CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-703

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PATENT CERTIFICATION

In accordance with the Federal Food, Drug and Cosmetic Act, as amended September 24, 1984, patent certification is hereby provided for our New Drug Application for PrismaSol, submitted pursuant to section 505(b)(2).

In the opinion and to the best knowledge of Gambro Lundia AB, there is no patent that claims the listed drug referred to in this application or that claims a use of the listed drug.

Marie-Armelle MOURET
Regulatory Affairs Group Manager

Date: 2005/06/13

Fei LAW
Quality Manager

Date: July 12, 2005

Edna M. O'Connor
Director, Intellectual Property
Group Patent Counsel, Gambro Group
Patent department

Date: April 11, 2005

Appears This Way
On Original

EXCLUSIVITY SUMMARY

NDA # 21-703 SUPPL # N/A HFD # 110

Trade Name PrismaSol Solutions

Generic Name PrismaSol Solutions (BK 0/3.5, BGK 2/0, BGK 2/3.5, BGK 4/3.5, BGK 4/2.5, BGK 4/0, BK 4/2.5, BGK 0/2.5, and BK 0/0)

Applicant Name Gambrio Lundia AB/ Gambro Renal Products

Approval Date, If Known October 25, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
 !

IND # YES ☐ ! NO ☐
 ! Explain:

Investigation #2 !
 !

IND # YES ☐ ! NO ☐
 ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
 !

YES ☐ ! NO ☐

Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Dianne Paraoan
Title: Regulatory Health Project Manager
Date: October 25, 2006

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
10/30/2006 01:39:49 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-703

Stamp Date: 28 Sep 05 **Action Date: 25 Oct 06**

HFD: 110 **Trade and generic names/dosage form: PrismaSol Solutions**

Applicant: Gambro Renal Products **Therapeutic Class: 3S**

Indication(s) previously approved: None. Approved as a device

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Use as a replacement solution in Continuous Renal Replacement Therapy (CRRT) to replace plasma volume removed by ultrafiltration and to correct electrolytes and acid-base imbalances

Is there a full waiver for this indication (check one)?

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☑ **Other: There are no safety concerns.**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Dianne C. Paraoan
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

cc: NDA 21-703
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: used in case of drug poisoning when CRRT is used to remove filterable substances.

Is there a full waiver for this indication (check one)?

☑ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☑ **Other: There are NO safety concerns.**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Dianne C. Paraoan
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

cc: NDA 21-703
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dianne Paraoan
10/30/2006 01:16:22 PM

DEBARMENT CERTIFICATION

PrismaSol solutions

Gambro Lundia AB hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Jon Risfelt
Officer for Gambro Lundia AB
President
Gambro Renal Products

Date: 21/06/2005

MODULE 1: ADMINISTRATIVE AND PRESCRIBING INFORMATION

1.3.1.5 Financial Disclosure

Not applicable. This application is a 505(b)(2) application; the applicant did not conduct clinical studies to support this application.

The information presented in this application to support the safety and efficacy of PrismaSol for its intended use is based on published articles and other information available in the public domain.

Refer to the Minutes of the December 9, 2004 Pre-NDA meeting with FDA (Division of Cardio-Renal Drug Products) personnel and the applicant (Gambro Renal Products) personnel and representatives. The minutes are located in Module 5, Volume 4, Section 5.4.1.

RHPM Overview of NDA 21-703
PrismSol ™ Solutions
October 24, 2006

Sponsor:	Gambro Ludia AB/ Gambro Renal Products
Classification:	3S
Receipt Date:	September 28, 2005
User Fee Goal Date:	July 28, 2006
AP Letter Issued:	October 25, 2006
Final Draft Labeling:	October 24, 2006

Background
PrismaSol Solutions is being developed for use in adults and children for use as a replacement solution in Continuous Renal Replacement Therapy (CRRT) to replace plasma volume removed by ultrafiltration and to correct electrolytes and acid-base imbalances. PrismaSol solution may also be used in case of drug poisoning when CRRT is used to remove dialyzable or filterable substances.

Continuous renal replacement therapy is dialysis continued for twenty four hours a day to treat critically ill patients with renal failure. The aims of CRRT are control of fluid balance, control of plasma electrolytes, control of acid-base balance and removal of products of metabolism.

The sponsor, Gambro Renal Products, has developed nine formulations. They seek to market 7 of the 9 formulations. The nine formulations fall within the approved range under the 510K clearance of PrismaSate, an FDA approved dialysate solution which is the basis for the PrismaSol Solutions.

A Request for Designation dated May 2, 2003 recommended that solutions intended to be infused into a patient would be managed by the Center for Drug Evaluations and Research (CDER) rather than the Center for Devices and Radiological Health (CDRH), which manages dialysate solutions that passes through a device.

Previous correspondence and meetings regarding the development of PrismaSol Solutions for the use in the management of patients undergoing CRRT:

1. Pre-NDA Meeting, December 9, 2003
2. Pre-NDA CMC Meeting, March 2, 2004
3. Guidance Teleconference, May 10, 2004

Division Director's Memo
In Dr. Stockbridge's memo dated October 24, 2006, he stated that PrismaSol is a 9-member set of sterile solutions for use to replace water and to correct acid-base and electrolyte disturbances caused during CRRT. The various solutions contain sodium, potassium, calcium, magnesium, chloride, dextrose, lactate, and bicarbonate only, in different combinations and amount.

Thus there are no novel or foreign molecular species and what constituents there are are not what one would ordinarily mean by "drugs." Their actions are no receptor-mediated and they are no heir to the complex potential interaction of drugs. The sponsor did not conduct clinical studies, rather referred to published literature to support their application.

Other infustate constituents may need to be added, but individualization of treatment renders it impractical to manufacture solutions suitable for all possible clinical scenarios. Thus, labeling provides some basic advice, but the instructions fro use heavily rely on the physician's judgment about how to perform CRRT.

The publications would not have been sufficient had we felt there was a need for clinical data supporting effectiveness or safety. However, the current view is that infusates are, effectively, bulk parenterals. The consequences of their use are predictable from first principles. Within a certain region of physiological

and near-physiological concentrations, the effects can be predicted with sufficient accuracy that no clinical experience is indicated to confirm them. The concentrations of electrolytes in PrismaSol are well within the bounds of comfort.

Medical Review
In his review dated July 7, 2006, Dr. Xiao stated that based on the results of published clinical studies, he concludes that there is sufficient documentation in the articles to adequately evaluate the safety and efficacy of the PrismaSol formulations in the indicated acute renal failure patient population when used as a replacement solution in CRRT. However, since the dialysate for hemodialysis use is regulated by CDRH, the indication of dialysate use of PrismaSol in hemodialysis and hemodiafiltration should be discussed with CDRH.

