

UNITED STATES PUBLIC HEALTH SERVICE
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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INTERNAL MEMORANDUM

DATE: December 19, 2008

FROM: Monique P. Gelderman-Fuhrmann, Ph.D.
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THROUGH: Jaroslav Vostal, M.D., Ph.D.
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TO: Heather Erdman, RAC
Regulatory Project Manager

SUBJECT: Summary Review Memo for approval of ANDA: **BA070025** –
Anticoagulant Citrate Phosphate Dextrose (CPD) Solution, USP by
Caridian BCT (Formerly Gambro BCT, Inc.)
Document date: 11-May-2007

Summary Review Memo

Recommendation:

I recommend the approval of the manufacturing and marketing of the anticoagulant Citrate Phosphate Dextrose Solution (CPD) in a single-use sterile whole blood collection set. These whole blood collection sets can only be used for further processing with the Atreus Whole Blood Processing System (510(k) number BK080010; determined substantially equivalent in June 2008). The whole blood collection sets are to be sterilely connected onto Atreus Processing sets for further processing which will need to be completed within 8 hours of the whole blood collection.

Review Responsibilities:

CMC Review: Jaroslav Vostal, Monique P. Gelderman-Fuhrmann
(CBER/OBRR/DH/LCH)

Chemistry Review: Raymond P. Frankewich (CDR/OPS/ONDQA/DPE)

Label Review: Kenneth Zemann (CBER/OBRR/DBA/BPB)

Sterility/Biocompatibility Review: Destry Sullivan (CBER/OCBQ/DMPQ/BII)

Introduction:

Gambro BCT seeks approval to manufacture and market anticoagulant Citrate Phosphate Dextrose Solution (CPD) in single-use sterile whole blood collection set. The product is an anticoagulant commonly associated with blood collection. The sets are used for collecting whole blood from altruistic donors. The whole blood collection sets are sterilely connected onto Atreus Processing sets for further processing which will be completed within 8 hours of whole blood collection. The set is referred to as the "Atreus collect set" or "collect set" throughout the submission. However, the sponsor decided in November 2008 to change the name to "Whole Blood Collection Set".

The drug that is the subject of this application is suitable for submission as an Abbreviated New Drug Application (ANDA) commensurate with the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984. This drug is equivalent to the reference listed drug, anticoagulant Citrate Phosphate Dextrose (CPD) Solution, USP, Baxter Healthcare Corporation (BN900224-0).

The submission consisted of three volumes containing the following information for the Agency's review:

VOLUME I of III (Sections I – XII)

Section I. FDA 356h

In this section the following is provided: a copy of FDA form 356h, the strength of anticoagulant (per 1000 mL-see below), an establishment list specifying the contact person, registration # and function of all 6 establishments involved (either as a manufacturing or testing site, and the referenced Drug Master Files (BB-MF-(b) (4) and MF-(b) (4)).

<u>Ingredients:</u>	<u>Per 1000 mL</u>
Citric Acid (monohydrate), USP	3.27 g
Sodium Citrate (dehydrate), USP	26.3 g
Sodium Dihydrogen Phosphate (dihydrate), USP*	2.51 g
Dextrose (monohydrate), USP	25.5 g

*In section VIII-a it is stated that this is not an USP monograph ingredient.

Section II. Basis for ANDA

The drug that is the subject of this application is suitable for submission as an ANDA commensurate with the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984. The drug is equivalent, per Gambro, to the reference listed drug, anticoagulant Citrate Phosphate Dextrose (CPD) Solution, USP, Baxter Healthcare Corporation (BN900224-0) stored in PL 2209 container.

Section III. Patent Certification and Exclusivity

A signed and dated copy of this certificate is provided. It states that there are no patents that claim the listed drug referred to in the ANDA and that there is no unexpired market exclusivity currently in effect.

Section IV. Comparison between Generic Drug and Reference Listed Drug (RLD)

Active Ingredients:

<u>RLD:</u>	<u>PROPOSED:</u>
Sodium Citrate (dihydrate) USP	Sodium Citrate (dihydrate) USP
Dextrose (monohydrate) USP	Dextrose (monohydrate) USP
Citric Acid (anhydrous) USP	Citric Acid (monohydrate) USP
Monobasic Sodium Phosphate	Dihydrogen Sodium Phosphate

(monohydrate) USP

(dehydrate) USP

Inactive Ingredients:

RLD:

Water for Injection

Sodium Hydroxide if needed

PROPOSED:

Water for Injection, USP

Not used

The route of administration, dosage form and strength of the proposed Gambro BCT drug product is the same as for the RLD. The labeling is the same as for the RLD except for minor changes required due to inactive ingredients, NDC numbers, manufacturers, as well as other minor editorial revisions.

