

INTERNAL LATE CYCLE MEETING MINUTES

Application Type and Number: Original BLA: STN 125574/0
Product Name: Antihemophilic Factor (Recombinant)
Proposed Proprietary Name: KOVALTRY
Proposed Indication: For use in adults and children with hemophilia A for: (1) routine prophylaxis to prevent or reduce the frequency of bleeding episodes; (2) on-demand treatment and control of bleeding episodes; and (3) peri-operative management of bleeding
Applicant: Bayer HealthCare Pharmaceuticals Inc.
Meeting Date & Time: September 3, 2015, 12:30 PM – 2:00 PM, EST
Committee Chair: Natalya Ananyeva, PhD
RPM: Pratibha Rana, MS

ATTENDEES:

REVIEW COMMITTEE BY DISCIPLINE

Natalya Ananyeva, PhD	Chair/CMC – Product, OBRR/DHRR/LH
Nancy Kirschbaum, PhD	CMC – Product, OBRR/DHRR/LH
Alexey Khrenov, PhD	CMC – Product, OBRR/DHRR/LH
Lokesh Bhattacharyya, PhD	In-support Testing, OCBQ/DBSQC/LACBRP
Claire H. Wernly, PhD	Analytical Methods, OCBQ/DBSQC/LACBRP
Karen Campbell, PhD	Lot Release Testing, OCBQ/DBSQC/LACBRP
Lori Peters, CSO	CMC – Facility, OCBQ/DMPQ/BI
La’Nissa Brown-Baker, PhD	Non-clinical Pharmacology/Toxicology, OBRR/DHCR/HPRB
Megha Kaushal, MD	Clinical, OBRR/DHCR/CRB
Lin Huo, PhD	Biostatistics, OBE/Division of Biostatistics
Bhanu Kannan, MS	Bioresearch Monitoring, OCBQ/DIS/BMB
Marthe Bryant, MD	Pharmacovigilance/Epidemiology, OBE/DE/AEB
Loan Nguyen, PharmD	Labeling, OCBQ/DCM/APLB
Pratibha Rana, MS	Regulatory Project Manager, OBRR/RPMS

ADDITIONAL ATTENDEES

Jay Epstein, MD	Director, OBRR
Ginette Michaud, MD	Deputy Director, OBRR
Basil Golding, MD	Director, OBRR/Division of Hematology Research and Review (DHRR)
Mahmood Farshid, PhD	Deputy Director, OBRR/DHRR
Paul Mintz, MD	Director, OBRR/Division of Hematology Clinical Review (DHCR)
Howard Chazin, MD, MBA	Deputy Director, OBRR/DHCR

Bindu George, MD	Acting Branch Chief; OBRR/DHCR/Clinical Research Branch (CRB)
Renee Rees, PhD	Lead Mathematical Statistician, OBE/Division of Biostatistics (DB)
Patricia Holobaugh, PhD	Branch Chief, OCBQ/DIS/Bioresearch Monitoring Branch (BMB)
Craig Zindermann, PhD	Acting Branch Chief, OBE/DE/Analytic Epidemiology Branch (AEB)
Anne Pilaro, PhD	Acting Branch Chief, OBRR/DHCR/Hematology Products Review Branch (HPRB)
Mitchell Frost, MD	Acting Branch Chief, OBRR/DHCR/HPRB
Iliana Valencia, MS	Chief, Regulatory Project Management Staff, OBRR/DBA/RPMB
Bindi Nikhar, MD	Associate Director for Clinical Review, OMPT/OSMP/OCP
Wei Hua, MD, PhD	OMPT/CDER/OSE/OPE

CMC/Product Late-Cycle Reviewer Report

Reviewer Name: Natalya Ananyeva, PhD
Discipline: Chemistry, Manufacturing and Controls
Branch Chief: Timothy K. Lee, PhD, Laboratory of Hemostasis (LH),
Division of Hematology Research and Review (DHRR),
Office of Blood Research and Review (OBRR)

INTRODUCTION

The active ingredient in KOVALTRY is a full-length coagulation factor VIII (FVIII) produced by recombinant DNA technology based on the human FVIII sequence and is expressed in baby hamster kidney (BHK) cells. The product is a further development of Bayer's licensed product, Antihemophilic Factor (Recombinant) Formulated with Sucrose [Kogenate FS] (STN 103332), and (b) (4)

Both Drug Substance (DS) and Drug Product are manufactured at Bayer HealthCare, (b) (4) facility. The manufacturing process for (b) (4) was developed based on that of Kogenate FS, with the following key changes:

- (b) (4)

The DP manufacturing process involves (b) (4) DS, dilution to target potency, sterile filtration, filling into vials, lyophilization, and packaging.