Dr. Xiao recommended the following labeling revisions:

1. When citrate is used as an anticoagulant agent during CRRT, adjustment of the composition of PrismaSol solutions may be needed. This should be added to the labeling.

2. Phosphate which is not in the PrismaSol solutions may be required at some stage during CRRT. This should be added to the labeling.

Financial Disclosure is included in the action package and is incorporated in the Medical Review.

The Integrated Summary of Safety and Effectiveness is incorporated in the Medical Review.

There is no Safety Update Review. The sponsor has submitted literature references to support the safety and efficacy of these products and have not provided additional literature submissions.

Statistical Review
No statistical review was warranted.

Pharmacology Review
No pharmacology review was warranted.

Biopharmaceutical Review
No biopharmaceutical review was warranted.

Chemistry Review
In her first review dated July 10, 2006, Dr. McLamore noted several unresolved deficiencies issued to the sponsor on both March 27 and May 22, 2006 CMC discipline review letters. After receipt of a major amendment on July 10, 2006 that addressed the unresolved deficiencies, the goal date was extended three months to provide Dr. McLamore with sufficient time to review the amendment.

Dr. McLamore recommended an approvable and would recommend an approval from the CMC standpoint contingent on an acceptable recommendation from the Office of Compliance and an adequate response to the CMC deficiencies.

A third discipline review letter was issued to the sponsor on September 13, 2006. In her second review signed on October 13, 2006, all CMC deficiencies were adequately addressed; thus recommending overall approval from the CMC perspective.

The Office of Compliance has issued an overall acceptable recommendation for all establishments.

The Environmental Assessment (EA) and the Finding of No Significant Impact (FONSI) were adequate addressed accordingly to Dr. McLamore's review signed October 13, 2006.

No Phase 4 commitments were proposed.

Microbiology
A discipline review letter was sent to the sponsor on March 27, 2006 aimed at evaluating the sterility assurance of the drug product. After review of the responses to the discipline review letter, Dr. Metcalfe in his review dated May 15, 2006, noted that there are no microbiology deficiencies and recommended approval from the product quality microbiology perspective.

DSI
During the filing meeting, it was concluded that no DSI consult was warranted.

Pediatric Rule
Based on the information provided the Division granted a full waiver from all pediatric studies because there are no safety issues.

Labeling
On October 24, 2006, the Division and GAMBRO Renal Products came up with a final draft package insert. After discussions with the Office of Combination Products and the CDRH/ GI Branch, it was decided that reference to the use of PrismaSol Solutions [redacted] The package insert should only reference the use of the product as an infusate, [redacted] Please refer to the Labeling section of the action package. Also included in the Labeling section of the action package is the proposed package insert.

DMETS

DMETS objects to the proposed tradename; however, because this product is already approved as a device, indicated for use as a hemodialysis solution under the same name, the Division accepted PrismaSol Solutions as the proposed name. This was communicated in an email dated November 15, 2005.

DDMAC
Please refer to review in the action package in Advertising section.

Advisory Committee Meeting
No Advisory Committee Meeting was warranted specifically for this NDA.

Project Manager's Summary
To my knowledge, there are no issues that might prevent action on this NDA.

An approval letter with enclosed labeling will be drafted.

Dianne C. Paraoan
Regulatory Health Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dianne Paraoan
10/30/2006 01:19:59 PM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-910	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug: PrismaSol Solutions (9 formulations)		Applicant: Gambro Ludia AB/ Gambro Renal Products	
RPM: Dianne Paraoan		HFD- 110	Phone # 301-796-1129

Application Type: ( ) 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** (X) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): The applicant has referred to published literature of the solutions (compounds) no a specific application. The products are physiological solutions. The solution has been approved as a dialysate with a 510(k) clearance in the Center for Devices and Radiological Health (CDRH).

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	July 28, 2006 Extended: October 28, 2006
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 3006155
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
arment certification: verified that qualifying language (e.g., willingly, knowingly) was ısed in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
nt	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) (X) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	Goal date extended: July 10, 2006
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	October 24, 2006
• Most recent applicant-proposed labeling	October 24, 2006
• Original applicant-proposed labeling	September 28, 2005
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS: June 23, 2006 DDMAC: May 26, 2006 Labeling Mtgs: June 23, July 6, October 13, 19, and 23, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	October 24, 2006
• Applicant proposed	October 24, 2006
• Reviews	DMETS: June 23, 2006
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	Clinical: December 9, 2003 Chemistry: March 2, 2004
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Guidance Teleconference: May 10, 2004
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Dr. Stockbridge: October 24, 2006 ✓
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	July 7, 2006 ✓
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A The sponsor has submitted literature references to support the safety and efficacy of these products and no additional literature was submitted.
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	October 30, 2006 ✓
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	July 10 and October 13, 2006 ✓
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	July 10, 2006
• Review & FONSI *(indicate date of review)*	October 13, 2006
• Review & Environmental Impact Statement *(indicate date of each review)*	October 13, 2006
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	May 15, 2006 ✓
❖ Facilities inspection (provide EER report)	Date completed: July 18, 2006 **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**(X)** Completed **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

Dianne Paraoan
10/30/2006 01:12:57 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-703

DISCIPLINE REVIEW LETTER

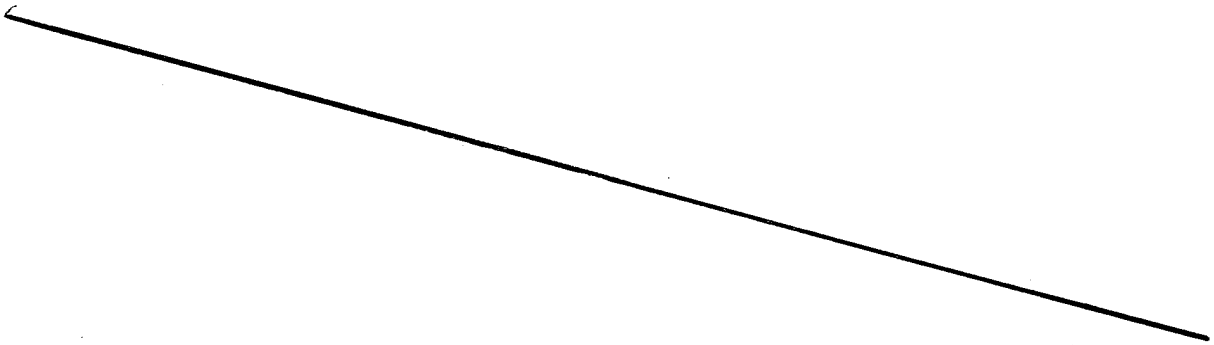
Gambro Renal Products
Attention: Fei Law
Quality and Regulatory Manager, US
1845 Mason Avenue
Daytona Beach, FL 32771

Dear Ms. Law:

Please refer to your September 27, 2005 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PrismaSol Injectable Solutions.

We also refer to your submission dated July 7, 2006.

