Cross-Discipline Team Leader Review

Date: see stamp date
From: R. Angelo de Claro, M.D.
Subject: Cross-Discipline Team Leader Review
NDA/BLA #: BLA 125545 (SDN 44)
Supplement #: Response to CR
Applicant: Hospira, Inc.
Date of Submission: 22 December 2016
BsUFA Goal Date: 22 June 2017

Nonproprietary Name: “Epoetin Hospira”*
Dosage forms / Strength: Injection, for intravenous or subcutaneous use
- Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL
Applicant’s Proposed Indication: Same as those approved for US-licensed Epogen/Procrit
Intended Population: Same as that intended for US-licensed Epogen/Procrit
Recommendation on Regulatory Action: Complete Response
Recommended Indication: Not applicable

* For purposes of this review, we generally refer to the proposed product by the descriptor “Epoetin Hospira,” FDA has not yet designated a nonproprietary name for Hospira’s proposed biosimilar product that includes a distinguishing suffix (see Final Guidance on Nonproprietary Naming of Biological Products).

Material Reviewed/Consulted

<table>
<thead>
<tr>
<th>Category</th>
<th>Team Members</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>Lori Ehrlich / R. Angelo de Claro</td>
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<tr>
<td>Statistical (Clinical)</td>
<td>Lola Luo / Yuan-li Shen</td>
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<td>Clinical Pharmacology</td>
<td>Vicky Hsu / Sarah Schrieber</td>
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<td>Pharmacology Toxicology</td>
<td>Natalie Simpson / Christopher Sheth</td>
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<td>Chemistry, Manufacturing, and</td>
<td>Application Team Lead: Maria-Teresa Gutierrez-Lugo</td>
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<td>Controls (CMC)</td>
<td>See CMC review for full review team</td>
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<td>Statistical (CMC)</td>
<td>Chao Wang / Meiyu Shen</td>
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<tr>
<td>OSI/DCCE</td>
<td>Anthony Orencia / Janice Pohlman</td>
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<td>OSE/DRISK</td>
<td>Naomi Redd / Elizabeth Everhart</td>
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Reference ID: 4113935
Reference ID: 4266940
1. Regulatory Recommendation

Regulatory Recommendation: Complete Response (CR)

Reason for Regulatory Recommendation: Inspection of Hospira, Inc. (FEI #1925262), the proposed drug product manufacturing facility, identified Good Manufacturing Practice (GMP) deficiencies, therefore, Division of Inspectional Assessment recommends withholding approval of this application. Issues in product quality microbiology (drug substance and drug product) were also identified.

Recommended Indications: Not applicable for applications that will receive a Complete Response

Overall Summary

The totality of the analytical data and publicly available information supports a demonstration of highly similar notwithstanding minor differences in clinically inactive components. Residual uncertainties in the analytical data including differences in glycosylation species and trisulfide species were adequately addressed by other data, including clinical data.

The clinical data, including PK, PD, efficacy, safety, and immunogenicity data, supports a demonstration of no clinically meaningful differences in terms of the safety, purity, and potency of the product.

Overall, the totality of the evidence supports a demonstration of biosimilarity between "Epoetin Hospira" and US-licensed Epogen/Procrit. Extrapolation to, and approval of "Epoetin Hospira" for, all indications for which US-licensed Epogen/Procrit is licensed is supported by the demonstration of biosimilarity and, among other information, the scientific understanding of the mechanism of action across indications.

Summary of FDA Review

Background. Section 351(k) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”

Chemistry, Manufacturing, and Controls. “Epoetin Hospira”, a proposed biosimilar to US-licensed Epogen/Procrit was evaluated and compared to US-licensed Epogen/Procrit using multiple orthogonal physicochemical and functional methods. The totality of the analytical similarity data and publicly available information support the conclusion that the two products are highly similar, notwithstanding minor differences in clinically inactive components.
data indicate that the amino acid sequences of “Epoetin Hospira” and US-licensed Epogen/Procrit are the same. The results from the analysis of the secondary and tertiary structures and the biological activity analyses met the predefined analytical similarity acceptance criteria. In addition, the stability profile of “Epoetin Hospira” was shown to be similar to that of US-licensed Epogen/Procrit with respect to degradation products and degradation pathways. Differences in the levels of some glycosylation species and higher levels of a Cys29-Cys33 trisulfide species were identified in “Epoetin Hospira”, however, these differences did not impact biological activity, in vitro, and in vivo specific activity. As noted in subsequent sections, the additional clinical studies confirm this assessment.

**Pharmacology/Toxicology.** The nonclinical pharmacology and toxicology data submitted demonstrate similar pharmacodynamic effects in dogs and the same target organs of toxicity in rats and dogs administered “Epoetin Hospira” or US-licensed Epogen/Procrit. Except in instances in rats with lower exposure to US-licensed Epogen/Procrit, exposure to “Epoetin Hospira” was generally lower in animals compared to US-licensed Epogen/Procrit after the dose on Day 1. However, the animal studies were not designed to support demonstration of biosimilarity.

**Immunogenicity.** Immunogenicity for erythropoietin is linked to the development of life-threatening pure red cell aplasia (PRCA). The incidence of immunogenicity for “Epoetin Hospira” and US-licensed Epogen/Procrit was compared in 3 multiple-dose, parallel-arm studies in 849 patients with chronic kidney disease (EPOE-10-01 and EPOE-10-13) and 129 healthy volunteers (HV) (EPOE-14-01). The results indicate similar rates and titers of anti-drug antibodies (ADA) for both products. No neutralizing ADA were detected in any of the clinical studies and no apparent impact of ADA on safety, pharmacokinetic, or pharmacodynamic endpoints were observed. Therefore, the data support a determination of no clinically meaningful differences in immunogenicity risk for “Epoetin Hospira” as compared to US-licensed Epogen/Procrit.

**Clinical Pharmacology.** Overall, the submitted clinical pharmacology studies adequately demonstrated similarity of PK and PD (reticulocyte count and hemoglobin level) between “Epoetin Hospira” and US-licensed Epogen/Procrit. Studies EPOE-12-02 and EPOE-14-01, conducted in healthy subjects using a subcutaneous administration route, are considered sufficiently sensitive to detect clinically significant differences in pharmacokinetics (PK) and pharmacodynamics (PD) (reticulocyte count and hemoglobin level) among the products. Single-dose PK and PD (reticulocyte count) and multiple-dose PD (hemoglobin level) similarity pre-specified margins were met. The demonstration of similar PK and PD (reticulocyte count and hemoglobin level) exposure supports a demonstration of no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit.

**Efficacy and Safety.** The Applicant submitted two comparative clinical studies (Study EPOE-10-13 and Study EPOE-10-01) that evaluated efficacy and safety endpoints in support of licensure of “Epoetin Hospira”. Both studies were randomized, double-blinded, parallel group studies that enrolled patients with chronic kidney disease on hemodialysis and receiving epoetin maintenance treatment with co-primary endpoints of difference between arms in mean weekly hemoglobin and mean weekly dose. Study EPOE-10-13 used the subcutaneous route of
administration, and Study EPOE-10-01 used the intravenous route of administration. FDA’s review of the data from these comparative clinical studies supports the Applicant’s conclusion that there are no clinically meaningful differences in efficacy and safety between “Epoetin Hospira” and US-licensed Epogen/Procrit.

**Extrapolation Across Indications.** The Applicant seeks licensure for all indications for which US-licensed Epogen/Procrit is licensed (listed in Introduction section above). The “Epoetin Hospira” clinical program, however, provides comparative clinical efficacy and safety data from a clinical program in patients with chronic kidney disease on hemodialysis. Scientific justification for extrapolation include the following considerations: same mechanism of action across indications, demonstration that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit based on extensive analytical characterization data, and demonstration that there are no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit based on clinical data on pharmacodynamics, pharmacokinetics, efficacy, safety, and immunogenicity.

**2. Background**

Hospira, Inc. (Applicant) submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for "Epoetin Hospira," a proposed biosimilar to US-licensed Epogen/Procrit\(^1\) (epoetin alfa) (BLA #103234).

The Applicant is seeking licensure of "Epoetin Hospira" for the same indications as approved for US-licensed Epogen/Procrit:

1) for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion

2) for the treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL

3) for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy

4) to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.