A. Date reviewer will complete the primary discipline review, if not complete.

Primary review of the CMC information in the BLA has been completed. Final review is planned to be completed in October 2015 pending responses to new Information Requests (IR) as discussed in section B.

B. Key findings and substantive issues with the information and data in the application.

The process- and product-related CMC information in the BLA was reviewed by this reviewer (process validation) and Dr. Nancy Kirschbaum (process development). Most issues with regard

to Process Control Strategy, Process Validation and Specification of DS were resolved through IRs (IRs sent on 11 May 2015, 29 June 2015 and 10 July 2015; responses received in Amendments 8, 18, 19, and 22).

Inspection of the manufacturing process for KOVALTRY was part of the GMP surveillance inspection of this site (Team Bio inspection) performed during (b) (4). The Form FDA 483 lists a number of deficiencies in general Quality Systems (mainly, with regard to Kogenate FS). Bayer submitted their resolution plan on 23 June 2015 which was found acceptable.

Remaining issues related to the process control strategy and stability claims can be resolved through information requests:

- Validation of a potential (b) (4) step at the (b) (4) step, which combines (b) (4).
- Control parameters and acceptance criteria for the sterile filtration step for DP, which are not adequately defined.
- Further negotiation with the Applicant regarding the Use Lives for (b) (4) the results from small-scale studies do not appear to support the claims; concurrent full-scale validation studies cover shorter Use Lives.
- Further negotiation with the Applicant regarding the stability claim for the intermediate (b) (4) – Formulated): currently available data for the conformance lots cover a (b) (4) period at (b) (4) (compared to the proposed claim of (b) (4) months)
- Updated stability data will be requested to support the claims of (b) (4) for DS and 30 months at 2-8°C for DP; currently available data for conformance lots cover, respectively, 9-month and 6-month periods at long-term storage conditions.
- In DP Specification, the acceptance criteria for a number of parameters need to be revised, consistent with the revisions of DS Specification.

Potential substantive issue is the choice of the primary method for Potency assignment for KOVALTRY:

With intent of global distribution, Bayer proposes using a Chromogenic Substrate (CS) assay for the release and labeling of KOVALTRY. Bayer performed comparative studies to fulfill agreements with FDA at the pre-BLA stage. However, it is position of the DHRR Product Office that a One-Stage Clotting (OC) assay is preferable for potency assignment.

Bayer's proposal is supported by:

- good agreement between the results from both assays during release testing of DP lots at Bayer, with the average CS/OC ratio of (b) (4) (expected range of (b) (4) difference);
- good agreement between the results from both assays during measurement of FVIII recovery in spiked plasma samples in a field study with participation of 41 laboratories. Average CS/OC ratios at low, medium and high concentration ranges were within (b) (4) (i.e., (b) (4) difference).
- comparable clinical outcome in cross-over clinical studies (Leopold I and Leopold II) where KOVALTRY was dosed based on either the CS or CS/Adjusted to OC potency

values, with a 6-month duration of each treatment period. Clinical outcome was assessed by Annual Bleeding Rate and number of bleeds within 24, 48, and 72 hours.

FDA's position is based on the following rationales:

- KOVALTRY is a further development of Kogenate FS which was labeled with the OC assay; labeling KOVALTRY with the CS assay would break continuity. Consistently higher potency values obtained with the CS assay will result in a (b) (4) reduction of FVIII protein filled per vial, compared to DP labeled with the OC potency assay.
- Clinical studies performed cover a limited, 12-month observation period and cannot be considered predictive of efficacy of the lower dose treatment regimen during life-time use of KOVALTRY.
- The OC assay remains the main assay used in clinical laboratories world-wide for testing patients' samples (also supported by the results of the field study). The current thinking is that the same method should be used for potency assignment and recovery measurements.

C&D. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

There are no substantive issues that can prevent approval of the BLA from a Product Reviewer perspective.

The remaining issues with the process control strategy and stability claims can be resolved through information requests. We do not expect that Bayer's responses to pending IRs will impact the review timelines.

Potency assignment is a potential item to be discussed at the External Late-Cycle Meeting. If agreement on the use of the OC assay is not reached with Bayer, the Product Office has an alternative plan to reflect their warnings in the Package Insert.