We have completed our review of the Chemistry, Manufacturing and Controls section of your submission, and we have identified the following deficiencies:



If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Ms. Dianne Paraoan, Regulatory Health Project Manager, at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
9/13/2006 09:34:04 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-703

Gambro Renal Products
Attention: Ms. Fei Law
Quality and Regulatory Manager, US
1845 Mason Avenue
Daytona Beach, FL 32771

Dear Ms. Law:

Please refer to your September 27, 2005 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PrismaSol Injectable Solutions.

On July 10, 2006, we received your July 7, 2006 major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 28, 2006.

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
7/14/2006 10:38:59 AM

Paraoan, Dianne

From: Paraoan, Dianne
Sent: Monday, June 19, 2006 12:53 PM
To: 'Law, Fei'
Subject: One additional CMC questions

Hi Fei,

I just received an email from your chemist requesting response to an additional question. Reference is made to the CMC discipline review letters of May 22 and June 15, 2006.

Please provide an acceptance criterion for permeability.

Please respond to this question with your other responses.

If you have any questions or need clarification, please contact me at 301-796-1129.

Thanks!
Dianne

Appears This Way
On Original

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/s/

Dianne Paraoan
6/23/2006 07:51:23 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-703

DISCIPLINE REVIEW LETTER

Gambro Renal Products
Attention: Fei Law
Quality and Regulatory Manager, US
1845 Mason Avenue
Daytona Beach, FL 32771

Dear Ms. Law:

Please refer to your September 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PrismaSol Injectable Solution.

Our initial review of the Chemistry, Manufacturing and Controls section of your submission is complete. We have identified the following deficiencies:

1. Please provide a description of the manufacturing processes used in the manufacture of Dextrose Monohydrate, Lactic Acid, Potassium Chloride, Sodium Chloride (manufactured [redacted] and Sodium Bicarbonate (manufactured by [redacted] If applicable, your response should include controls of materials, critical steps and intermediates.

2. Please provide certificates of analyses for all starting materials and reagents used in the manufacture of each of the drug substances. Additionally, if any of these starting materials are not compendial grade, provide the test methods and specifications to control the quality of these materials.

3. Please provide certification that the contact materials of the containers used to store each of the drug substances meet the appropriate 21 CFR food contact regulations.

4. Please provide stability data for each of the drug substance to support the proposed [redacted] re-test period.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
5/22/2006 09:01:35 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-703

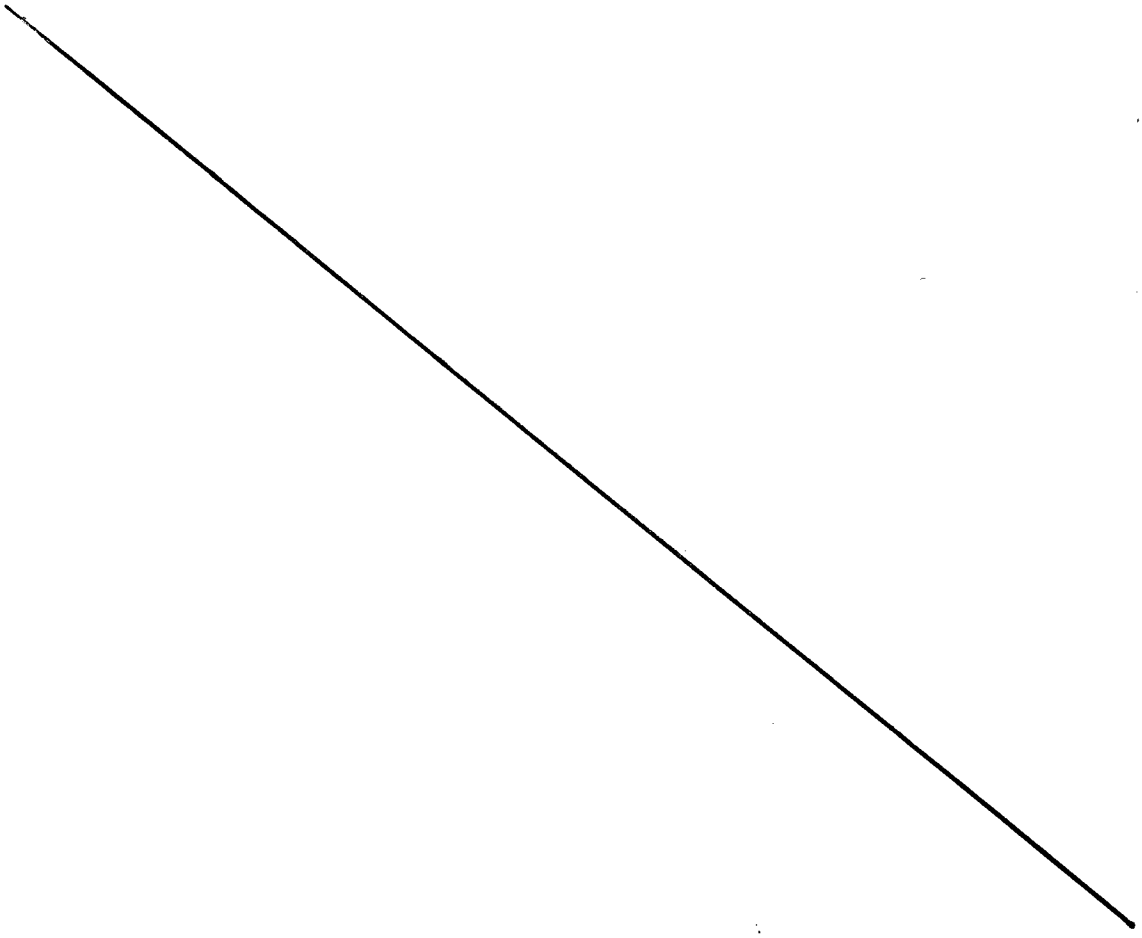
DISCIPLINE REVIEW LETTER

Gambro Renal Products
Attention: Fei Law
Quality and Regulatory Manager, US
1845 Mason Avenue
Daytona Beach, FL 32771

Dear Ms. Law:

Please refer to your September 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PrismaSol Solutions.

Our review of the Microbiology section of your submission is complete. The following information requests resulting from this review are aimed at evaluating the sterility assurance of the subject drug product. Reference is made to the Agency's 1994 *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.