\(^1\) For certain figures and tables in this briefing document, the abbreviation “US-Epogen” or “US-Epogen/Procrit” may be used instead of “US-licensed Epogen/Procrit” due to space limitations.
The Applicant conducted the following clinical studies to support the application:

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<td>Subcutaneous</td>
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<td>Healthy subjects</td>
<td>100 U/kg</td>
<td>Single dose</td>
<td>PK and PD similarity (reticulocyte count)</td>
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<td>EPOE-14-01</td>
<td>Parallel</td>
<td>Subcutaneous</td>
<td>129</td>
<td>Healthy subjects</td>
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<td>PD similarity(Hb)</td>
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<td>EPOE-10-13</td>
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<td>Subcutaneous</td>
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<td>EPOE-10-01</td>
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<td>Intravenous</td>
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<td>Patients with CKD</td>
<td>Variable</td>
<td>1-3 times / week</td>
<td>Mean weekly Hb and Mean weekly dose</td>
</tr>
</tbody>
</table>

PK: pharmacokinetic, PD: pharmacodynamic, Hb: hemoglobin, CKD: chronic kidney disease

**Regulatory Background**

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was enacted as part the Affordable Care Act on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product (the “reference product”). This abbreviated licensure pathway under section 351(k) of the Public Health Service (PHS) Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data.

Section 351(k) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a “stand-alone” marketing application). The goal of a “stand-alone” development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and
clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that Applicants use a stepwise approach to developing the data and information needed. At each step, the Applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be analytically and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and, once the Applicant has established that the proposed biosimilar meets the analytical similarity prong of the biosimilarity standard, the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences. Additional data, such as nonclinical and/or clinical data, can then be tailored to address these residual uncertainty(-ies).

The ‘totality of the evidence’ submitted by the Applicant should be considered when evaluating whether an Applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

3. Product Quality

Source: CMC Review (Original and Response to CR)

CMC Team Recommendation: Complete Response

- Overall assessment

All of the product quality, microbiology, and immunogenicity CR issues described in the CR Letter dated October 16, 2015 were adequately addressed by the Applicant.

The analytical similarity data submitted by the Applicant support a conclusion that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit notwithstanding minor differences in clinically inactive components. The data also support that the proposed presentations of “Epoetin Hospira” have the same strength as the respective presentations of US-licensed Epogen/Procrit. The manufacturing data and information provided in the submission are sufficient to support a conclusion that the manufacturing process of “Epoetin Hospira” is well controlled and leads to a product that is safe, pure, and potent for the duration of the product shelf life.
However, the Division of Inspectional Assessment (DIA) recommends a Complete Response be issued to the Applicant based on the compliance status of Hospira, Inc. (FEI #1925262), the proposed “Epoetin Hospira” drug product manufacturing facility. Issues in product quality microbiology (drug substance and drug product) were also identified. The quality microbiology issues identified during the review of this 351(k) BLA are listed in the Action Letter as "Additional Comments" to be conveyed to the Applicant.

- General product quality considerations

The manufacturing processes and control strategy of “Epoetin Hospira” are sufficient to ensure drug safety and effectiveness for patients. However, a recent inspection of Hospira, Inc. (FEI #1925262), the proposed drug product facility identified Good Manufacturing Practice (GMP) deficiencies, therefore DIA recommends withholding approval of this application.

As part of a demonstration of biosimilarity, Hospira conducted analytical similarity studies. Fifty-four (54) lots of Epogen/Procrit, 35 lots of “Epoetin Hospira” drug product (DP), and 9 lots of “Epoetin Hospira” drug substance (DS) were evaluated, including lots used in the PK/PD similarity and additional clinical studies. This assessment was supported by comparative statistical analysis. To determine the comparative analyses that would be used to support similarity, quality attributes were ranked into categories of high, medium and low criticality using information about the importance of that attribute to product safety, potency, PK and immunogenicity. The sponsor then selected the two high criticality attributes most important for the mechanism of action of the product and evaluated their similarity using statistical equivalence testing. These attributes are referred as Tier 1 attributes. Per FDA advice, if a Tier 1 attribute was measured using more than one analytical method, results from only one of the methods need to be evaluated using statistical equivalence testing. Results from other attributes were assessed using descriptive statistics, comparison of “quality ranges” and comparison of graphical data Tier 2 and Tier 3 attributes, respectively.

FDA’s independent analysis using the Applicant’s data showed that attributes selected for Tier 1 analysis, in vivo biological activity and in vitro specific activity, passed the statistical equivalence test.

The totality of the analytical similarity support a conclusion that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit notwithstanding minor differences in clinically inactive components. The following residual uncertainties were identified but were adequately addressed by additional data, including clinical data:

1. Levels of some glycosylation species were different between “Epoetin Hospira” and the US-licensed Epogen/Procrit. Difference in glycosylation could potentially impact biological activity in vivo. However, the different levels of glycosylation
species do not preclude a conclusion that “Epoetin Hospira” and US-licensed Epogen/Procrit are highly similar because they did not result in observable differences in in vivo biological activity using a sensitive mouse assay. Data supporting the sensitivity of the mouse assay to changes in this attribute were provided by the Applicant.

2. Trisulfide species Cys29-Cys33, a product related substance that results from insertion of an extra sulfur atom into the Cys29-Cys33 disulfide bond in erythropoietin (EPO), was observed at 4.5% higher levels in “Epoetin Hospira” compared to US-licensed Epogen/Procrit. The potential impact of this difference is on EPO folding and therefore functional activity. However, the difference does not preclude a conclusion that “Epoetin Hospira” and US-licensed Epogen/Procrit are highly similar because analysis of “Epoetin Hospira” containing higher levels of Cys29-Cys33 trisulfide species did not result in differences in receptor binding, higher order structure, and biological activity as measured by multiple orthogonal methods.

Immunogenicity was assessed in four studies in HV and in patients with CKD dosed with the products by SC and IV administration. Three parallel designed studies, one in HV (EPOE-14-01) and two in patients with CKD (EPOE-10-01 and EPOE-10-13), were the most informative for immunogenicity assessment. The data from these studies indicated similar rates of treatment-induced anti-drug antibody (ADA) in the two subject populations. No neutralizing antibodies and no cases of PRCA were reported. These results indicate no increase in immunogenicity risk and support a conclusion that there are no clinical meaningful differences between “Epoetin-Hospira” and US-licensed Epogen/Procrit.

- Facilities review/inspection

A recent inspection of Hospira, Inc. (FEI #1925262), the proposed drug product facility, identified GMP deficiencies, therefore Division of Inspectional Assessment recommends withhold approval of this application.

- Other notable issues: None

**4. Clinical Microbiology**

Not applicable.

**5. Nonclinical Pharmacology and Toxicology**

*Source: Pharmacology and Toxicology Reviews (Original and Response to CR)*

**Pharmacology Toxicology Team Recommendation: Approval**
General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

“Epoetin Hospira” was compared head-to-head with US-licensed Epogen/Procrit in 13-week animal studies to assess the pharmacodynamics (PD), pharmacokinetics (PK), and toxicity of the products. A meaningful evaluation of the potential differences between “Epoetin Hospira” and US-licensed Epogen/Procrit at three times weekly doses of 150, 450, and 1500/900 IU/kg could only be conducted for the intravenous (IV) route in Beagle dogs. Meaningful comparisons could not be made in the comparative toxicology study in Sprague-Dawley rats evaluating the subcutaneous route (SC) of administration due to reduced exposure and PD activity in US-licensed Epogen-treated rats, which was also associated with a high incidence of neutralizing anti-drug antibody (ADA) development at Week 13.

The nonclinical pharmacology and toxicology data submitted demonstrate similar pharmacodynamic effects in dogs and the same target organs of toxicity in rats and dogs administered “Epoetin Hospira” or US-licensed Epogen/Procrit. Except in instances in rats with lower exposure to US-licensed Epogen/Procrit, exposure to “Epoetin Hospira” was generally lower in animals compared to US-licensed Epogen/Procrit after the dose on Day 1.

Other notable issues:

Pharmacology-toxicology team stated in their review dated 1 June 2017 that:

“... the animal studies should not be included along with the clinical and analytical similarity studies to support a demonstration of biosimilarity since the animal studies were designed and conducted prior to passage of the BPCI Act to support a stand-alone biologic 351 (a) BLA. This change in thinking has no major effect on the regulatory recommendation for approval, which like the previous review cycle, will still be based on clinical and analytical similarity data.

Pharmacology/Toxicology presented at the ODAC Meeting on May 25, 2017 conclusions made from the animal studies comparing head-to-head “Epoetin Hospira” and US-Epogen/Procrit for completeness, even though the studies were not designed to support a demonstration of biosimilarity. Also noted during the presentation was that a more tailored approach can be taken to the amount and type of animal data needed to support a demonstration of biosimilarity depending on the strength of the analytical similarity data (FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product).”

