We do not agree with your approach of not correcting the defined potency of your reference standard because the conversion factor from IU to U and the qualification of future biological reference standards relies on data obtained using this value. Therefore, you should revise the defined potency of BRS-EPO-101 and PBRS-EPO-101.

d. To establish an IU to U conversion factor for use in evaluating historical potency data generated in IU, you divided the in vitro potency of US-licensed reference product measured against BRS-EPO-101 (in Units) by the in vitro potency measured against BRP3 (in IU). An alternative approach would be to divide the potency of BRS-EPO-101 in Units (measured against labeled US-licensed reference product) by the potency of BRS-EPO-101 in IU (measured against BRP3). The second scenario eliminates the use of any theoretically defined potency (\( \text{U/mL} \)) for BRS-EPO-101. In addition, the data you provided in Tables 5, 6, and 7 of section 3.2.P.6 of your BLA suggest that the second scenario may result in a slightly different IU to U conversion factor. Accurate determination of the IU to U conversion factor is important to ensure that the potency data generated against BRP3 in IU is accurately converted to Units. Please clarify why the first scenario was chosen and if you choose not to use the proposed second scenario, provide a scientific justification as to why you think it is not appropriate.

e. Update tables 5 (in vitro potency), 6 (receptor binding), and 7 (in vivo potency) of the biological reference standards document in Section 3.2.P.6, to include the corresponding specific activity and the erythropoietin content values.

f. The qualification protocol for future biological reference standards (BRS) is inadequate because the acceptance criteria do not ensure adequate control of quality attributes of future reference standards and prevent drift over time. For example, the acceptance criteria for potency and erythropoietin content of \( \% \), respectively are too wide and should be revised to more stringent criteria. In addition, clarify whether the potency of future BRS will be determined based on that
of PBRS-EPO-101 or whether it will be defined based on the measured erythropoietin content.

g. You did not provide protocols to monitor stability and requalification (if applicable) of PBRS-EPO-101 and BRS-EPO-101. Please provide stability and requalification protocols for these and future reference standards. The protocols should include but not limited to testing parameters, frequency of testing, and acceptance criteria.

h. You prepared two assay control samples for use in the system suitability evaluation of the in vitro cell based assay and receptor binding. You stated that the expected potencies of these control samples are 80% and 100% of a 10,000 U/mL sample i.e. 8000 U/mL and 10,000 U/mL, respectively. Please clarify whether the potencies of the control samples are experimentally determined or defined based on the biological reference standard potency.

Microbiology

Drug Substance:

1. The ________ (b) (4) in the DS manufacturing process is not monitored for bioburden and endotoxin. Monitor and establish bioburden and endotoxin limits at the ________ (b) (4) process.

2. The ________ (b) (4) bioburden limits at the ________ (b) (4) step are high and should be re-adjusted to reflect process capabilities. Re-adjust the bioburden limits from ≥ ________ (b) (4) CFU/10 mL to ≥ ________ (b) (4) CFU/10 mL. In addition, re-adjust the ________ (b) (4) limits for bioburden in the ________ (b) (4) from ≥ ________ (b) (4) CFU/10 mL to ≥ ________ (b) (4) CFU/10 mL.

3. The bioburden action limits for the ________ (b) (4) are the same throughout the process and do not reflect the capabilities of the ________ (b) (4) as the process proceeds toward the ________ (b) (4). Re-evaluate and re-adjust the bioburden and endotoxin in-process action limits to reflect process capabilities after the execution of 30 lots at scale.

4. Only one batch was completed at scale to validate the ________ (b) (4) step. Conduct another two runs to support the established hold conditions of ________ (b) (4).

5. Only one lot was used to qualify the method for the ________ (b) (4) in-process samples and for the ________ (b) (4) (S.4.3). Submit the qualification data from two additional batches of in-process samples and for the ________ (b) (4).