We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
301-796-1129.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
3/27/2006 01:46:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-703

Gambro Renal Products
Attention: Ms. Fei Law
1845 Mason Avenue
Daytona Beach, FL 32117

Dear Ms. Law:

Please refer to your September 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PrismaSol Injectable Solution.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 27, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call:
Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
12/2/2005 03:37:11 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-703

Trade Name: PrismaSol
Generic Name: PrismaSol
Strengths:
#1 PrismaSol BK 0/3.5
#2 PrismaSol BGK 2/0 mEq/L
#3 PrismaSol BGK 2/3.5 mEq/L
#4 PrismaSol BGK 4/3.5 mEq/L
#5 PrismaSol BGK 4/2.5 mEq/L
#6 PrismaSol BGK 4/0 mEq/L
#7 PrismaSol BGK 4/2.5 mEq/L
#8 PrismaSol BGK 0/2.5 mEq/L
#9 PrismaSol BGK 0/0 mEq/L

Applicant: Gambro Renal Products

Date of Application: September 27 , 2005
Date of Receipt: September 28, 2005
Date clock started after UN: September 28, 2005
Date of Filing Meeting: November 7, 2005
Filing Date: November 27, 2005 (Sun)
User Fee Goal Date: July 28, 2006

Indications requested: 1) for use in CRRT as a replacement solution for HF and HDF [redacted]

2) for use in drug poisoning when CRRT is used to remove [redacted] or filterable substances

Type of Original NDA: (b)(2)

Therapeutic Classification: Standard
Chemical Classification: 3

Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee Status: PAID- July 20, 2005

? Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO

? Does another drug have orphan drug exclusivity for the same indication? NO

? If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

N/A

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

? Is the application affected by the Application Integrity Policy (AIP)? NO

?	Does the submission contain an accurate comprehensive index?	YES
?	Was form 356h included with an authorized signature? **If foreign applicant, both the applicant and the U.S. agent must sign.**	YES
?	Submission complete as required under 21 CFR 314.50?	YES
?	If an electronic NDA, does it follow the Guidance?	N/A
?	If in Common Technical Document format, does it follow the guidance?	YES
?	Is it an electronic CTD?	NO
?	Patent information submitted on form FDA 3542a?	N/A
?	Exclusivity requested? ***NOTE:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	NO
?	Correctly worded Debarment Certification included with authorized signature?	YES
?	Financial Disclosure forms included with authorized signature? **(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)**	N/A
?	Field Copy Certification (that it is a true copy of the CMC technical section)?	YES

Refer to 21 CFR 314.101(d) for Filing Requirements

?	PDUFA and Action Goal dates correct in COMIS?		YES
?	Drug name/Applicant name correct in COMIS?		YES
?	List referenced IND numbers:		N/A
?	End-of-Phase 2 Meeting?		NO
?	Pre-NDA Meeting(s)?	Dates:	December 9, 2003 (clinical) March 2, 2004 (CMC)

Project Management

?	All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	YES
?	Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS?	YES
?	MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS?	N/A

?	If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?	N/A

If Rx-to-OTC Switch application:

?	OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?	N/A
?	Has DOTCDP been notified of the OTC switch application?	N/A

Clinical

?	If a controlled substance, has a consult been sent to the Controlled Substance Staff?	N/A

Chemistry

?	Did applicant request categorical exclusion for environmental assessment?	YES
?	Establishment Evaluation Request (EER) submitted to DMPQ?	YES
?	If a parenteral product, consulted to Microbiology Team (HFD-805)?	YES

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 7, 2005

BACKGROUND:

Gambro Renal Products (Gambro) has developed PrismaSol proposed 1) for use in Continuous Renal Replacement Therapy (CRRT) as a replacement solution for HF and HDF [redacted] and 2) for use in drug poisoning when CRRT is used to remove [redacted] or filterable substances. The same product is marketed as a hemodialysis solution under the brand name PrismaSate regulated by the Center for Devices and Radiological Health (CDRH). Gambro seeks approval of 9 formulations of PrismaSol, containing different concentrations of dextrose and electrolytes. It was agreed by the Division and the Office of Medical Policy that the 9 different formulations be regulated under one NDA similar to other drugs with multiple doses. The sponsor has met with the Division on December 9, 2003 (Pre-NDA Meeting), March 2, 2004 (Pre-NDA CMC Meeting), and May 10, 2005 (Guidance Teleconference).

ATTENDEES:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardiovascular and Renal Products (DCaRP)
Ellis Unger, M.D.	Deputy Director, DCaRP
Shari Targum, M.D.	Acting Team Leader, Medical
Juan Carlos Pelayo, M.D.	Medical Officer
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry
Monica Cooper, Ph.D.	Chemist
Sherita McLamore, Ph.D.	Chemist
John Metcalfe, Ph.D.	Microbiologist
Edward Fromm	Chief, Project Management Staff
Dianne Paraoan	Regulatory Health Project Manager

ASSIGNED REVIEWERS:

Discipline	Reviewer	Expected Completion Date
Medical:	Juan Carlos Pelayo, M.D.	April 3, 2006
Statistical:		
Pharmacology:		
Chemistry:	Sherita McLamore, Ph.D.	May 31, 2005
Biopharmaceutical:		
Microbiology:	John Metcalfe, Ph.D.	May 1, 2005
DSI:		
Regulatory Project Management:	Dianne Paraoan	
Other Consults:		

Per reviewers, are all parts in English or English translation? YES

CLINICAL FILE X REFUSE TO FILE ___

- Clinical site inspection needed: NO
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A

MICROBIOLOGY		FILE X	REFUSE TO FILE ___
STATISTICS	N/A X	FILE ___	REFUSE TO FILE ___
BIOPHARMACEUTICS	N/A X	FILE ___	REFUSE TO FILE ___
PHARMACOLOGY	N/A X	FILE ___	REFUSE TO FILE ___
CHEMISTRY		FILE X	REFUSE TO FILE ___

- Establishment(s) ready for inspection? YES
  Microbiology YES

ELECTRONIC SUBMISSION:
Any comments: None

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__X__ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

__X__ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74 -December 9, 2005.
List (optional):

_____
Dianne Paraoan
Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

Draft: 11/9/05 Final: 12/1/05
R.D.
Stockbridge: 11/30/05
Fromm:11/30/05
Unger: 11-29-05
Targum: 11-28-05
Pelayo: 11-28-05
Srinivasachar:11-25-05
Cooper: 21-Nov-2005
McLamore: 11-21-05
Metcalfe:11-21-05

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/s/

Dianne Paraoan
12/2/2005 02:16:01 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-703

NDA ACKNOWLEDGMENT

Gambro Renal Products
Attention: Ms. Fei Law
1845 Mason Avenue
Daytona Beach, FL 32117

Dear Ms. Law:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	PrimaSol Injectable Solution
Review Priority Classification:	Standard (S)
Date of Application:	September 27, 2005
Date of Receipt:	September 28, 2005
Our Reference Number:	NDA 21-703

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 27, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 28, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, Room 4169
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, please call;

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc: Gambro
Attention: Ms. Melanie Baviere
1/3 Bld Charles de Gaulle
92707 Colombes Cedex, France

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/s/

Edward Fromm
10/31/2005 11:23:57 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-703