CDTL Comment: I agree with the pharmacology-toxicology review team assessment that the animal studies should not be included as part of the data considered to support a demonstration of biosimilarity of "Epoetin Hospira" to US-licensed Epogen/Procrit, because the animal studies were not designed to support a demonstration of biosimilarity.
6. Clinical Pharmacology

Source: Clinical Pharmacology Review (Original and Response to CR)

Clinical Pharmacology Team Recommendation: Approval

- General clinical pharmacology considerations

Based on original Clinical Pharmacology Review (dated 8 September 2015), the Applicant submitted two clinical pharmacology studies EPOE-12-02 and EPOE-14-01 to evaluate single- and multiple-dose pharmacokinetics (PK) and pharmacodynamics (PD) similarity (reticulocyte count and hemoglobin level) of “Epoetin Hospira” and US-licensed Epogen/Procrit in healthy subjects:

- Study EPOE-12-02 was a single-center, randomized, open-label, cross-over study to determine the PK and PD (reticulocyte count) of “Epoetin Hospira” and US-licensed Epogen/Procrit following a single-dose of 100 U/kg administered subcutaneously in healthy subjects (N=81). The pre-specified PK endpoints were baseline-adjusted erythropoietin AUC0-120h, AUC0-INF, and CMAX. The prespecified PD endpoints were reticulocyte count (expressed as a percentage of erythrocytes) AUEC0-456h and EMAX. The washout period was 28 days.

- Study EPOE-14-01 was a single-center, randomized, open-label, parallel group study to determine the PK and PD (hemoglobin level) of “Epoetin Hospira” and US-licensed Epogen/Procrit following multiple-doses of 100 U/kg administered subcutaneously three times weekly (TIW) for 4 weeks in healthy subjects (N=129). The pre-specified PD endpoint was hemoglobin level AUEC0-28d. FDA also considered hemoglobin level EMAX as a primary PD endpoint. In addition, the Applicant evaluated multiple-dose PK, which was considered supportive by the FDA. The pre-specified PK endpoints were erythropoietin AUC0-48h and CMAX post-final dose on Day 26.

In both studies, PK and PD (reticulocyte count and hemoglobin level) similarity between “Epoetin Hospira” and US-licensed Epogen/Procrit were met — 90% confidence intervals of the geometric mean ratios of all PK and PD endpoints were contained within prospectively defined criteria of 80 – 125%. This resubmission contained re-tested immunogenicity results using updated analysis with validated in-study cut points. The updated immunogenicity results showed similar rates and titers of anti-drug antibodies (ADAs) for both “Epoetin Hospira” and US-licensed Epogen/Procrit, including no detection of neutralizing ADAs. Importantly, PK and PD similarity conclusions from studies EPOE-12-02 and EPOE-14-01 were not affected by the updated immunogenicity results.

Overall, the PK, PD and immunogenicity results from studies EPOE-12-02 and EPOE-14-01 support a demonstration of no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit. These results add to the totality of
the evidence to support a demonstration of biosimilarity between “Epoetin Hospira” and US-licensed Epogen/Procrit.

7. Clinical/Statistical- Efficacy

Source: Statistical and Clinical Reviews (Original and Response to CR)

Statistical Team Recommendation: Approval

Clinical Team Recommendation: Approval

BLA125545 has two comparative clinical studies that evaluated efficacy and safety endpoints in support of licensure of “Epoetin Hospira”. Both studies were randomized, double-blinded, parallel group studies that enrolled patients with chronic kidney disease on hemodialysis and receiving epoetin maintenance treatment with co-primary endpoints of difference between arms in mean weekly hemoglobin and mean weekly dose during the last four weeks of the treatment period. One study (EPOE-10-13) used subcutaneous (SC) route of administration, and the other study (EPOE-10-01) used intravenous (IV) route of administration.

Statistical team noted in their review dated 1 June 2017, that

“The purpose of this review is to perform re-analyses of the efficacy data by removing patients from the GCP non-compliance (8% from the SC study and 11% from the IV study based on ITT population). In summary, the 90% CIs for the differences between “Epoetin Hospira” and US-licensed Epogen/Procrit in both primary endpoints, difference between arms in mean weekly hemoglobin and mean weekly dose during the last four weeks of the treatment period, are within the equivalence margins of ±0.5g/dL and ±45U/kg/week, respectively, in both SC and IV studies, and results obtained from the GCP-population are similar to the results obtained from the ITT population. Data support a demonstration of no clinically meaningful differences in efficacy between “Epoetin Hospira” and US-licensed Epogen/Procrit.”

Clinical team review also concluded that efficacy results from both comparative clinical studies (EPOE-10-13 and EPOE-10-01) support the conclusion that there are no clinically meaningful differences in efficacy between “Epoetin Hospira” and US-licensed Epogen/Procrit.

8. Safety

Source: Clinical Review (Original and Response to CR)

Clinical Team Recommendation: Approval

Hospira submitted two comparative clinical studies that evaluated comparative safety endpoints in support of licensure of “Epoetin Hospira”. In both studies, subjects with CKD on hemodialysis were randomized to "Epoetin Hospira" or US-licensed Epogen/Procrit in the
double-blinded maintenance period. One study (EPOE-10-13) used the subcutaneous route of administration and the other study (EPOE-10-01) used the intravenous route of administration. Sensitivity analyses were conducted removing subjects from sites with GCP non-compliance. Safety outcomes were similar for patients treated with either “Epoetin Hospira” or US-licensed Epogen/Procrit. The FDA review of the data from both comparative clinical studies supports the Applicant’s conclusion that there are no clinically meaningful differences in safety between “Epoetin Hospira” and US-licensed Epogen/Procrit. Refer to CMC review for clinical immunogenicity assessment.

CDTL Comment: Postmarketing safety information is available for Hospira's EU-approved Retacrit. In the absence of a scientific bridge between EU-approved Retacrit, “Epoetin Hospira”, and US-licensed Epogen/Procrit, the Applicant has not justified the relevance of the clinical data from the EU-approved Retacrit studies to support a demonstration of biosimilarity between “Epoetin Hospira” and US-licensed Epogen/Procrit.

**Risk Evaluation and Mitigation Strategy (REMS)**

On 13 April 2017, FDA determined that the ESA Risk Evaluation and Mitigation Strategy (REMS) for Epogen/Procrit and Aranesp, which was limited to treating patients with anemia due to associated myelosuppressive chemotherapy, was no longer necessary to ensure that the benefits outweigh its risks of shortened overall survival and/or increased risk of tumor progression or recurrence in patients with cancer. Therefore if “Epoetin Hospira” is approved, a REMS is not necessary to address the risks of shortened overall survival and/or increased risk of tumor progression or recurrence in patients with cancer. While the REMS is no longer necessary to ensure the benefits outweigh the risks, the serious risks of shortened overall survival and/or increased risk of tumor progression or recurrence associated with these drugs remain. The prescribing information for “Epoetin Hospira” will communicate appropriate information about the increased risk of tumor progression or recurrence, as well as death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access.

9. **Advisory Committee Meeting**

FDA requested discussion at the Oncologic Drugs Advisory Committee (ODAC) which occurred on 25 May 2017. After FDA and Applicant presentations, and clarifying questions to FDA and Applicant, and discussion, ODAC discussed the following questions:

1. **DISCUSSION:** Please discuss whether evidence from analytical studies supports a demonstration that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit, notwithstanding minor differences in clinically inactive components.

2. **DISCUSSION:** Please discuss whether there are no clinically meaningful differences between “Epoetin Hospira” and US-licensed Epogen/Procrit based on the results from the clinical studies.

3. **DISCUSSION:** Please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications.
4. **VOTE:** Does the totality of the evidence support licensure of “Epoetin Hospira” as a biosimilar product to US-licensed Epogen/Procrit for the following indications for which US-licensed Epogen/Procrit is currently licensed and for which the Applicant is seeking licensure?

**PROPOSED INDICATIONS FOR “EPOETIN HOSPIRA”:**

1) for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion

2) for the treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL

3) for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy

4) to reduce the need for allogeneic RBC transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery

Please explain the reasons for your vote.

Discussion Question 1: Regarding the evidence supporting a demonstration that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit, notwithstanding minor differences in clinically inactive components, ODAC members did not have major concerns.

Discussion Question 2: Regarding the evidence supporting a demonstration that there are no clinically meaningful differences between the products, members of the ODAC discussed that the clinical data presented support that finding within the limitations of data that can be measured in the clinical studies. For example, the occurrence of rare events such as development of neutralizing anti-drug antibodies cannot be estimated in clinical studies of limited duration.

Discussion Question 3: Regarding the scientific justification to support licensure for all proposed indications, some ODAC members expressed concerns on the broad range of the proposed indications for “Epoetin Hospira”, noting that the clinical studies for “Epoetin Hospira” were conducted in patients with chronic kidney disease on hemodialysis, and that there was lack of data regarding safety and immunogenicity in patients with HIV and in patients with cancer receiving chemotherapy.

Voting Question: ODAC voted **14 Yes** and **1 No**. The "no" vote was explained by the AC member as related to concerns regarding extrapolation and use of “Epoetin Hospira” in patients with cancer, due to the lack of immunogenicity data and basic safety data in patients with HIV and cancer. However, the members of the ODAC generally agreed that the totality of the evidence supports licensure of "Epoetin Hospira" as a biosimilar to US-licensed...
Epogen/Procrit for the indications for which US-licensed Epogen/Procrit is currently licensed and for which the Applicant is seeking licensure.