6. Recent studies indicate that USP <85> Bacterial Endotoxin Test may underestimate the amount of endotoxin in formulations containing certain excipients such as phosphate and
polysorbate (Chen, J. 2013 PDA Annual; Williams and Chen 2013, PDA Letter; Meeting; Hughes, et al., BioPharma Asia, 4/2, 2015). The finished drug product are formulated with phosphate and polysorbate 20 and are likely to be affected by low endotoxin recovery. In order to assess the validity of the USP <85> Kinetic Turbidimetric Assay, conduct a study to assess recoverability of endotoxin from the spiked with known amounts of endotoxin (RSE or CSE).

**Drug Product:**

1. Incomplete information was submitted for container closure integrity validation testing. Provide the following additional details for the microbial ingress and dye immersion tests:
   a. To assess the sensitivity of both tests, perform a study to confirm that both test methods are capable of detecting small defects that could allow microbial ingress. Perform the studies with positive controls that have defect sizes of ≤ 20 microns and test containers subjected to vacuum and/or pressure. Additionally, for the dye immersion test, use an analytical method other than visual analysis for detection of dye in test units because visual analysis is not considered a reproducible and accurate analytical method.
   b. For the dye immersion test, indicate the length of time that the test and positive control vials were immersed in the dye solution and exposed to vacuum conditions.

2. Incomplete information was submitted for environmental monitoring of the manufacturing areas for the drug product. Respond to the following comments:
   a. Provide the media and incubation conditions used for environmental monitoring of microorganisms in air, on surfaces, and on personnel in the Class areas.
   b. It is stated that results exceeding the alert and action levels for surfaces, air, and personnel prompt an investigation per the SOP X-0332. However, details of this investigation, other than are not provided. Provide additional details regarding the actions taken during and as a result of an investigation when an environmental monitoring sample result exceeds the alert and/or action level.
   c. Indicate the alert and action levels established for bioburden and endotoxin of the that will be used in the compounding of the drug product. Additionally, indicate if there is a rotation of monitoring various points in the system, such that there is daily monitoring of at least one point.

3. Regarding the studies for monitoring the in-process samples for bioburden, it is not clear whether the 40,000 U/mL formulation used in the method validation for USP <61> Microbial Enumeration Tests is representative of the 40,000 U/mL commercial product formulation. In addition, data supporting the designation of the 40,000 U/mL product formulation as worst-case for microbial recovery was not provided. Respond to the following comments:
   a. Report MP-194-R-008-14, Attachment 1 in Section R.3 indicates that the 40,000 U/mL formulation had a revision in the content of sodium chloride and sodium phosphate. Clarify whether the 40,000 U/mL formulation used in the method validation for USP <61> Microbial Enumeration Tests is the exact same formulation as that to be used for
commercial production. If the formulation used for validation of the enumeration testing has any difference in concentration of sodium chloride or sodium phosphate from what will be used in commercial production, then provide justification for not using the revised formulation. Although the osmolality may not have changed, the differences in the salts could affect microbial growth. Additionally describe studies performed to determine that the slight changes in salt concentration and type do not affect microbial recovery.

b. Report MP-194-R-008-14, Attachment 1 in Section R.3 indicates that the concentration of sodium chloride and sodium phosphate in all drug product formulations (2000, 3000, 4000, 10,000, and 40,000 U/mL) varies, such that the formulation with the higher concentration of drug substance has a proportionally lower concentration of the salts and the lower concentration has a proportionally higher concentration of salts. Further, it was proposed that the highest concentration of the drug substance would be the worst-case. Provide data from studies performed to determine whether microbial recovery for the USP <61> Enumerations Test differs depending on the product formulation.
8. The release testing strategy for pyrogen and/or endotoxin testing of finished product is not clearly described. Section P.5.1 states that the finished product release specification for all configurations of the drug product includes the Rabbit Pyrogen Test conducted per USP <151>. However, this test is not included on the certificates of analysis for the commercial scale drug product batches provided in Section P.5.4. Clarify whether the commercial finished drug product will be subject to both USP <85> and <151> testing prior to release. Additionally, statements in Section P.5.6 suggest that rabbit testing will only be performed as an interim test. Explain how interim testing will be implemented.