Section V. Labeling

In this section examples of the following labels are provided: 63 mL bag label (for 450 mL collection), 70 mL bag label (for 500 mL collection), 63 Foil Pack label (for 450 mL collection), 70 Foil Pack label (for 500 mL collection), 63 mL Carton (case) label (for 450 mL collection), 70 mL Carton (case) label (for 500 mL collection), and the Instructions For Use Document.

Section VI. *In vivo* Bioavailability/Bioequivalence and *in vitro* Test Data

In this section Gambro provides formulation comparisons with the RLD, such as: 1) qualitative composition, and 2) quantitative composition, which includes proposed commercial batches with a theoretical yield of 1000 mL/Batch. In addition, Gambro requests a "Waiver of *in vivo* Bioequivalence" pursuant to 21 CFR 320.22(a) (b) [see pp. 186-188 of 2006 CFR]. The basis of this request is that this parenteral solution is intended for administration *ex vivo* for blood component collection procedures. Since this product is not intended for direct *in vivo* use, issues of bioequivalence in terms of absorption, distribution, metabolism and excretion are not relevant.

Section VII. Components and Composition

Gambro lists the components/ingredients for the CPD solution and each function and safety. In addition, the quantitative composition and comparison of the "submission batch" versus the "full-scale" commercial production batches are disclosed in 3 tables.

Section VIII. Raw Material Controls

This section lists the page numbers of where to find: commercial release testing and acceptance criteria, manufacturer certificate of analysis etc.

Section VIII-a. Active Ingredients

pp. 83 – 173: The sponsor provides in this section the manufacturers of the active ingredients, specifications and test methods.

Section VIII-b. Inactive Ingredients

pp. 174 – 205: The sponsor provides in this section the manufacturers of the inactive ingredients, specifications and test methods.

Section IX. Description of Manufacturing Facility

The CPD solution, USP is (b) (4)

(b) (4) at Ivex Pharmaceuticals in Larne, Northern Ireland. The facility for the (b) (4) is Gambro BCT, Inc. at Lakewood, CO. A copy of the CGMP certification which applies to both locations is also provided (dated 05/01/07).

Section X. Outside Firms/Contract Laboratories

Four firms/contract testing laboratories are listed w/ contact information and the activity they perform. It is also stated that written procedures are in place for collecting and shipping samples from Ivex to these outside firms.

Section XI. Manufacturing and Processing Instructions

This section includes the comparison between the submission batch and the full-scale production batches. A comparison of: formulation, equipment, manufacturing, production etc.

Section XII. In-Process Controls

This section includes the executed Batch Records for both submission batch solutions (USP 63 mL and USP 70 mL).

VOLUME II of III (Sections XIII – XVIII)

Section XIII. Packaging Material Controls

As per current USP, Gambro BCT CPD Solution, USP is packaged into a single-dose container of colorless, transparent suitable plastic material. Propose are two fill volumes of anticoagulant of 63 mL or 70 mL in the same size bags, labeled for 450 mL and 500 mL blood collection volumes respectively. This configuration is referenced as Atreus Collect Kit, Collection Kit, or Collect Set. The collection set is manufactured in 2 phases.

Phase 1 at Gambro BCT: (b) (4)

(b) (4)

(b) (4) Phase 2 at Ivex: (b) (4)

(b) (4)

This section contains diagrams of all components of the collection set.

Section XIV. Finished Dosage Form Controls

Provided in this section are the specifications that include the acceptance criteria and test methods proposed for release of the finished product. EP acceptance criteria and test methods are proposed.

Section XV. Analytical Methods

Section XVI. Stability Data of Finished Dosage Form

Section XVII. Reserved

Only one page with the wording “not applicable” is provided.

Section XVIII. Samples Statement

A table with the Ivex lot #, manufacturer lot # each of the raw materials used to manufacture the CPD solution is provided.

Section XIX. Environmental Assessment Statement

A dated statement (05/01/2007) is provided: ..”The requested action, approval of this ANDA, qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(b)”....

Section XX. Debarment Certification and conviction Statement

A dated statement (05/01/2007) is provided to certify that Gambro has not used and will not use the services of any person or firm debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Section XXI. Other

Provided are authorization letters (2) to access two related DMFs (DMF# BB MF (b) (4) and DMF Type III No. (b) (4)).

VOLUME III of III (Section XXII)

Section XXII. Sterilization

This volume, pp 1132-1406, consists of sterilization assurance information and data.

Critical issues and disagreements with the applicant and/or within the review team:

There were no critical issues and disagreements with the applicant and/or within the review team. All reviewers submitted their requests for additional information which were conveyed to the sponsor via the RPM. The sponsor acknowledged all requests and supplied the requested information.