10. Pediatrics

No pediatric studies were conducted as part of this clinical program. The Agency agreed with the Applicant’s pediatric study plan to support the Pediatric Research Equity Act requirement. Refer to Table 17 in the clinical review that describes the approach for the pediatric assessment for “Epoetin Hospira”.

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): No issues.

- Exclusivity or Patent Issues of Concern: Refer to Purple Book at [http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm](http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm) for a list of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations.

- Financial Disclosures: No issues. Refer to clinical review of original application for assessment of financial disclosures.

- Other GCP Issues: The Sponsor identified sites in studies EPOE-10-13 and EPOE-10-01 that were GCP non-compliant. In study EPOE-10-13, 3 sites were closed during the conduct of the study which impacted 10% of enrolled subjects and 8% of the subjects in the intent-to-treat population. In study 10-01, a total of 7 sites were closed during the conduct of the study and 2 additional sites were identified in a post-study GCP audit and excluded from the final sensitivity analysis, representing 14% of subjects enrolled and 11% of subjects in the ITT population. The Agency conducted sensitivity analyses for both efficacy and safety endpoints excluding the GCP non-compliant sites to confirm the integrity of the initial analysis.

The Applicant submitted a Post-Study GCP Assessment Report which detailed the GCP compliance issues with each site, including the auditing reports and measures taken for the clinical studies to address the GCP compliance issues. Office of Scientific Investigations notes in their review dated 19 May 2017 that “The GCP compliance items and other noncompliance items were addressed adequately in this Post-Study GCP Assessment Report. They also do not appear to result in an alteration of findings described in the original Clinical Inspection Reports.”

- Office of Scientific Investigation (OSI) Audits: Clinical site and Sponsor inspection were not conducted during this review cycle. During the review of the original submission, studies EPOE-10-01 and EPOE-10-13, submitted in support of the sponsor’s 351(k) application were selected for clinical site inspections by FDA. Five clinical investigator (CI) sites and the sponsor were inspected. Four of the five CI sites
inspected were classified as voluntary action indicated (VAI) and one CI site, No Action Indicated (NAI). The Sponsor inspection was classified as VAI. For details of those inspections, refer to the Clinical Inspection Summary dated 10 July 2015.

- Other outstanding regulatory issues: None

12. Labeling

- Proprietary name: The proposed proprietary name, Retacrit was found conditionally acceptable by FDA on 20 March 2017.

- Nonproprietary name: As noted at the beginning of this review, FDA has not yet designated a nonproprietary name for Hospira’s proposed biosimilar product that includes a distinguishing suffix (see Final Guidance on Nonproprietary Naming of Biological Products). FDA issued a General Advice Letter on 12 May 2017, and concluded that the Applicant’s proposed suffixes were unacceptable.

- Labeling recommendations: The review teams reserve comment on the proposed labeling, container labels, and carton labeling until the application is otherwise adequate.

13. Postmarketing Recommendations

- Risk Evaluation and Management Strategies (REMS): The review teams did not identify a need for REMS to ensure the safe use of “Epoetin Hospira”.

- Postmarketing Requirements (PMRs) and Commitments (PMCs): Not applicable for this review cycle because the application will receive a Complete Response action.

14. Recommended Comments to the Applicant

None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROMEO A DE CLARO
06/20/2017
Cross-Discipline Team Leader Review

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>From</td>
<td>R. Angelo de Claro, M.D.</td>
</tr>
<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
</tr>
<tr>
<td>NDA/BLA #</td>
<td>BLA 125545 (Original submission)</td>
</tr>
<tr>
<td>Applicant</td>
<td>Hospira, Inc.</td>
</tr>
<tr>
<td>Application Type</td>
<td>351(k)</td>
</tr>
<tr>
<td>Date of Submission</td>
<td>16 December 2014</td>
</tr>
<tr>
<td>PDUFA Goal Date</td>
<td>16 October 2015</td>
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**Proposed Trade Name / Established (USAN) names**
- Retacrit / To be determined¹ (referred to as “Epoetin Hospira” by the Applicant)

**Reference Product**
- US-licensed Epogen/Procrit

**Dosage forms / Strength**
- Single-dose vial: 2000, 3000, 4000, 10,000, and 40,000 Units/1 mL

**Proposed Indication(s)**
- Same as the reference product

**Recommended:**
- Complete response

**Material Reviewed/Consulted**

<table>
<thead>
<tr>
<th>Reviewer</th>
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<tbody>
<tr>
<td>Clinical Review</td>
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<tr>
<td>Saleh Ayache M.D. / R. Angelo de Claro M.D.</td>
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<td>Statistical Review</td>
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<tr>
<td>Lola Luo, Ph.D. / Yuan Li Shen, Dr.P.H.</td>
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<td>Nonclinical Review</td>
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<td>Natalie Simpson, Ph.D. / Christopher Sheth, Ph.D.</td>
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<td>Clinical Pharmacology Review</td>
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<td>Vicky Hsu, Ph.D. / Bahru Habtemariam, Pharm.D.</td>
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<td>CMC OBP</td>
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<tr>
<td>Frances Namuswe, Ph.D. / Maria-Teresa Gutierrez-Lugo, Ph.D.</td>
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<tr>
<td>CMC Statistics</td>
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<td>Xiaoyu Dong / Meiyu Shen, Ph.D. / Yi Tsong, Ph.D.</td>
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<td>CMC Immunogenicity</td>
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<td>Steven Bowen, Ph.D. / Daniela Verthelyi, Ph.D. / Susan Kirshner, Ph.D.</td>
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<td>CMC Microbiology</td>
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<td>DS: Reyes Candau-Chacon, Ph.D. / Patricia Hughes, Ph.D. / Kassa Ayalew, M.D., M.P.H.</td>
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<td>OPQ OPF</td>
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<td>Michael Shanks / Peter Qiu, Ph.D.</td>
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<td>OSI/DCCE</td>
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<td>Anthony Orencia, M.D. / Janice Pohlman, M.D., M.P.H. / Kassa Ayalew, M.D., M.P.H.</td>
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<td>OSE/DRISK</td>
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<tr>
<td>Amarilys Vega, M.D., M.P.H. / Naomi Redd, Pharm.D. / Cynthia LaCivita, Pharm.D.</td>
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<tr>
<td>OND/DPMH</td>
</tr>
<tr>
<td>Erica Radden, M.D. / Hari Sachs, M.D. / Lynne Yao, M.D.</td>
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</tbody>
</table>

¹ For purposes of this review, we generally refer to Hospira’s proposed product by the Hospira descriptor “Epoetin Hospira.” FDA has not yet designated a nonproprietary name for Hospira’s proposed biosimilar product that includes a distinguishing suffix (see Draft Guidance on Nonproprietary Naming of Biological Products).
1. Introduction

On 16 October 2014, Hospira, Inc. (Applicant) submitted a 351(k) Biologics License Application (BLA) for Retacrit (“Epoetin Hospira”) as a proposed biosimilar product to the reference product, US-licensed Epogen/Procrit (also referred to in this review as US-Epogen). US-Epogen was initially licensed in 1989 and the current licensed indications include:

- Treatment of anemia due to
  - Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis
  - Zidovudine in HIV-infected patients
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
- Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

The Applicant’s proposed indication for “Epoetin Hospira” includes all of the indications for which the reference product is licensed. The proposed dosing regimen for “Epoetin Hospira” is the same as the US-licensed reference product. US-Epogen is licensed for intravenous and subcutaneous routes of administration.

The 351(k) BLA submission included analytical, nonclinical, clinical pharmacology, and clinical studies. Complete response issues, including analytical and clinical issues were identified during the review of the application, and are discussed below.

CDTL Comment: For this review, I use the term “complete response issue” to describe deficiencies that will be included in the Complete Response letter.

2. Background

Regulatory Pathway for Biosimilars

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product (the “reference product”). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data.

Section 351(k) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” A 351(k) application must contain, among other things,
information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a “stand-alone” marketing application). The goal of a “stand-alone” development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that Applicants use a stepwise approach to developing the data and information needed. At each step, the Applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be analytically and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences.

The level of residual uncertainty after the comparative analytical characterization drives both the type and amount of data needed to resolve remaining questions about whether the proposed product is “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and whether there are “no clinically meaningful differences” between the proposed product and the reference product in terms of safety, purity, and potency. The results of nonclinical and/or clinical studies to resolve remaining questions should further reduce residual uncertainty and support a demonstration of biosimilarity. For example, additional data may resolve certain questions (e.g., a structural difference with unknown impact may show no difference(s) when evaluated in appropriate functional assays) or may identify other differences (e.g., pharmacokinetic (PK) differences) that would raise concerns as well as residual uncertainty such that additional studies/data would be necessary. In both examples, while the differences may raise questions about whether the proposed biosimilar product is highly similar to the reference product, or whether there may be clinically meaningful differences between the products, identified differences should not be considered in isolation and do not necessarily preclude continued development to support a demonstration of biosimilarity. However, the Applicant would need to evaluate the observed differences and explain why the differences between the proposed biosimilar product and the reference product
should not preclude FDA from finding the proposed product meets the standard for biosimilarity.