Gambro Renal Products
Attention: Ms. Fei Law
1845 Mason Avenue
Daytona Beach, FL 32117-5102

Dear Ms. Lei:

We have received your presubmission of non-clinical and clinical data information for the following:

Name of Drug Product: PrimaSol

Date of Submission: July 14, 2005

Date of Receipt: July 18, 2005

Our Reference Number: NDA 21-703

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application. Send the submission that completes this application and is intended to start the review clock as well as all submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Attn: Division of cardio-Renal Drug Products
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 594-5308

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Center for Drug Evaluation and Research

cc: Ms. Melanie Bavière
Gambro
1/3 bld Charles de Gaulle
92707 Colombes Cedex
France

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/s/

Edward Fromm
8/29/2005 07:26:18 AM

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
GAMBRO RENAL PRODUCTS Fei Law 1845 Mason Avenue Daytona Beach FL 32117 US	021-703
2. TELEPHONE NUMBER 386-274-2811 143	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? [X] YES [ ] NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: [X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME PrismaSol	6. USER FEE I.D. NUMBER PD3006155

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,Drug, and Cosmetic Act

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	QUALITY AND REGULATORY MANAGER, US SOLUTIONS	July 13, 2005

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$672,000.00

Form FDA 3397 (12/03)

IBE_PRMT_CLOSE_G) (Print Cover sheet)

Minutes of a Teleconference

Meeting Date:	May 10, 2004
Application:	Pre-NDA 21-703 (PrismaSol)
Sponsor:	Gambro Renal Products
Type of Meeting:	C
Classification:	Guidance
Meeting Request:	NA; Division Request
Sponsor Notified:	April 26, 2004
Confirmation Faxed:	April 27, 2004
Briefing Pkg. Date:	NA
Meeting Chair:	Dr. Throckmorton
Meeting Recorder:	Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Douglas C. Throckmorton, M.D.	Acting Deputy Center Director, Center for Drug Evaluation and Research
Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Carolyn Neuland, Ph.D.	Chief, Gastroenterology and Renal Devices Branch, HFZ-470, CDRH
Jeffrey Cooper, D.V.M.	Veterinary Medical Officer, Gastroenterology and Renal Devices Branch, HFZ-470, CDRH
Edward Fromm, R.Ph.	Acting Chief, Project Management Staff
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

Gambro Renal Products

Fei Law	Quality Assurance Manager, Gambro Renal Products
Mélanie Baviere	Regulatory Affairs Deputy Manager, Gambro SAS
David Zuchero	Regulatory Affairs Consultant, U.S. Agent

Background

Gambro Renal Products (Gambro) is developing PrismaSol as a replacement solution for use in Continuous Renal Replacement Therapy. The same product is marketed as a hemodialysis solution under the brand name PrismaSate regulated by the Center for Devices and Radiological Health. A Pre-NDA meeting between Gambro Renal Products and the Division of Cardio-Renal Drug Products was held on December 9, 2003. In that meeting, Dr. Throckmorton stated he had proposed, to the Office for Medical Policy, FDA, that the multiple solutions containing different concentrations of dextrose and electrolytes should be considered and regulated under a single NDA similar to other drugs with multiple doses. The Office of Medical Policy subsequently concurred with the Division's proposal. The purpose for this teleconference is to convey this information and discuss the regulatory pathway for Gambro Renal Products to submit a NDA for PrismaSol replacement solution.

Discussion Points

Regulatory Pathway for NDA Submission
Dr. Throckmorton stated that the Office for Medical Policy, FDA approved the Division's proposal that multiple solutions containing different concentrations of dextrose and electrolytes could be submitted and regulated under a single NDA similar to other drugs with multiple doses.

The dextrose and electrolyte concentrations for the multiple replacement solutions need to fall within the range of the dialysate solutions currently approved by CDRH. Gambro could rely, in part, on the data that they have submitted to CDRH for safety and efficacy. They would also need to provide literature or other data sources that are closely related to the product they plan to use, e.g., lactate or bicarbonate based solutions, to reassure us that the infusion of the product does not change the safety for the product. Additional clinical 'efficacy' data would not be required providing the active ingredients were within the range for the approved [redacted] and Gambro was not seeking new indications in the labeling.

Chemistry, Manufacturing and Controls
Gambro stated in the Pre-NDA meeting on December 9, 2003 that they were aware of and followed the good manufacturing practices and guidances for new drug development for their currently approved dialysate solutions. Gambro discussed the CMC issues in a Pre-NDA Chemistry meeting with the Office of New Chemistry I on March 2, 2004.

Labeling
Gambro asked if the labeling format should be similar to device or drug labeling and whether the device and the drug labeling could be combined into one. Dr. Throckmorton suggested that Gambro look at the device labeling and other approved large volume solutions, e.g. peritoneal dialysis solutions. Dr. Neuland noted that labeling changes could be cumbersome and she is unclear as to where labeling changes should be sent (CDER or CDRH). It was noted that the CDER labeling requirements were more stringent and it seemed logical that the drug labeling requirements should be followed. Dr. Stockbridge stated that, if the more stringent regulations apply, there should be a sensible way forward for approving original and revised labeling. Gambro suggested that labeling changes related to one of the seven replacement solutions under the NDA could be submitted to CDER and labeling changes related to dialysates only could be submitted to CDRH. It was mutually agreed that labeling logistics would be discussed and resolved as part of the review process.

[redacted]

The Division recommended that Gambro submit two sets of proposed labeling (one combined labeling and one more drug centered labeling) with the NDA. We would review the labeling, suggest modifications and have labeling discussions as part of the review and approval process.

Review of Portions of the NDA and Priority Review
Gambro stated that they would have some sections of the application completed ahead of the full NDA and asked if the Division would consider reviewing these sections prior to submitting the full NDA. Dr. Throckmorton stated that we would prefer they submit the full NDA in this case because the application essentially would contain the CMC information and the referenced data (device data and published literature) that support safety and efficacy based on the predicate for the 510K approval for the dialysates in CDRH. If there was an on-going clinical trial, we could discuss further submitting portions of the application.

The Division stated that Gambro could request a Priority Review at the time of the NDA submission and we would determine the review status at that time.

Conclusions/Recommendations

Gambro Renal Products plans on submitting the full NDA during the last quarter of the 2004 calendar year.

We recommend that Gambro contact the Division if they have additional questions in preparing their NDA for submission.

Signature Recorder: *(See appended signature page)*
Daryl Allis, M.S., F.N.P.

Concurrence, Chair: *(See appended signature page)*
Douglas C. Throckmorton, M.D.

Draft:	05/12/04	**Final:**	05/27/04
RD:			
Cooper	05/12/04		
Neuland	05/18/04		
Marroum	05/18/04		
Marciniak	05/21/04		
Karkowsky	05/25/04		
Stockbridge	05/27/04		
Fromm	05/27/04		
Throckmorton	05/27/04		

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/s/

Daryl L. Allis
5/27/04 03:11:52 PM
A copy of the minutes will be faxed to
the sponsor upon Dr. Throckmorton's final signature.