CMC/Product Late-Cycle Reviewer Report

Reviewer Name: Nancy Kirschbaum, PhD
Discipline: Chemistry, Manufacturing and Controls
(Process Development, In-Process Controls)
Branch Chief: Timothy K. Lee, PhD, LH/DHRR/OBRR

A. Date reviewer will complete the primary discipline review, if not complete.

September 2015

B. Key findings and substantive issues with the information and data in the application.

No substantive issues: minor outstanding issues to be resolved through information requests

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

Not applicable

D. Plan for addressing issues and the reason for the suggested approach

Not applicable

CMC/Product Late-Cycle Reviewer Report

Reviewer Name: Alexey Khrenov, PhD
Discipline: Chemistry, Manufacturing and Controls
(Analytical Methods for In-Process and Release Testing)
Branch Chief: Timothy K. Lee, PhD, LH/DHRR/OBRR


A. Date reviewer will complete the primary discipline review, if not complete.

The primary discipline review is complete

B. Key findings and substantive issues with the information and data in the application.

No substantial issues were identified in the reviewed analytical method validations.

(b) (4)



C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

NA

D. Plan for addressing issues and the reason for the suggested approach

Suggest discussing the (b) (4) assay at the External Meeting and request Bayer to validate a (b) (4) assay for Kovaltry as a post-marketing commitment.

CMC/Lot Release Test Methods Late-Cycle Reviewer Report

Reviewer Name: Lokesh Bhattacharyya, PhD
Discipline: CMC review of analytical methods for lot release
Branch Chief: William McCormick, Division Director, Division of Biological Standards and Quality Control (DBSQC), Office of Compliance and Biologics Quality (OCBQ)

A. Date reviewer will complete the primary discipline review, if not complete.

Primary Discipline Review Memo was uploaded in EDR on 26 August 2015.

B. Key findings and substantive issues with the information and data in the application.

The following analytical methods used for lot release of Drug Product were reviewed:

1. Factor VIII Potency by the Chromogenic Assay
2. Factor VIII Potency by Clotting Assay
3. (b) (4)
4. Total Protein Content
5. Residual Moisture Content by (b) (4)
6. Moisture by (b) (4)
7. (b) (4)
8. Sucrose content by (b) (4)
9. Sodium and Calcium Content by (b) (4)
10. Polysorbate 80 content
11. (b) (4)
12. pH
13. Color and Clarity
14. Solubility and Appearance

Information requests were sent on April 16th, May 4th, June 16th and July 23rd, 2015, and responses were received in Amendments 6, 7 and 17. There are outstanding IRs for the following methods due to deficiencies in method validation:

- Factor VIII Potency by Clotting Assay (to further assess accuracy and robustness)
- (b) (4) (to assess the effect of the presence of (b) (4), accuracy of the method, and assess (b) (4) by an (b) (4) method)
- Moisture by (b) (4) (deficiencies in assessment of method specificity and range)
- Sucrose content by (b) (4) (deficiencies in method validation)

From our review of the information in the original BLA and Amendments 6, 7 and 17, we conclude that all other methods have been described and validated adequately and can be considered suitable for quality control lot-release testing.

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

Responses to additional IRs are under review.

D. Plan for addressing issues and the reason for the suggested approach

CMC/Analytical Methods Late-Cycle Reviewer Report

Reviewer Name: Claire H. Wernly, PhD
Discipline: CMC review (bioburden, endotoxin and sterility)
Branch Chief: William McCormick, Division Director, DBSQC/OCBQ

A. Date reviewer will complete the primary discipline review, if not complete.

Final review memo was uploaded to EDR on 8-24-2015.

B. Key findings and substantive issues with the information and data in the application.

After a thorough review of this BLA, and the response to CBER's Information Requests (Amendments 125574/0.3 and 125574/0.9 - received on 27 March and 05 June of 2015), this reviewer finds Bayer's bioburden, endotoxin, and sterility test methods were qualified in accordance with (b) (4) respectively, by demonstrating the Drug Product matrix is suitable for these intended test methods.

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

NA

D. Plan for addressing issues and the reason for the suggested approach

NA

CMC/Facility&Equipment Late-Cycle Reviewer Report

Reviewer Name: Lori Peters, CSO
Discipline: Chemistry, Manufacturing and Controls
(Facilities, Equipment)
Branch Chief: Carolyn Renshaw, PhD, Division of Manufacturing and
Product Quality (DMPQ), Branch I/OCBQ

A. Date reviewer will complete the primary discipline review, if not complete.

DMPQ has completed a review of the pertinent facility and equipment information provided in the BLA for the drug substance, drug product, and sterile diluent. In completion of the primary review of the BLA, DMPQ has identified the need for a third information request and this request will be sent to Bayer by September 15th, 2015. The substance of the information request is to provide additional data and information beyond what was provided in the BLA and to address questions with the information provided in Amendment 26 (DMPQ IR#2). No issues are identified as show-stopping.