The ‘totality of the evidence’ submitted by the Applicant should be considered when evaluating whether an Applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

In general, an Applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the US-licensed reference product. When an Applicant’s proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the Applicant must provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

3. CMC/Device

- General product quality considerations

Source: OBP Product Quality Review

The analytical similarity data submitted by Hospira indicate that most quality attributes evaluated in “Epoetin Hospira” and the reference product are highly similar. However the erythropoietin content in “Epoetin Hospira” is approximately 4.0% higher than that in the reference product. In addition, Hospira needs to evaluate whether the two products contain highly sialylated species using orthogonal methods. Thus, at this time there is insufficient data to conclude that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit.

The manufacturing data and information provided in the submission are insufficient to support that the manufacturing process of “Epoetin Hospira” is well controlled and leads to a product that is pure and potent for the duration of the product shelf life. From a CMC perspective, OBP recommends a Complete Response be issued to Hospira Inc. to outline the complete response issues noted below and the information and data that will be needed to support approval.

The following complete response issues were identified regarding the characterization, manufacturing process and control strategy of “Epoetin Hospira”:

1. Deficient protocol for the manufacture of future working cell banks.
2. “Epoetin Hospira” DS manufacturing process validation:
   a. Insufficient information to support consistency and control of product yield.
   b. Insufficient information about the [b][4] used in manufacture.
   c. Insufficient information to support [b][4] at commercial scale.
d. Inadequate small scale model and data used to support [ ].

3. Inadequate acceptance criteria defined in the protocol for concurrent validation of [ ].


5. Insufficient information on potential leachables from the [ ] used to store “Epoetin Hospira” DS.

6. Deficient protocol for concurrent validation of “Epoetin Hospira” DP shipping.

7. Insufficient data to support the manufacture of the 3,000 U/mL, 4,000 U/mL and 40,000 U/mL strengths of “Epoetin Hospira” DP.

8. Missing tests in the post-approval stability protocols for “Epoetin Hospira” DS and DP.

9. Control of “Epoetin Hospira” DS and DP:
   a. Missing information on the designation of product-related species (e.g. product-related substances or product-related impurities).
   b. Inadequate release and stability acceptance criteria for potency of DS and DP.
   c. Insufficient information to support the use of size exclusion chromatography (SEC) to monitor high molecular weight species (HMWS).
   d. Deficient acceptance criteria for identity assays.
   e. Inadequate release and stability acceptance criterion for pH for DS.
   f. Inadequate release and stability acceptance criteria for product-related species (product-related impurities and substances) for DS and DP.
   g. Deficient acceptance criterion for extractable volume for DP.
   h. Insufficient information to evaluate coverage of the host cell proteins assay.
   i. Lack of analytical method transfer reports

The following analytical similarity complete response issues need to be addressed:

1. Differences in protein content between “Epoetin Hospira” and the US-licensed reference product.

2. Investigate whether highly sialylated species potentially present in “Epoetin Hospira” may be also present in the reference product.

3. Clarification on inconsistencies in the information provided in the 351 (k) BLA regarding the “Epoetin Hospira” lots used in PK/PD similarity study EPOE-12-02.

4. Revision on a in vivo potency assay dataset used to compare “Epoetin Hospira” and the reference product.

5. Clarification on the performance of the trypsin peptide map method used in the analytical similarity assessment.

Source: CMC Statistics Review

The Division of Biometrics VI review provides results of statistical equivalence test for the critical quality attributes of In-vivo Biopotency (%RP) and in-vitro Specific Activity (U/μg) to support a demonstration that the proposed biosimilar “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit.

The summarized results of statistical equivalence test are provided in Table 1.
• For In-vivo Biopotency (%RP), the results of statistical equivalence test support the demonstration that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit because statistical equivalence in means is established between the proposed biosimilar product and US-licensed reference product.

• For In-vitro Specific Activity (U/μg), the results of statistical equivalence test support the demonstration that “Epoetin Hospira” is highly similar to US-licensed Epogen/Procrit because statistical equivalence in means is established between the proposed biosimilar product and US-licensed reference product.

**Table 1 Summarized Results of Statistical Equivalence Test from FDA Reviewer’s Analyses**

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Comparison</th>
<th>Number of Lots</th>
<th>Mean Difference</th>
<th>Confidence Interval</th>
<th>Equivalence Margin</th>
<th>Statistical Equivalence?</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-vivo Biopotency (%RP)</td>
<td>“Epoetin Hospira” vs. US-licensed Epogen/Procrit</td>
<td>26 vs. 26</td>
<td>3.02</td>
<td>(-0.47, 6.51)</td>
<td>(-11.02,11.02)</td>
<td>Yes</td>
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<tr>
<td>In-vitro Specific Activity (U/μg)</td>
<td></td>
<td>25 vs.35</td>
<td>0.80</td>
<td>(-1.63,3.23)</td>
<td>(-7.26, 7.26)</td>
<td>Yes</td>
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</tbody>
</table>

*a Equivalence margin is set as $1.5 \times \sigma_R$, where $\sigma_R$ is the standard deviation of the reference product;

*b Statistical equivalence in mean values is established if the obtained confidence interval of the mean difference is completely within the equivalence margin.

*Source: Product Microbiology Review*

The CMC microbiology review team identified multiple deficiencies (Complete Response issues) related to microbial control and microbiology product quality of the drug substance (DS) and drug product (DP). In addition, sterility assurance was also an issue for the DP.

Refer to action letter for Complete Response issues identified during the CMC microbiology review of the DS and DP.

• **Facilities review/inspection**

*Source: Facilities Review*

At the time of completion of the CDTL review, the application is recommended for approval from a facility review perspective. Given the Complete Response issues with the current application, the report regarding facilities review and inspection will need to be updated if the application is resubmitted.

• **Other notable issues (resolved or outstanding)**

Refer to action letter for final wording of the above CMC-related Complete Response issues. As discussed above, the issues include analytical similarity, CMC manufacturing, and CMC
microbiology. Complete Response issues related to immunogenicity are described in Section 8 of the CDTL review.

**CDTL Comment:** I agree with the recommendations from the CMC review teams.

**4. Nonclinical Pharmacology/Toxicology**

*Source: Primary and Secondary Pharmacology/Toxicology Reviews*

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The nonclinical data submitted to the BLA demonstrate the similarity (i.e., similar pharmacodynamics characteristics and similar toxicity) of “pilot scale” “Epoetin Hospira” and US-licensed Epogen via the intravenous route, but not for subcutaneous administration.

Two GLP-compliant 13-week comparative toxicology studies were submitted to support the similarity of “Epoetin Hospira” to US-Epogen. Subcutaneous and IV injection routes of administration, with a three times weekly dosing regimen for 13 weeks, were assessed in Sprague-Dawley rats and Beagle dogs, respectively, at doses of 150, 450, and 1500/900 IU/kg for “Epoetin Hospira” and US-Epogen. The rat comparative toxicology study does not support similarity via that SC route of administration due to the lower exposures and differences in several PD endpoints, including lower red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), and absolute reticulocytes in US-Epogen treated rats compared to those treated with “Epoetin Hospira”. These differences were associated with a higher incidence of anti-drug antibody (ADA) development to the reference product compared to “Epoetin Hospira”. The Applicant suspects that the high incidence of ADA is related to the route of administration (evidence supports SC is more immunogenic than IV administration) and the presence of human serum albumin (HSA) as a stabilizer in the reference product. In dogs, PD endpoints, including RBC, HGB, HCT, and reticulocytes were similar for “Epoetin Hospira” and US-Epogen, supporting similarity via the IV route of administration.

Both the rat and dog comparative toxicology studies revealed similar pharmacologically driven mechanisms of toxicity for “Epoetin Hospira” and US-Epogen. However, there were some differences between “Epoetin Hospira” and US-Epogen toxicokinetics (lower exposure for the biosimilar compared to the reference product in both rats and dogs on Day 1 and faster clearance in dogs on Day 89), but differences were generally within the range of individual animal variability.