Doug Throckmorton
6/2/04 10:49:37 AM

Pre-NDA Meeting Minutes

Meeting Date:	March 2, 2004
Type of Meeting:	Pre-NDA CMC Meeting
P-NDA Application:	21-703
Drug:	PrismaSol
Sponsor:	Gambro Renal Products
Classification:	B
Meeting Request Date:	January 15, 2004
Confirmation Date:	January 23, 2004 (faxed confirmation sent)
Briefing Package Received:	November 10, 2003
Meeting Chair:	Hasmukh B. Patel, Ph.D.
Meeting Recorder:	Dianne C. Paraoan

Attendees:

Division of Cardio-Renal Drug Products

Hasmukh B. Patel, Ph.D.	Deputy Director, Office of New Drug Chemistry I, HFD-810
Kasturi Srinivasachar, Ph.D	Team Leader, Chemistry, HFD-810
Jahver Advani, Ph.D.	Chemist, HFD-810
Stephen Langille, Ph.D.	Microbiologist, HFD-805
Dianne C. Paraoan	Regulatory Health Project Manager, HFD-110

Gambro Renal Products

Fei Law	Manager Regulatory Affairs, Gambro Renal Products
Marie-Armelle Mouret, R. Ph.	Regulatory Affairs Group Manager, Gambro
David Zuchero, M.S., J.D.	Regulatory Affairs Consultant

BACKGROUND

During the Pre-NDA Meeting held on 10 December 2004, Dr. Throckmorton recommended that the sponsor schedule a separate CMC meeting.

Gambro Renal Products requested a Pre-NDA Chemistry, Manufacturing, and Control (CMC) meeting to discuss their CMC questions for PrismaSol, a replacement [redacted] solution for use in Continuous Renal Replacement Therapy.

DISCUSSION POINTS

Questions and Answers

General

1. **The CMC information provided was prepared from the approved European CTD documentation. Is the information provided sufficient to support a US NDA/CTD?**

   The CMC information provided is sufficient and should be submitted in the US NDA/CTD format.

2. **Is any additional information needed?**

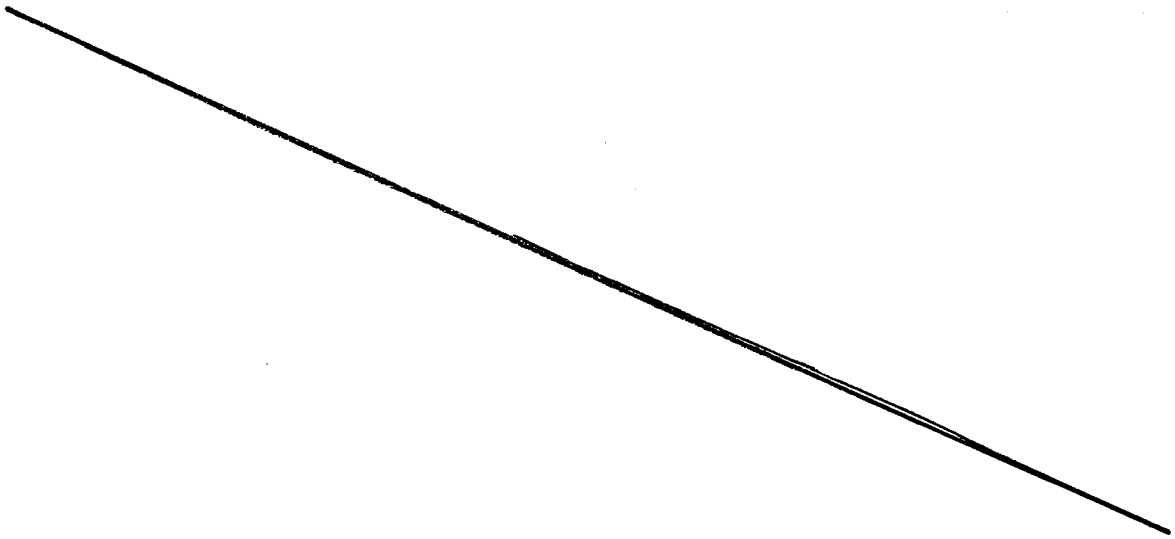
   The sponsor should consult FDA Guidance Documents and the CFR for the CMC information needed for an NDA submission. Looking at the submitted information, some additional information would be needed to include, executed and master batch records, environmental assessment or a categorical exclusion, if applicable, and documentation on the cGMP manufacturing, packaging and testing sites.

   The Division informed the sponsor that whether or not the sponsor chooses an American or European manufacturing site, cGMP standards must be met, and the facilities should be ready for inspection at the time of NDA filing.

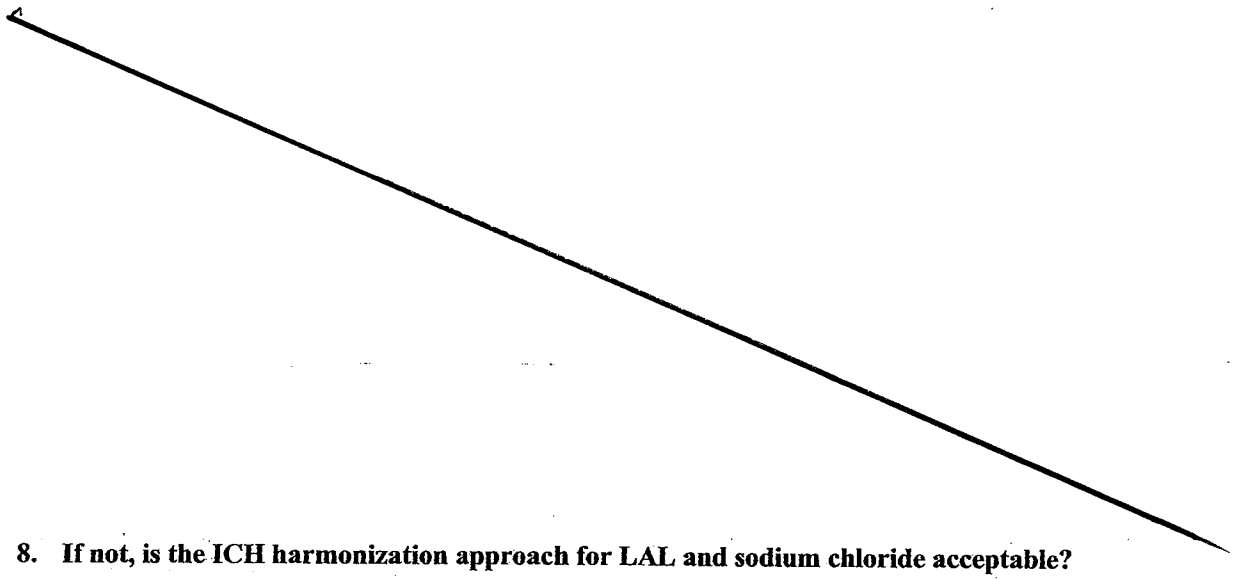
3. **Is any of the information provided in this package not required in the NDA/CTD?**

   At this stage, all of the CMC information provided seems to be relevant to an NDA. The sponsor was reminded to refer to the FDA Guidance Documents.