9. Incomplete information was provided for the validation of the USP <71> Sterility Test for finished product release. Respond to the following comments:

a. Report MP-194-R-001-13, Attachment 1 in Section R.3 indicates that the 40,000 U/mL formulation had a revision in the content of sodium chloride and sodium phosphate. Clarify whether the 40,000 U/mL formulation used in the bacteriostasis/fungistasis validation for the USP <71> Sterility Test is the exact same formulation as that to be used for commercial production. If the formulation used for bacteriostasis/fungistasis testing
has any difference in concentration of sodium chloride or sodium phosphate from what will be used in commercial production, then provide justification for not using the revised formulation. Additionally, describe studies performed to determine that the slight changes in salt concentration and type do not affect microbial recovery.

b. Report MP-194-R-001-13, Attachment 1 in Section R.3 indicates that the concentration of sodium chloride and sodium phosphate in all drug product formulations (2000, 3000, 4000, 10,000, and 40,000 U/mL) varies, such that the formulation with the higher concentration of drug substance has a proportionally lower concentration of the salts and the lower concentration has a proportionally higher concentration of salts. Further, it was proposed that the highest concentration of the drug substance would be the worst-case. Provide data from studies performed to determine whether microbial recovery of the USP <71> Sterility Test differs depending on the product formulation.

10. Incomplete information was submitted for qualification of the USP <85> Bacterial Endotoxins Test. Respond to the following comments:

a. Method Validation report MP-194-R-001-09 (p. 5 of 35) states that “a minor revision to the calculated amount of salts added to the 40,000 U/mL formulation was made post-validation; however, this change does not impact the validity of this microbiological validation.” Confirm that the revised and currently proposed 40,000 U/mL formulation (that will be used in commercial production) was used in the August 2012 and March 2014 inhibition/enhancement studies described on page 10 of 35 of the report.

b. The effect of hold times during manufacturing on the recovery of endotoxin from the finished product was not assessed. Provide endotoxin recovery data from studies performed by spiking a known amount of endotoxin standard (RSE or CSE) into undiluted finished drug product and then testing for recoverable endotoxin at various points. Perform these studies with the 2000 U/mL, 10,000 U/mL, and 40,000 U/mL formulations that were used in the inhibition and enhancement studies for validation of the bacterial endotoxin test. Use sample containers of similar composition to those that will be used during routine production.

11. Clarify the maximum patient dose listed in the package insert. Values of are indicated in the application. Additionally, clarify that the correct dose was used in the performance of the USP <151> rabbit pyrogen test.

12. The stability testing strategy for pyrogen and/or endotoxin testing of the finished product is not clearly described. The post-approval stability specification provided in Section P.8.2 includes both bacterial endotoxins testing per USP <85> and the rabbit pyrogen test per USP <151>. However, statements in Section P.5.6 suggest that rabbit testing will only be performed as an interim test. Explain how interim testing will be implemented.

13. Respond to the following comments regarding hold time validation and in-process bioburden sampling.

a. For the laboratory-scale hold time study, clarify whether the term (P.3.5, page 16 of 136) refers to
b. Clarify whether the bulk drug product sample taken immediately prior to [redacted] during commercial-scale [redacted] was collected upstream of both of the [redacted].

c. Clarify whether the bulk drug product sample taken immediately prior to [redacted] during commercial production will be collected upstream of [redacted]. In addition, clarify whether the bulk drug product will be sampled for [redacted] step during routine commercial production.

**Immunogenicity**

1. Regarding the radioimmunoprecipitation (RIP) screening and confirmatory assays:
   
a. In your July 9, 2015 response to an agency information request, you reported that you established fixed screening assay cut points based on the analysis of pre-dose study samples from chronic kidney disease (CKD) patients or healthy volunteers. We note that:
      
      1) You did not provide data showing that the mean and the variance of the negative controls are consistent across plates for the screening assay. Note that if means and variances are not similar amongst plates, the use of a fixed cut point is not appropriate.