Overall, the toxicological findings between “Epoetin Hospira” and the reference product administered intravenously in the comparative dog toxicology study were similar and related to the exaggerated pharmacology of erythropoietin — early mortality associated with multi-organ congestion, hemorrhage, infarction, and necrosis; body weight loss and reduced body weight gain; increased vascular retinal pattern (size) and tortuosity of the eye (of note, this finding was more pronounced in high dose “Epoetin Hospira” treated dogs compared to US-Epogen treated dogs); and, pharmacologically driven/inflammatory related microscopic findings in organs of the hematopoietic (bone marrow, spleen, lymph nodes, and thymus),
digestive (stomach, small intestine, large intestine), and nervous (brain, sciatic nerve, and spinal cord) systems, as well as the kidney, liver, heart, and lungs. Skeletal muscle (moderate edema or marked infarction) was observed only in high dose “Epoetin Hospira” treated animals, but at low incidence.

- Carcinogenicity

The Applicant did not conduct carcinogenicity studies for “Epoetin Hospira” and proposes to reference FDA’s finding of safety and effectiveness for the reference product as set forth in the carcinogenicity sections of the reference product labeling.

- Reproductive toxicology

The Applicant did not conduct reproductive toxicology studies for “Epoetin Hospira” and proposes to reference FDA’s finding of safety and effectiveness for the reference product as set forth in the reproductive toxicology sections of the reference product labeling.

- Other notable issues (resolved or outstanding)

The totality of the nonclinical data indicate that “Epoetin Hospira” is similar to US-Epogen for the intravenous route of administration, based on the original “pilot-scale” “Epoetin Hospira” formulation, but does not support such a finding for subcutaneous administration. Considering the differences observed with subcutaneous administration, there are discipline-specific uncertainties regarding the biosimilarity of “Epoetin Hospira” to US-Epogen from the Pharmacology/Toxicology perspective. Therefore from a Pharmacology/Toxicology perspective, approval is not recommended.

**CDTL Comment**: BLA 125545 includes clinical and clinical pharmacology data to assess the similarity of US-Epogen to “Epoetin Hospira” with the subcutaneous route of administration. After clinical Complete Response (CR) issues are resolved, the Agency will evaluate the adequacy of the clinical and clinical pharmacology data whether this addresses uncertainties raised in the pharmacology/toxicology review regarding the subcutaneous route of administration.

### 5. Clinical Pharmacology/Biopharmaceutics

*Source: Primary Clinical Pharmacology Review*

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

To support the Biologic License Application (BLA) for Retacrit (“Epoetin Hospira”) as a proposed biosimilar to US-licensed Epogen/Procrit (licensed under BLA 103234 by Amgen), the Applicant submitted two pivotal clinical pharmacology studies:

- Study EPOE-12-02 was a single-center, randomized, open-label, cross-over study to determine the pharmacokinetics (PK) and pharmacodynamics (PD) similarity of
“Epoetin Hospira” and US-licensed Epogen following a single 100 U/kg subcutaneous (SC) dose in healthy subjects. The PK endpoints were baseline-adjusted epoetin AUC_{0-T} and C_{MAX}. The PD endpoints were reticulocyte response AUEC_{0-T} and E_{MAX}.

- Study EPOE-14-01 was a single-center, randomized, open-label, parallel group study to determine the PK and PD similarity of “Epoetin Hospira” and US-licensed Epogen following multiple 100 U/kg SC doses in healthy subjects. The PK endpoints were epoetin AUC_{0-T} and C_{MAX}. The PD endpoint was hemoglobin AUEC_{0-T}.

The Applicant submitted two pharmacokinetic (PK) and pharmacodynamics (PD) studies that evaluated single and multiple subcutaneous (SC) doses of 100 U/kg in healthy subjects to evaluate the PK and PD similarity of “Epoetin Hospira” with US-licensed Epogen/Procrit. In both studies, PK and PD similarity between “Epoetin Hospira” and US-licensed Epogen/Procrit was demonstrated—90% confidence intervals of geometric mean ratios of PK and PD endpoints were contained within prospectively defined criteria of 80 and 125% (Table 2):

<table>
<thead>
<tr>
<th>Table 2. Summary of single- and multiple-dose PK and PD similarity assessments</th>
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<tr>
<td>Study</td>
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<tr>
<td>PK</td>
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**Clinical Pharmacology Conclusion:** Both studies met the pre-specified PK and PD similarity criteria between “Epoetin Hospira” and US-licensed Epogen/Procrit. The PK and PD component of the BLA application is acceptable to support a demonstration of no clinically meaningful differences. However, the applicant needs to fully characterize the immunogenicity of “Epoetin Hospira” as recommended by the immunogenicity reviewers and provide a comparative immunogenicity assessment between Epogen and “Epoetin Hospira”. In addition, the applicant needs to address the data integrity issues identified by the OSI inspection report.

**CDTL Comment:** I agree with the assessment of the clinical pharmacology review team.

### 6. Clinical Microbiology

Not applicable. Product microbiology is addressed in the CMC section.
7. Clinical/Statistical- Efficacy

Source: Statistics and Clinical Review

The Applicant submitted data and final study report of clinical study 10-13(subcutaneous (SC) administered) along with clinical study Epogen-10-01(intravenous (IV) administered) to seek licensure for “Epoetin Hospira” as a proposed biosimilar product to the reference product US-licensed Epogen (Amgen) for the same indications as the reference product.

Both studies were multi-centered, randomized, active-controlled, parallel group, and double-blind. The Intent-to-Treat (ITT) population was used for the efficacy analysis with 246 subjects in study Epogen-10-13 (124 in the “Epoetin Hospira” arm and 122 in the US-licensed Epogen arm) and 612 subjects in study Epogen-10-01 (306 in “Epoetin Hospira” and in US-Epogen arm. The primary co-endpoints in both studies were the mean weekly Hb level and the mean weekly dosage per kg body weight during the last 4 weeks of the clinical study. The primary objectives of the studies were to demonstrate that there are no clinically meaningful differences between SC “Epoetin Hospira” compared to US-Epogen (Amgen) based on the two co-primary endpoints with equivalence margin of ±0.5 g/dL for the Hb level and ±45 U/kg/week for the dosage per kg body weight. For study Epogen-10-13, the least square (LS) mean for the difference between the “Epoetin Hospira” arm and the US-Epogen arm in weekly Hb during the last 4 weeks of the study was 0.04 g/dL with a 90% CI of -0.13 to 0.21 g/dL. The LS mean for the difference in weekly dosage per kg body weight was 2.34 U/kg/week with a 90% CI of -12.54 to 7.85. For study Epogen-10-01, the LS mean for the difference between the “Epoetin Hospira” arm and the US-Epogen arm was -0.12 g/dL with a 90% CI of -0.22 to -0.01 g/dL. The LS mean for the difference in weekly dosage per kg body weight was 0.37 U/kg/week with a 90% CI of -8.67 to 9.40.

Statistics Team Conclusion: The CIs for both primary endpoints in both studies were contained within the pre-defined acceptance limits. Sensitivity analyses were performed by both the applicant and FDA’s statistical reviewer showed the primary analysis results were robust for both primary endpoints and the results from the secondary endpoints further supported the findings.

However, several GCP non-compliant sites were discovered after the submission and it was determined that at least 10% of the data from the ITT population in each study were derived from GCP non-compliant sites and therefore potentially unreliable (Summary of Clinical Efficacy, Module 2.7.3, page 62 of 140). The Agency expressed concerns about the quality of the clinical data. At this time, a definite conclusion cannot be made due to the on-going investigation of the clinical sites.

Clinical Team Conclusion: The efficacy analyses should be re-analyzed based on the issues identified in Section 3 (of the Clinical Review), which noted multiple sites that were GCP non-compliant. The efficacy results should be interpreted with caution. As such, conclusions regarding the comparative assessment of efficacy between the proposed biosimilar and the reference product cannot be made at this time.
**CDTL Comment**: I agree with the statistics and clinical review teams regarding limitations on the comparative assessment of efficacy of “Epoetin Hospira” to the reference product.

**Complete Response Issue**

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.

**CDTL Comment**: I agree with the clinical complete response issue related to the efficacy assessment.

**8. Safety**

*Source: Clinical Review*

A detailed analysis of the safety outcomes for “Epoetin Hospira” was conducted using data from studies EPOE-10-13, EPOE-10-01, EPOE-11-03, and EPOE-11-04. Studies EPOE-10-13 (SC) and EPOE-10-01 (IV) were randomized, double-blind studies conducted in 859 patients (423 “Epoetin Hospira” and 426 US-licensed Epogen) on dialysis and compared “Epoetin Hospira” to the US-licensed Epogen for the treatment of anemia due to Chronic Kidney Disease (CKD) to decrease the need for red blood cell (RBC) transfusion. Supportive safety data was submitted from two open-label long term safety studies, EPOE-11-04 (SC) and EPOE-11-03 (IV), conducted in 189 subjects with CKD on HD. These four studies constitute the combined clinical development program, in which patients were randomized and received treatment with either the US-licensed Epogen or “Epoetin Hospira” administered either IV or SC. The study drug regimen was consistent with the proposed dose-schedule and according to the reference drug label for the treatment of anemia in patients with CKD. The mean duration of study drug exposure was approximately 18 weeks.