Manufacturing Process



Inactive pharmaceutical substances and excipients



8. **If not, is the ICH harmonization approach for LAL and sodium chloride acceptable?**

   The Division informed the sponsor that we only accept USP specifications. If the current USP specifications follow the ICH harmonization for methods and specifications, then it is acceptable to use the ICH harmonization approach.

9. **Are COAs from the manufacturer of the raw materials (electrolytes, dextrose and excipients) required or are COA issued only by the Gambro sufficient?**

   At least one representative Certificate of Analysis (COA) is required from **both** the manufacturer and the Gambro.

10. **Because the electrolytes used are inorganic salts (sodium chloride, magnesium chloride, calcium chloride, potassium chloride, sodium hydrogen carbonate), are DMF(s) necessary?**

    Drug Master Files (DMF)s are required. If DMFs are not available, equivalent information is required to be submitted in the NDA.

11. **Gambro proposed to include DMF references for dextrose and lactic acid and propose a brief description for the other ingredients in the registration file. Is this acceptable?**

    This is not acceptable to the Division. The sponsor must submit either the DMF or equivalent information in the NDA submission. The sponsor informed the Division that some of the information may be difficult to obtain. The Division suggested that the sponsor be as detailed as possible in their NDA submission. After review of the provided information, we will inform them of any additional information needed for their submission.

Packaging Components

12. **Gambro would like FDA to clarify the definition of "component" as it applies to this product: "each individual part of the packaging composing the final Container Closure System that the drug products manufacturer will receive separately and control in its site before production."**

    The Division informed the sponsor that all parts of the packaging are considered components. The sponsor clarified that they refer to the empty bag, stopper, and connector as components and what makes up the bag as the raw materials.

    The Division informed the sponsor that their reference is acceptable, but to ensure that they include all required packaging information including the frangibles.

13. **In Europe, Drug Master Files are only applicable for drug substances and not for packaging materials. Consequently, Gambro Renal Products proposes to limit the DMF if available to the components in contact with the solution. Is this acceptable?**

    Drug Master Files are required. If DMFs are not available, equivalent information is required to be submitted in the NDA.

14. **If DMFs are required, for which parts of the system: the completed affixed components or the plastic materials (i.e. connector or the material used in the production of the connector)?**

    Drug Master Files are required for the completed affixed components and plastic materials. If DMFs are not available, equivalent information is required to be submitted in the NDA.

15. **If no DMF(s) are available, what level of information should be provided?**

    The Division suggested that the sponsor refer to the FDA Guidance Document for Container Closure Systems for the Packaging of Drugs.

16. **Is supplier technical information (e.g., IR for the PVC) needed for each packaging component including bags, stoppers, luer connectors and spike connectors?**

    DMFs provide all the technical information, therefore, the information should be included.

17. **Gambro Renal Products proposes to perform biocompatibility testing on the materials used to produce the packaging components. Is this sufficient to support our registration?**

    The Division informed the sponsor that all standard USP tests should be performed.

18. **Are Gambro COAs sufficient for each packaging component or are COAs from the component manufacturer also needed?**

    At least one representative COA is required from both the manufacturer and Gambro. All information that qualifies the components is required.

19. If not, is one supplementary COA from the supplier needed for each packaging component?

One supplementary COA from the supplier is needed for each packaging component.

20. For the overwrapping (not in direct contact with the solution), which is essential to the stability of the product due to its physical barrier (prevent excessive water evaporation and loss of carbon dioxide from the bag), Gambro intends to submit information on the thickness of the material and a Gambro COA. Is this acceptable?

One supplementary COA from the supplier is needed whether or not there is direct contact with the solution.

21. The applicant considers that no DMF for the overwrapping material is needed because it is not in direct contact with the solution. Is it acceptable?

Yes, no DMF for the overwrapping material is needed if it is not in direct contact with the solution.

22. Gambro Renal Products would like to register these solutions with two different packaging (ex: PVC and non PVC) with the same shelf-life, and two different packaging (ex: PVC and non PVC) with two different shelf-lives. Are both cases acceptable?

This is acceptable as long as the sponsor provides stability data to support the shelf-life in the different packaging.

Drug Product

23. Solutions for hemofiltration and hemodialysis are described in Ph. Eur. drug product monographs and the sponsor has used those specifications in this file. In the European approved file, the methods described and validated are the ones from Ph. Eur. Is this acceptable?

USP has no drug product monographs on solutions for hemofiltration and hemodialysis; therefore, full validation information is required.

24. If not, which general tests must be validated against the USP tests?

All methods would require validation.

25. Would the ICH harmonization approach for LAL and sterility be applicable?

The ICH harmonization approach for LAL and sterility or the equivalence is applicable.

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

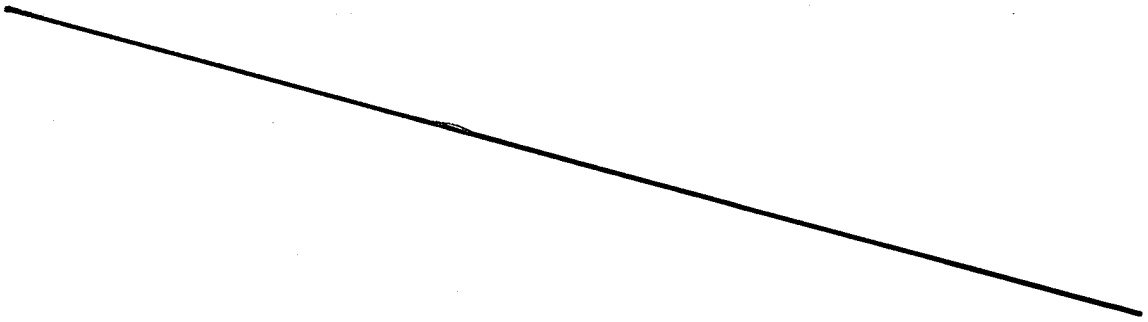
31. Is the approach for determining the water loss explained in the ICH Stability testing of new drug substances and products (paragraph 2.2.7.3 Drug products packaged in semi-permeable containers of the ICH Q1A (R2)- Step 5) acceptable?

This approach is acceptable to the Division.