B. Key findings and substantive issues with the information and data in the application.

DMPQ requested a significant number of equipment qualification reports and cleaning validation reports in the DMPQ IR #2 in order to ensure the new process equipment was installed and operating as intended and to ensure the cleaning process were adequate to remove residual product and cleaning agent. In addition, the DMPQ IR#2 requested a significant amount of information regarding the similarities of the drug product process with the existing product, Kogenate-FS. Bayer provided the requested information, reports, and data in Amendment #26 received August 21, 2015. The Amendment appears to contain the necessary information in order for DMPQ to complete the facility and equipment review of the BLA.

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

DMPQ does not foresee any new issues to arise during the review that could not be resolved with Bayer prior to the action due date.

D. Plan for addressing issues and the reason for the suggested approach

DMPQ proposes sending a third information request to Bayer for additional information; this will be sent no later than September 15th, 2015.

Pharmacology/Toxicology Late Cycle Reviewer Report

Reviewer Name: La’Nissa A. Brown, PhD
Discipline: Non-clinical Pharmacology/Toxicology
Branch Chief: Anne Pilaro, PhD, Hematology Product Review
Branch (HPRB), Division of Hematology
Clinical Review (DHCR), OBRR

A. Date reviewer will complete the primary discipline review, if not complete.

Complete September 2015

B. Key findings and substantive issues with the information and data in the application.

N/A

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

N/A

D. Plan for addressing issues and the reason for the suggested approach

N/A

Clinical Pharmacology Late-Cycle Reviewer Report

Reviewer Name: Carl-Michael Staschen, MD, PhD
Discipline: Clinical Pharmacology
Branch Chief: Bindu George, MD, Clinical Review Branch, DHCR, OBRR

A. Date reviewer will complete the primary discipline review, if not complete.

The review of clinical pharmacology information in the BLA is completed. The final memo was uploaded in EDR on 19 August 2015.

B. Key findings and substantive issues with the information and data in the application.

The clinical pharmacology section of the submission consists of the following three studies:

1. **Study Title:** A two-part, randomized, cross-over, open-label trial to evaluate the pharmacokinetics, efficacy, and safety profile of plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973) in previously treated subjects with severe hemophilia A under prophylaxis therapy. Report No. A62366.
2. **Study Title:** A phase II/III, randomized, cross-over, open-label trial to demonstrate superiority of prophylaxis over on-demand therapy in previously treated subjects with severe hemophilia A treated with plasma protein-free recombinant FVIII formulated with sucrose (BAY 81-8973). Report No. PH-37042.
3. **Study Title:** A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 in children with severe hemophilia A under prophylaxis therapy. Report No. A51496.

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

Overall, the study designs for the clinical trials and the PK results are acceptable and there are no hold issues at this time.

- The review is finished and there are no clinical pharmacology issues associated with this submission.
- The clinical pharmacology labeling section needs modification and will be sent to the sponsor at appropriate time.

D. Plan for addressing issues and the reason for the suggested approach

N/A

Clinical Late-Cycle Reviewer Report

Reviewer Name: Megha Kaushal, MD
Discipline: Clinical
Branch Chief: Bindu George, MD, Clinical Review Branch, DHCR, OBRR

STN 125574 is an original biologics license application (BLA) submitted by Bayer for recombinant coagulation factor VIII (rFVIII) product formulated with sucrose referred to as BAY 81-8973 and under the trade name KOVALTRY. Kovaltry is a full length recombinant human factor FVIII produced in baby hamster kidney (BHK) cells and is (b) (4) to the currently marketed product Kogenate FS, as the rFVIII protein concentration is the same as Kogenate FS (STN 103332). Key changes to the drug substance production include: (b) (4)

[REDACTED]

A. Date reviewer will complete the primary discipline review, if not complete.

Preliminary review is complete and this reviewer will complete final review by the end of September 2015.