Analysis of the safety data for Studies EPOE-10-13 (SC) and EPOE-10-01 (IV) showed:

- Deaths: Seventeen patients (2%) (9 patients (2%) in the “Epoetin Hospira” group and 8 patients (2%) in the US-licensed Epogen group) in the combined randomized...
treatment groups experienced a TEAE resulting in death. For the combined LTSS, 18 patients (10%) experienced a TEAE resulting in death.

- Serious Adverse Events (SAEs): The rate of patients who experienced at least one SAE in the randomized studies was 24% in the “Epoetin Hospira” group compared to 27% in the US-licensed Epogen group. The most common SAEs in the both groups were pneumonia, non-cardiac chest pain, dyspnea, cellulitis, fluid overload, and vascular access thrombosis, with similar incidences between the two treatment groups. In the combined LTSS, 38% of subjects reported at least one SAE. The most common SAEs were pneumonia, cardiorespiratory arrest, hyperkalemia, and cardiac failure congestive.

- Adverse Events of Special Interest: In general the rates of adverse events of Special Interest in the randomized studies were similar between the two treatment groups.
  - Hypertension was reported in 6% of patients in the “Epoetin Hospira” and 5% in the Epogen group reported.
  - The rates of myocardial infarction and the cerebrovascular events were similar between the treatments groups and reported in 1% of patients.
  - Seizure reported in 1 patient in the US-licensed Epogen with no event in the “Epoetin Hospira”.
  - The rate of thromboembolic events was 8% in the “Epoetin Hospira” compared to 6% in the US-licensed Epogen group. Vascular access thrombosis was the most common thromboembolic event with incidence of 6% in the US-licensed Epogen group compared to 4% in the US-licensed Epogen group.
  - Allergic reaction was reported in 2% of patients in the “Epoetin Hospira” compared to 1% in the US-licensed Epogen group.
  - There were no reported events of pure red cell aplasia (PRCA) reported in the clinical studies. However, a case report of pure red cell aplasia (PRCA) reported in a patient who was enrolled in a long-term, non-interventional, observational post approval study (PASCO II) with European (EU)-approved Retacrit.

- The rates of treatment-emergent adverse event (TEAE) were approximately 75% of patients in the randomized studies (10-13 and 10-01) and approximately 80% of patients in the 48-week open-label LTSS studies.

- Adverse Events Leading to Study Drug Discontinuation: The incidences of TEAEs leading to study drug discontinuation were comparable between the “Epoetin Hospira” (3%) and US-licensed Epogen (4%) treatment groups. In the combined analysis, 9% of patients experienced an adverse event (AE) leading to study drug discontinuation.

Clinical Team Conclusion: The safety analyses should be re-analyzed based on the issues identified in Section 3 (of the Clinical Review), which noted multiple sites that were GCP non-compliant. The above safety results should be interpreted with caution. As such, conclusions regarding the comparative assessment of safety between the proposed biosimilar and the reference product cannot be made at this time.
The clinical team also recommended to include the following comment (non-CR issue) in the CR letter:

**Additional Comment (non-CR issue to include in CR letter)**

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”.

*Source: Immunogenicity Review*

**Immunogenicity Review Team Recommendation:** The Sponsor conducted seven clinical studies in which immunogenicity was assessed; anti-drug antibody formation was monitored in all studies. However, the FDA assessment of immunogenicity was based on three multiple-dose parallel arm studies, two of which (EPOE-10-01 and EPOE-10-13) enrolled patients with chronic kidney disease and one of which (EPOE-14-01) enrolled healthy volunteers. The Sponsor’s overall approach to evaluate immunogenicity was appropriate, however unresolved issues with the GCP practices at selected testing sites and with the confirmatory assay cutpoint render the data not reviewable because of potential unreliability, and thus no conclusions can be currently drawn regarding the immunogenicity of “Epoetin-Hospira” relative to US-licensed Epogen. OBP is recommending a Complete Response Action.

**Complete Response Issues**

Refer to wording of clinical CR issue under Clinical/Statistical Section of the CDTL review.

Refer to action letter for final wording of CR issue related to immunogenicity assays.

**CDTL Comment:** I agree with the clinical complete response issue related to the assessment of safety and immunogenicity.

*Source: Division or Risk Management (DRISK) Review*

**Risk Evaluation and Mitigation Strategies (REMS) for Erythropoiesis Stimulating Agents (ESAs)**

In 2007, the FDA held an advisory committee meeting to discuss the risks associated with the use of ESAs and approved a boxed warning for the increased risk of death and tumor progression based on ESA clinical trial evidence. In 2010, FDA determined that a risk evaluation and mitigation strategy (REMS) was necessary due to evidence demonstrating that the effects of concomitant myelosuppressive chemotherapy with an ESA do not outweigh the risks of shortened overall survival and increased risk of tumor progression or recurrence.
The Aranesp and Epogen/Procrit REMS programs are referred to as the ESA REMS and jointly fall under a common implementation program, the ‘ESA APPRISE Oncology Program’. The goal of the approved ESA REMS Program, modified on December 2013, is to support informed discussions between patients with cancer and their healthcare providers by: (1) educating healthcare providers about ESAs’ risks and safe use conditions for patients with cancer and (2) informing patients about the risk of shortened overall survival and/or increased risk of tumor progression or recurrence when ESAs are used to treat anemia due to concomitant myelosuppressive chemotherapy.

The most recent modification of the REMS on December 31, 2013 consisted of: (1) revision of goal statement (focus on oncology indication), (2) removal of the MG from the REMS, (3) revision of the Acknowledgement Form to be used as the primary oncology patient counseling tool, (4) removal of the CP and relocation of all communications activities under the corresponding ETASU, (5) revision of all training modules, (6) simplification of the risk messages communicated through the Acknowledgement Form, (7) revision of audit sampling methodology to assess compliance with Acknowledgement Form, (8) elimination of clinic requirement to return Acknowledgement Forms to REMS Program Call Center, (9) enforcement of noncompliance with Acknowledgement Form by placement of the private clinic or hospital on the Suspension List, (10) added requirement that a copy of the Acknowledgement Form must be given to the patient, and (11) revision of REMS Assessment Plan.

**DRISK Conclusion and Recommendations:** DHP determined that the data included in this application do not support a conclusion that “Epoetin Hospira” is biosimilar to US-licensed Epogen/Procrit; therefore, FDA will take a complete response action. DRISK will provide comments to the sponsor regarding their proposed REMS program during the next review cycle.

**9. Advisory Committee Meeting**

Discussion at the Oncologic Drugs Advisory Committee was planned, but was not held due to complete response issues noted with the application.

**10. Pediatrics**

*Source: Clinical Review and Division of Pediatric and Maternal Health Consult*

No pediatric studies were conducted as part of the clinical development program for “Epoetin Hospira”. The Agency reached agreement with the Applicant regarding the pediatric study plan to support the Pediatric Research Equity Act requirement.

The revised iPSP was reviewed by the Pediatric Review Committee (PeRC) on November 19, 2014. With PeRC’s concurrence, DHP provided feedback and recommendations regarding the proposed waiver rationale, in addition to potential supporting data for each proposed indication.
in correspondence dated December 11, 2014. Hospira was issued an agreed iPSP letter on January 20, 2015, prior to the filing meeting for the BLA on February 3, 2015.

The table below summarizes the specific recommendations to address PREA for the proposed indications.

**Table 3 Pediatric Development Plan for "Epoetin Hospira"**

<table>
<thead>
<tr>
<th>Adult Indications</th>
<th>Pediatric Information in Package Insert Labeling for US-licensed Epogen</th>
<th>Approach for “Epoetin Hospira” Study Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia due to CKD in patients on dialysis and not on dialysis</td>
<td>US-licensed Epogen is indicated in pediatric patients, ages 1 month to 16 month years of age, for the treatment of anemia associated with CKD requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established. The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with CKD.</td>
<td>Extrapolation of the pediatric information from the US-licensed Epogen®, to the proposed biosimilar product, “Epoetin Hospira”, for patients 1 month and older in the context of the proposed biosimilar development program. Partial Waiver Requested for Age Group 0 to &lt;1 Month.</td>
</tr>
<tr>
<td>Anemia due to concomitant Myelosuppressive chemotherapy</td>
<td>US-licensed Epogen is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in pediatric patients less than 5 years of age have not been established. The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with cancer.</td>
<td>Extrapolation of the pediatric information from the US-licensed Epogen®, to the proposed biosimilar product, “Epoetin Hospira”, for patients 5 years and older in the context of the proposed biosimilar development program. Partial Waiver Requested for Age Group 0 to &lt;5 Years.</td>
</tr>
<tr>
<td>Anemia due to Zidovudine in HIV-infected patients</td>
<td>Published literature has reported the use of the US-licensed Epogen in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of red blood cell transfusions were observed.</td>
<td>Extrapolation of the pediatric information from the US-licensed Epogen®, to the proposed biosimilar product, “Epoetin Hospira”, for patients 8 months to 17 years in the context of the proposed biosimilar development program. Partial Waiver Requested for Age Group 0 to &lt;8 Months.</td>
</tr>
</tbody>
</table>
11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** The overall integrity of the 351(k) application will be re-evaluated once response to the clinical CR issue is received. The clinical CR issue is potentially resolvable with resubmission of information as described in Section 7 of this review. AIP was not invoked during the review of the application. Refer to [http://www.fda.gov/downloads/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm072631.pdf](http://www.fda.gov/downloads/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm072631.pdf).