32. The applicant would like to harmonize the storage conditions with the already worldwide approved products. But due to the labeling request of the European Pharmacopoeia monograph, the Gambro Renal Products proposal for the storage conditions is "Do not store below 4° C". In this case, is it mandatory to perform additional studies at 4°C?

The Division does not agree with the labeling statement "Do not store below 4° C" because this is not supported by stability studies conducted at 30°C. A standard statement of "Do not freeze" on the label may be more appropriate. The Division, again, recommended that the sponsor propose a stability protocol.

Additional Questions



34. What are FDA requirements concerning module 3.2 R Regional information?

The sponsor should refer to the guidances available on the FDA website. Some examples of information to include are the executed batch records, methods validation, and if desired, comparability protocols.

CONCLUSIONS/ RECOMMENDATIONS

The Division and Office of New Drug Chemistry I recommended that the sponsor consider the discussions and suggestions described above in preparing their NDA application. They were encouraged to contact the Division if they need additional assistance.

Signature recorder: *{See appended electronic signature page}*
Dianne C. Paraoan

Concurrence, Chair: *{See appended electronic signature page}*
Hasmukh B. Patel, Ph.D.

Draft: 3/4/04 Final: 03/24/04
RD:

Patel: 03/15/04
Srinivasachar: 03/11/04
Advani: 03/04/04
Langille:

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/s/

Hasmukh Patel
3/24/04 01:52:49 PM

Pre-NDA Meeting Minutes

Meeting Date:	December 9, 2003
Type of Meeting:	Pre-NDA Meeting
P-NDA Application:	21-703
Sponsor:	Gambro Renal Products
Classification:	B
Meeting Request Date:	October 15, 2003
Confirmation Date:	October 17, 2003 (faxed confirmation sent)
Briefing Package Received:	November 10, 2003
Meeting Chair:	Douglas C. Throckmorton, M.D.
Meeting Recorder:	Dianne C. Paraoan

Attendees:

Division of Cardio-Renal Drug Products

Douglas C. Throckmorton, M.D.	Director, Division Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Albert DeFelice, Ph.D.	Team Leader, Pharmacologist, HFD-110
Kasturi Srinivasachar, Ph.D	Team Leader, Chemistry, HFD-810
Carolyn Neuland, Ph.D.	Chief, CDRH, Gastroenterology and Renal Devices Branch, HFZ-470
Jeffrey Cooper, D.V.M.	Veterinary Medical Officer, CDRH, Gastroenterology and Renal Devices Branch, HFZ-470
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110
Dianne C. Paraoan	Regulatory Health Project Manager, HFD-110

Gambro Renal Products

Susie Lew, M.D.	Clinical/Medical Consultant, GW University
Jeffery Shideman, Ph.D.	Director of Therapy Groups Americas, Gambro
Marie-Armelle Mouret, Pharmacist	Regulatory Affairs Group Manager, Gambro
Melanie Voisin, Pharmacist	Regulatory Affairs Deputy Manager, Gambro
David Zuchero, M.S., J.D.	Regulatory Affairs Consultant

BACKGROUND

Gambro Renal Products requested a Pre-NDA meeting to discuss the submission for PrismaSol, a replacement and dialysis solution for use in Continuous Renal Replacement Therapy. When used as a dialysis solution, this product has already been approved as a medical device under a different brand name (PrismaSate). Gambro Renal Products seeks approval of these products as replacement solutions and intends to seek common labeling for ____ replacement solution ____

DISCUSSION POINTS

General Discussion

Dr. Throckmorton provided the sponsor with three general recommended guidelines to consider in their NDA submission for PrismaSol Replacement Solutions as an infusate.

1. Claim Structure
The sponsor assured the Division that the product is intended only for the current claim as an infusate in hemofiltration, and that they were not seeking any additional claims.
Dr. Throckmorton said that if the sponsor intended to seek additional claims beyond as an infusate, they would need to provide data to support that claim.

2. Chemistry, Manufacturing, and Control (CMC)
The CMC requirements of a dialysate and an infusate differ. Dr. Throckmorton stated to the sponsor that all CMC data would need to meet the CDER standard, and would need to be complete at the time of submission. The sponsor stated that they were aware of and followed the good manufacturing practices and guidances regarding new drug development. The sponsor should provide sufficient evidence that they know enough about modality and can support their indication with sufficient clinical data.

3. General Safety
As a part of the submission, the sponsor must provide data, perhaps in the form of articles, to support their position that the product given as an infusate is just as safe or safer than when used as a dialysate.

Proposed PrismaSol Formulations

Dr. Throckmorton recognized that the sponsor is seeking approval for nine proposed PrismaSol formulations. The ranges of proposed solutes for seven of the nine products are covered by a previous approval of a dialysate by the Center for Devices and Radiological Health (CDRH). Dr. Throckmorton stated that he has proposed that these products be considered dosing changes, rather than substantial differences in composition, such that each one of them will not be seen as new drugs. As soon as the Division knows if this is an acceptable policy by the upper management in CDER they will let the sponsor know as well.

Dr. Throckmorton added that because only seven of the nine products have a basis for predicate approval by CDRH, it may be more difficult for the sponsor to provide sufficient clinical data for the remaining two (Products #7 and 9). ____

[redacted]

Pre-Clinical

Dr. Throckmorton informed the sponsor that based on the information provided, no pre-clinical studies are required. However, the sponsor should submit sufficient references to support their claim in order to support their contention that the infusate has no new safety concerns not seen with the dialysate (as discussed above for the General Safety). The sponsor inquired whether or not the references submitted had to be bicarbonate based versus lactate based solutions. Dr. Throckmorton recognized that lactate based solutions are more common, but encouraged the sponsor to focus on bicarbonate based solutions as their references since their solution is bicarbonate based.

CMC

Dr. Throckmorton suggested that the sponsor arrange a separate meeting to discuss CMC issues. The sponsor will contact Ms. Dianne Paraoan when they are prepared for the CMC meeting.

Labeling

[redacted]

Regulatory Discussion

The sponsor informed the Division that they will be prepared to submit an NDA application by the middle of 2004.

CONCLUSIONS/ RECOMMENDATIONS

The Division recommended the sponsor consider the discussions and suggestions described above in preparing their NDA application. We encouraged them to contact the Division if they need additional assistance.

The sponsor should contact Ms. Dianne Paraoan to arrange a CMC meeting prior to their NDA submission.

Signature recorder: _____
Dianne C. Paraoan

Concurrence, Chair: *{See appended electronic signature page}*
Douglas C. Throckmorton, M.D.

Draft: 12/22/03 Final: 1/5/04
RD:

Throckmorton: 1/5/2004
Stockbridge: 1/5/2004
Marciniak: 1/5/04
DeFelice:1/2/04
Srinivasachar:1-2-04
Allis: 12/24/03

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/s/

Dianne Paraoan
1/6/04 11:21:02 AM

Doug Throckmorton
1/7/04 08:23:51 AM