One major concern of the lead reviewer was the possibility of platelet activation, red cell hemolysis etc., especially since Caridian's device has been associated with high unacceptable hemolysis levels (a reference to data that were provided in support of IND (b) (4) and IDE (b) (4)). The ANDA did not include any *in vitro* data. The following was the final request by the lead reviewer which was conveyed to the sponsor by the RPM (February 2008):

The agency is concerned about possible platelet activation, red cell hemolysis, etc. In addition, your device has been associated with high unacceptable hemolysis levels (a reference to data that were provided in support of IND (b) (4) and IDE (b) (4)). It needs to be defined for how long the whole blood will be stored in the Atrius Collect Set (i.e., 2 hours, 4 hours etc. Quoting 21CFR640 will **not** be sufficient!). The *in vitro* studies that should be conducted to define the storage period could be conducted as follows: Collect human whole blood in the Atrius Collect Set (with CPD) and store it in the collect set for the duration that it will be labeled for, i.e., 8 hours and at that time point, test for hemolysis etc. (For specific tests and the acceptance criteria see section below entitled: "Our current thinking for *in vitro* studies").

In addition, the intended use of the collected whole blood with CPD in the Atrius Collect Set needs to be firmly defined. The agency is still not sure if it is intended for transfusion or if it is intended for further processing? There is mentioning of both uses in different sections of the original ANDA. If it is intended for transfusion, the listed parameters for platelet activation and plasma need to be determined in addition to the red blood cell studies and the data should be provided to the agency for review. If the blood collected by the Atrius Collect Set is intended for further processing only, the "processing device" has not been cleared yet. This suggests that the blood could not be processed into a licensed transfusion product. This should be mentioned in the IFU. The suggested hemolysis studies should still be conducted in anticipation of a future clearance of the "processing device".

Our current thinking for *in vitro* studies is as follows:

We recommend that you perform the following tests for each blood component (perform tests at day 0 (zero), immediately after collection, and at the end of the maximal allowable storage period).

1.Red Blood Cells

(Maximum allowable storage period at 1 to 6°C as appropriate for anticoagulant/preservative solution combination).

- Hemolysis¹
 - Intracellular ATP (adenosine triphosphate) (% compared to day 1)
-

- Extracellular pH
- Extracellular glucose and lactate
- Extracellular potassium (Supernatant potassium)
- Intracellular 2,3-DPG (diphosphoglycerate) (% compared to day 0-1)
- Oxygen affinity
- Osmotic fragility
- Hematocrit
- Supernatant hemoglobin and total hemoglobin
- Residual White Blood Cells

¹The hemolysis of each test unit will be evaluated at the end of storage. A success is defined as hemolysis less than 1%. The success rate is estimated as the proportion of test units with hemolysis less than 1%. The acceptance criterion is that the one-sided 95% lower confidence limit for the true population success rate be greater than 0.95. We recommend that the lower confidence limit be constructed based on a binominal distribution.

2. Platelets

(Current maximal allowable storage period at 20 to 24°C is 3, 5, or 7 days, depending on product).

- Platelet product volume
- Platelet count per unit and per μL
- pH
- Mean platelet volume
- Extent of shape change
- P-selectin (CD-62P) expression on the platelet surface

3. Plasma

(12-month storage at $\leq -18^\circ\text{C}$).

Storage container surfaces as well as leaching chemical additives have the potential to affect labile proteins and/or to activate coagulation. We recommend the following in vitro tests for monitoring labile plasma proteins and coagulation activation.

Labile proteins:

- Factor V
- Factor VIII
- Protein S
- Coagulation activation:
 - Visual inspection
 - Prothrombin time
 - Activated partial thromboplastin time
 - Fibrinogen
 - Prothrombin Fragment 1+2
 - Fibrinopeptide A
 - Soluble Fibrin monomer

You may elect to provide data from performance of one or more of the recommended tests or substitute other established laboratory markers of

coagulation in comparison with an FDA-approved plastic container. The above laboratory markers recommended for coagulation activation are sensitive for detecting minimal coagulation activation that may occur during plasma storage.

In addition, cellular transfusion products should also be evaluated with *in vivo* radiolabeling studies.

The Agency received an amendment dated 16-July-2008 which included a reference to the *in vitro* data that was supplied in a premarket 510 (k) submission for the Atreus Whole Blood Processing System (510(k) number BK080010; determined substantially equivalent in June 2008). This data was reviewed.

Conclusions from all reviewing disciplines:

All reviewers recommended approval for this submission after all their issues raised were resolved to the Agency's satisfaction. The reviews and recommendations from all reviewers for this ANDA are on file.