      2) There was poor reproducibility between the results obtained for individual samples in the screening assay used to derive the cut point and the results obtained in the confirmatory assay for the same samples. Specifically, in most of the samples retested the % cpm was markedly reduced in the confirmatory assay without added competitor, as compared to the corresponding samples in the screening assays. This, together with the high percent reduction in binding required to confirm a sample as positive (52.1% inhibition for EPOE-10-01 and EPOE-10-13, 45.1% inhibition for EPOE-14-01) raises concerns about the reproducibility of the screening assay and the sensitivity of the confirmatory assay even when using a 99 percentile cut point.

      3) You validated the suitability of your assay using several dilutions of the positive control and demonstrated that the assay was capable of detecting low levels of your positive control (36 ng/ml). However, you used 1.2 µg/ml of the same control as your Low Positive suitability control (LPC) when establishing the assay cut point and testing the samples from study EPOE-10-01 and EPOE-10-13. This concentration is much higher than the FDA recommendation for suitability controls and does not ensure adequate assay performance during routine use. The more appropriate LPC concentration of 60 ng/ml determined during the 2014 re-validation was not used for the testing of ADA for studies EPOE-10-01 and EPOE-10-13.

To address the above deficiencies, you should:

   I. Confirm the on-board drug tolerance and matrix interference for the screening and confirmatory assays using adequate LPC concentrations for both “Epoetin Hospira” and US-licensed Epogen.

   II. Confirm the cut points for your screening and confirmatory assays using in-study samples from treatment naïve subjects.
a. Assay cut points should be confirmed separately for samples from patients with chronic kidney disease (CKD) and healthy volunteers. For the patients with CKD, include at least 50 samples from patients treated SC (EPOE-10-13) and 50 samples from patients treated IV (EPOE-10-01). For the healthy volunteers, include at least 40 samples from subjects treated SC (EPOE-14-01). Samples should be selected using a randomization process. The randomization process you suggested in the response to the IR dated June 3rd, 2015 is adequate but you should exclude samples from clinical sites that were not GCP compliant.

b. Retest your baseline samples in the presence and absence of competitor using appropriate suitability controls that ensure that your assay can identify samples with low levels of antibodies consistently.

c. Provide the raw data and statistical analysis for evaluation. Identify any samples that were excluded from the cut point calculations statistical outliers or baseline positive samples. If a fixed screening assay cut point is selected, provide a justification demonstrating that the mean and variance between runs and analysts is not statistically different.

d. Confirm the sensitivity of the assays using the new cut points.

e. Consider including several LPCs ranging from 60 ng to 300 ng to ensure that the true sensitivity of the assay is known.

III. Determine whether the study samples need to be rescreened for antibodies using adequate suitability controls that ensure the sensitivity of the assays used.

IV. All samples deemed positive in the screening assay should be tested in the confirmatory assay using the appropriate cut point, suitability controls and concentration of inhibiting drug.

V. All samples that confirm positive should be evaluated for titer and neutralizing activity.

2. Regarding the assay to detect neutralizing ADA:

a. You derived the cut point for the neutralizing antibody (NAB) assay from commercial samples that may have been collected and handled differently than those in your study. We note that you did not confirm the cut point using in-study samples and the differences noted above may affect the results and the interpretation of your NAB assay. Confirm the cut point of the NAB assay with at least 20 in-study samples from treatment naïve subjects. Provide the raw data in a table showing for each serum sample tested side by side the cell proliferation in the presence and absence of added erythropoietin. A 99% CI cut point is recommended to reduce the risk of false negative results. Provide the data and calculations that support the new cut point.

b. Proliferation of the TF-1 cell line can be affected by multiple molecules in patient serum (G-CSF, IL3, GM-CSF). We note that, in order to verify that serum concentrations of these molecules do not interfere with assay performance, you tested the effect of sera on TF-1 cell proliferation in the presence and absence of erythropoietin stimulation. Provide...
these results when reporting the neutralizing antibody assay data to facilitate interpretation.