- **Exclusivity or Patent Issues of Concern:** Refer to Purple Book at [http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm](http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm) for a list of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations.

- **Financial Disclosures:** No issues. The Applicant obtained financial disclosure information (Form 3454) from investigators for clinical studies EPOE-10-08, EPOE-12-02, EPOE-14-01, EPOE-10-01, EPOE-10-13, EPOE-11-03, and EPOE-11-04. None of the investigators in any of the studies was identified as an employee of the applicant, and no disclosable financial interests or arrangements were identified on any of the financial disclosure forms.

- **Office of Scientific Investigation (OSI) Audits:** The following is from the 15 July 2015 and 7 August 2015 OSI assessment of findings and recommendations:
  
  **Clinical Site Inspections for BLA 125545:**
  
  Two clinical studies, EPOE-10-01 and EPOE-10-13 were inspected for this BLA. Four clinical sites covering five clinical investigators (Steven Zeig, M.D., Anant Desai, M.D., Kamal Gandhi, M.D., Mark Lee, M.D., and Susan Diamond, M.D.) and the sponsor (Hospira, Inc.) were inspected.
  
  The final regulatory classification for Dr. Diamond is No Action Indicated (NAI). The final regulatory classification for Drs. Zeig, Dr. Desai, Dr. Gandhi, and Hospira, Inc. is Voluntary Action Indicated (VAI). The preliminary classification for Dr. Lee is VAI.
  
  Although regulatory violations were noted at three of the clinical sites (covering four clinical investigators) inspected, the observations are unlikely to significantly impact...
efficacy assessment or human subject safety. Although initial interim monitoring visits by the sponsor (and/or CRO) were delayed and did not conform to the clinical management plans for the study, the sponsor monitoring process did result in identification of noncompliant sites and appropriate reporting of protocol deviations to the BLA based upon inspections of a sample of clinical sites.

Clinical investigator/IRB inspections related to IND 100685 complaints:

Under IND 100685, the following clinical study sites were also inspected following receipt of complaints by OSI related to GCP conduct: Mohammed El-Shahawy, M.D., Warren B. Shapiro, M.D., Raffi R. Minasian, M.D., Paul Crawford, M.D., Satya Ahuja, M.D., and Moustafa Moustafa, M.D.

The CDER regulatory classification for Dr. El-Shahawy is Official Action Indicated and an OAI-Untitled Letter has been issued. The CDER regulatory classification for the inspection of Drs. Crawford and Satya is Voluntary Action Indicated (VAI). The CDER regulatory classification for the inspection of Dr. Moustafa is No Action Indicated (NAI). The preliminary classification for Drs. Shapiro and Minasian is Voluntary Action Indicated (VAI).

With exception of the Dr. El-Shahawy site, data integrity from the other clinical study inspection sites, albeit with regulatory deficiencies, do not appear compromised.

In the Clinical Study Reports for EPOE-10-01 and EPOE-10-13, Hospira acknowledged closure of the Drs. El-Shahawy, Shapiro, and Moustafa sites due to GCP violations. Although the study reports indicated that all subjects (including those enrolled at sites closed for GCP noncompliance) were included in the Intent to Treat analysis, it is not clear how all subjects from sites with GCP violations were considered for inclusion/exclusion from the Per Protocol analysis population, since only those subjects with “major” protocol deviations at the non-GCP compliant site were excluded.

Concluding OSI Comments:

OSI conclusions about the data submitted to the BLA are unchanged based upon review of information obtained from inspections requested because of complaints reported to OSI and reported to IND 100685. Data from the clinical sites inspected as submitted by this sponsor appear acceptable in support of the requested indication with the exception of the Dr. Mohammed El-Shahawy site.

The sponsor reported the closure of seven and three clinical sites for Study EPOE-10-01 and Study EPOE-10-13, respectively in the clinical study reports submitted in the current BLA. The sponsor has indicated that all subjects randomized into the maintenance period of the studies were included in the intent-to-treat analysis population, however subjects with important protocol deviations (not defined) including those at sites closed for GCP compliance were excluded from the per protocol analysis. It is unclear whether important protocol deviations are consistent with “major protocol deviations” in the 16.2.2 Protocol Deviations data listings in Module 5.3.5.1 EPOE-10-01 and EPOE-10-13.

DHP may consider working with the sponsor to more clearly define the GCP deficiencies (as already identified by the sponsor) that caused closure of the clinical
sites. Alternatively, additional clinical study sites could be audited upon request if the review division’s regulatory decision will be made based on the outcome of these clinical studies.

Note: The inspectional observations for Dr. Lee for the BLA 125545 submission are based on preliminary communications with the field investigator. A clinical inspection summary addendum will be generated if conclusions on the current inspection report change significantly, upon receipt and review of the Establishment Inspection Report (EIR).

The inspections conducted in response to complaints received by OSI for Drs. Shapiro and Minasian have been reviewed by CEB and GCP For-Cause Team and are preliminarily classified as VAI pending completion and issuance of correspondence to the inspected entity.

**CDTL Comment:** The assessment and recommendations from OSI/DCCE are noted. The Division plans to work with the Sponsor regarding clarification of the GCP deficiencies and steps to address these deficiencies, including submission of amended datasets and clinical study reports. The determination to request additional clinical study sites for audit will be determined if the application is resubmitted.

Based on the above data integrity issues identified, we recommended that the Sponsor submit the following:

a. Full auditing reports for studies EPOE-10-01 and EPOE-10-13. The reports must include 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.

• **Other GCP Issues:** Refer to above.
• **Other discipline consults:** Refer to Section 7 of CDTL review regarding consult response from DRISK regarding proposed REMS.

Refer to Section 10 of CDTL review regarding consult response from Division of Pediatric and Maternal Health regarding pediatric development program for “Epoetin Hospira”.

• **Other outstanding regulatory issues:** None

**12. Labeling**

• Proprietary name: Refer to correspondence dated, 6 April 2015, which addresses the proposed proprietary name, Retacrit. This name was found acceptable pending approval of the application in the current review cycle.
Nonproprietary name: As noted at the beginning of this review, FDA has not yet designated a nonproprietary name for Hospira’s proposed biosimilar product that includes a distinguishing suffix (see Draft Guidance on Nonproprietary Naming of Biological Products).

Labeling recommendations: The review teams reserve comment on the proposed labeling, container labels, and carton labeling until the application is otherwise adequate.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: Complete Response

Risk Benefit Assessment

Section 351(k) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

As discussed in Section 3 (CMC/Device) of the CDTL Review, the following issues need to be addressed regarding analytical similarity.

1. Differences in protein content between “Epoetin Hospira” and the US-licensed reference product.
2. Investigate whether highly sialylated species potentially present in “Epoetin Hospira” may be also present in the reference product.
3. Clarification on inconsistencies in the information provided in the 351 (k) BLA regarding the “Epoetin Hospira” lots used in PK/PD similarity study EPOE-12-02.
4. Revision on a in vivo potency assay dataset used to compare “Epoetin Hospira” and the reference product.
5. Clarification on the performance of the trypsin peptide map method used in the analytical similarity assessment.

Regarding the demonstration of no clinically meaningful differences between “Epoetin Hospira” and the reference product in terms of the safety, purity, and potency, the Good Clinical Practice (GCP) issues identified in Section 7 and 8 of the CDTL review preclude the completion of the assessment, including for benefit-risk. In addition, Complete Response issues were identified regarding the interpretation of the immunogenicity assay results.
In addition to biosimilarity-related CR issues, general manufacturing and product microbiology Complete Response issues were identified.

During the review of the application, the review team met multiple times internally to discuss the Complete Response issues. All the teams agree with the overall recommendation to take a Complete Response action on this application.

Refer to final wording of Complete Response issues in the action letter.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

As noted in Section 8 of the CDTL review, the reference product has a REMS. DRISK will provide comments to the sponsor regarding their proposed REMS program during the next review cycle.

- Recommendation for other Postmarketing Requirements and Commitments

No recommendations can be made at this time regarding postmarketing requirements and commitments as the Division will take a Complete Response action.

- Recommended Comments to Applicant

Refer to final wording in action letter.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROMEO A DE CLARO
10/14/2015