The following information requests are pending:

- 1) Safety and Efficacy assessment per PREA

B. Key findings and substantive issues with the information and data in the application.

- The bleeding rates in both potency periods (CS/EP with chromogenic based dosing and CS/ADJ with one-stage based dosing) were comparable, with similar median number of bleeds per year.
- The data show that prophylaxis is more effective than on-demand treatment regarding the reduction of occurrence of bleeds per year.
- Prophylaxis treatment with Kovaltry administered either twice or three times per week was efficacious in the prevention of bleeds.
- In terms of safety, there were no allergic reactions including anaphylaxis and no evidence of vascular thrombosis in PTPs. One low titer inhibitor has been reported in a 10 year old PTP during an episode of acute pneumonia.
- Kovaltry was used for hemostatic control in major and minor surgeries and rated as good or excellent for all types of surgery.

Substantive Issues:

- In an update safety report, 6 out of 14 (43%) of PUPs have developed inhibitors.
- BIMO inspection site 14006 with multiple concerning issues (2 subjects).

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline.

The above issues can be addressed by labeling and do not affect approval.

D. Plan for addressing issues and the reason for the suggested approach

- PUP inhibitor development:
 - Completion of PUPs study with 25 subjects as stated in the protocol
 - State current PUP data in the Prescribing Information
 - Addition of Post-Marketing Experience of Kogenate FS into label as comparable to Kovaltry
- Site 14006:
 - Statistical Analysis for Efficacy and Safety with the deletion of Site 14006
 - Site monitoring data from 2 additional sites to be discussed with BIMO.

Other Updates:

- Indication Language- refer to Bayer response in PI

Bioresearch Monitoring Late-Cycle Reviewer Report

Reviewer Name: Bhanumahti Kannan, MS
Discipline: Bioresearch Monitoring
Branch Chief: Patricia Holobaugh, PhD, Bioresearch Monitoring Branch,
Division of Inspections and Surveillance, OCBQ

A. Date reviewer will complete the primary discipline review, if not complete.

September 30, 2015. The inspection reports are pending and may affect the review timelines.

B. Key findings and substantive issues with the information and data in the application.

The bioresearch monitoring (BIMO) inspections of two clinical investigators for Leopold II study (Study 14319) at two Romanian sites did not reveal significant problems that impact the data submitted in the Biologics Licensing Application (BLA). BIMO inspection at one U.S. site for Leopold I study (Study 12954) revealed deficiencies in study conduct. The inspection reports are pending for all three clinical investigator inspections. The summary will be finalized upon receipt of all inspection reports.

The inspection conducted at one U.S. site for Leopold I study (Study 12954) noted violative study conduct as issued on the Form FDA 483 as described here:

1. For both subjects enrolled at the site and for both Part A and Part B screening/baseline visits, a second sample was not drawn for inhibitor antibody measurement as required by the protocol.
2. For one of two subjects enrolled in the study, at least two bleeds found on the source documents were not reported by the sponsor in the BLA.
3. For both subjects enrolled in the study, a total of six adverse events were not reported by the sponsor in the BLA. The sponsor reported two adverse events for one subject in the BLA.

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

Pending a final review of the inspection reports our preliminary review noted inadequate oversight of the study by the clinical investigator at the U.S. site for Leopold I study.

D. Plan for addressing issues and the reason for the suggested approach

We defer the decision to include the study data from two subjects at this U.S. site to the review committee. We consider requesting monitoring reports for the two largest trial sites for Leopold I study (which were not inspected by FDA).

Statistical Late-Cycle Reviewer Report

Reviewer Name: Lin Huo, PhD
Discipline: Biostatistics
Branch Chief: Renee Reese, PhD, Therapeutics Evaluation Branch,
Division of Biostatistics, Office of Biostatistics and
Epidemiology (OBE)

A. Reviewer's assigned areas *not* completely reviewed to-date

All finished.

B. Key findings and substantive issues with the information and data in the application.

The primary objectives are met for the two pivotal studies and the pediatric study.

Leopold I: The annualized and the observed mean number of total bleeds during the 1-year treatment period was 3.8 ± 5.2 bleeds (median: 1.0 bleed).

Leopold II: The median annualized bleeding rates were 59.96 bleeds/year in the on-demand group and 1.98 bleeds/year in the prophylaxis group. Comparison of the bleeding rates demonstrated a statistically significant difference ($p < 0.0001$).

Leopold Kids: The median annualized bleeding rate within 48 hour after prophylactic injection was 0.00 bleed/year (mean: 2.04 ± 2.91).

The non-inferiority of CS/EP dosing versus CS/ADJ dosing was demonstrated by combining the efficacy data of Leopold I and Leopold II.