3. For all samples that test positive for binding or neutralizing antibodies, provide an analysis of the correlation with observed PK, safety and efficacy signals for the subject.

**PRESCRIBING INFORMATION**

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

**CONTAINER LABEL AND CARTON LABELING**

We acknowledge receipt of your container labels and carton labeling submission dated December 15, 2014, that we received December 16, 2014. We reserve comment on the proposed container labels and carton labeling until the application is otherwise adequate.

**MEDICATION GUIDE**

We reserve comment on the proposed labeling until the application is otherwise adequate.

**PROPRIETARY NAME**

Please refer to correspondence dated, April 6, 2015, which addresses the proposed proprietary name, Retacrit. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

We acknowledge the submission of your proposed REMS on December 16, 2014, which contains We also acknowledge the submission of your proposed REMS audit plan on February 13, 2015. FDA will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.
SAFETY UPDATE

When you respond to the above deficiencies, you should include a safety update. You are advised to contact the Division of Hematology Products regarding the extent and format of your safety update prior to responding to this letter.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. We note the reported case of pure red cell aplasia (PRCA) in a patient who was treated with European (EU)-approved Retacrit. The significance of this finding related to your proposed “Epoetin Hospira” product is uncertain. We recommend that you provide a root-cause analysis, and provide additional details regarding the PRCA case within the context of the development program for “Epoetin Hospira”.

2. You use PRCA patient sera as a positive control in the validation of your immunogenicity assays. Describe the basis for selection of the “high” and “low” serum concentrations used in your studies.

3. Include the agreed initial Pediatric Study Plan (iPSP) with your resubmission to the 351(k) BLA.

Product Quality

4. The molecular weight of “Epoetin Hospira” drug substance reported in sections 3.2.S.1.2 and 3.2.S.1.3 is “approximately 30,400 Da”. It is not clear whether this value was experimentally determined or if it is based on the information from the US-licensed reference product labeling. Please clarify.

5. On May 29, 2015, you amended your 351 (k) BLA with up to 12 months of stability data for the 40,000 U/mL presentation stored under the proposed long-term storage conditions of 2 – 8°C. The shelf life of a product should be based on real time data for product stored under the recommended storage conditions. Thus, these stability data support a shelf life of 12 months for the 40,000U/mL presentation. If you propose to establish a longer shelf life for the 40,000 U/mL presentation, provide additional stability data generated under the long-term storage conditions.

6. The acceptable time for [time range] during drug product formulation is NLT [time limit] min. The [time range] time for PPQ lots ranged from [time range] min for line [product name] during DP manufacture to [time range]. Revise your range for [time range] during DP manufacture to establish an upper limit for [time limit].

7. In Section 3.2.P.7, you provided Hospira’s representative certificates of analysis for the DP container closure components received by Hospira. The certificates of analysis indicate an accept/reject rate of [percentage] for vial dimensions. Clarify the meaning of the “accept/reject rate of
and provide a justification as to why this is appropriate for your control of raw materials.

8. You state in your 351 (k) BLA in the post approval stability commitments section that testing beyond 60 months for “Epoetin Hospira” DS and 24 months for “Epoetin Hospira” DP may be performed on selected lots to generate data in support of increasing the “Epoetin Hospira” shelf life.” It is not clear if you plan to amend your 351 (k) BLA with protocols to extend the shelf-life of “Epoetin Hospira” DS and DP for approval. Please note that if you choose to submit protocols for extension of DS and DP shelf life to your 351 (k) BLA and the protocols are approved, the extension of shelf life may be reported in an annual report. Otherwise, you will have to submit a prior approval supplement to request extension of DS or DP shelf life.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, “Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants,” March 2013 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
10/16/2015