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

N/A

D. Plan for addressing issues and the reason for the suggested approach

N/A

Epidemiologic Late-Cycle Reviewer Report

Reviewer Name: Marthe Bryant-Genevier, MD
Discipline: Epidemiology
Branch Chief: Wei Hua, MD, Analytic Epidemiology Branch, Division of Epidemiology, OBE

A. Date reviewer will complete the primary discipline review, if not complete.

Pharmacovigilance Plan (PVP) review memo is completed and undergoing management review.

B. Key findings and substantive issues with the information and data in the application.

Inhibitor development in PUPs. The Leopold Kids Part B in PUPs has not been completed yet the most recent update shows that 6/15 PUPs (40%) have developed inhibitors. The study has enrolled 15 out of 25 subjects and the rate of inhibitor development is in the upper values of the expected range.

In addition, observational studies have suggested an increased risk of inhibitor development in PUPs with Kogenates FS when compared to Advate. This was the objective of label change for Kogenate FS. Kovaltry is (b) (4) to Kogenate FS yet the Kovaltry label does not mention these findings.

C. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

The risk of inhibitor development in PUPs cannot be completely assessed because the Leopold Kids Part B (PUPs study) is ongoing and is not expected to be completed before licensure.

D. Plan for addressing issues and the reason for the suggested approach

- 1- Routine pharmacovigilance
- 2- Active surveillance: two registry studies conducted as PMC to monitor a list of AEs including inhibitor development. Specifically, the following events are included: new inhibitors, infections, allergic reactions, thrombosis, new malignancies and death.
- 3- Include in the Kovaltry label the Kogenate FS wording related to inhibitor development in PUPs. Kovaltry and Kogenate FS are essentially identical and the known safety profile of Kogenate FS should be reflected in the Kovaltry label.
- 4- In our opinion, the best way to assess whether Kovaltry presents a greater than expected risk of inhibitor development is to complete the Leopold Kids Part B. Post-marketing studies using registries will not answer the question adequately due to the many limitations inherent to registries. Cohort studies comparing Advate with Kovaltry would

be a method of choice to post-marketing studies however, such method would take a long time due to the small incidence of infants with severe hemophilia A. In order to assess the risk of inhibitor development in PUPs, the Leopold Kids Part B study should be completed prior to granting approval of Kovaltry in PUPs. Depending of the results of the Leopold Kids Part B study, the number of subjects may have to be increased to 100 PUPs with an accumulated 50 EDs each.

- 5- Consider a class label change to explicitly describe the difference in risk of inhibitor development in PUPs and PTPs.

CDRH Late-Cycle Reviewer Report

Reviewer Name: Ryan McGowan
Discipline: Device Design (container closure system component)
Branch Chief: Richard Chapman, General Hospital Devices Branch,
Division of Anesthesiology, Office of Device Evaluation,
CDRH

a. Reviewer's assigned areas *not* completely reviewed to-date

Device constituent part(s) clinical experience under the clinical study
Device constituent part(s) stability information
Master file (b) (4) for syringe design (including luer adapter and functional device performance)
Updated device information for the vial adapter

b. Outstanding Information Requests

Information request and letter of internal questions sent to Pratibha Rana on 9-1-2015, which contained:

- Internal request for clarification on leachable/extractable review
- External request for information on:
 - o Verification information for the vial adapter
 - o Updates to changes made on the vial adapter since the 510(k) clearance
 - o Verification of device performance at time of kit expiration

c. Date reviewer will complete the primary discipline review, if not complete.

Reviewer will continue to update review as responses to internal and external questions are resolved. Reviewer plans to complete review of items listed under a, above by September 18, 2015.

d. Key findings and substantive issues with the information and data in the application.

1. The sponsor does not appear to have provided verification information for the vial adapter component. Additional information is pending for this portion of the review.
2. The sponsor does not appear to reference the most current version of the vial adapter device CDRH clearance within their LOA. Additional information is pending for this portion of the review.

3. The sponsor does not appear to have included information which verifies the device components will perform as expected after aging and shipping. Additional information is pending for this portion of the review.

e.f. Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline AND Plan for addressing issues and the reason for the suggested approach

Item 1 (verification of vial adapter): Requested follow-up via IR. Considered resolvable within review clock.

Item 2 (510(k) information for vial adapter): Requested via IR. Considered resolvable within review clock.

Item 3 (Aging information): Requested via IR. Considered resolvable within review clock
OR acceptable under post-marketing commitment